UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF FLORIDA
ORLANDO DIVISION

NANCY GUENTHER and DONALD GUENTHER,

Plaintiffs,

v. **Case No: 6:08-cv-456-Orl-31DAB**

NOVARTIS PHARMACEUTICAL CORPORATION,

Defendant.

ORDER

This matter comes before the Court after a hearing on the Motion in Limine (Doc. 162) filed by the Defendant, Novartis Pharmaceutical Corporation ("Novartis"), the responses in opposition (Doc. 172, 175-76) filed by the Plaintiffs, and the reply (Doc. 177) filed by Novartis.

I. Background

Nancy Guenther was diagnosed with breast cancer in February 1999. In October 2001, her doctor found that the cancer had metastasized to her bones. In May 2002, she was prescribed Zometa by her oncologist. Zometa, which is produced and marketed by Novartis, is prescribed to reduce the incidence of pathological fractures and other problems occurring in the bones of patients with certain types of cancer.

After she began taking Zometa, Nancy Guenther began to suffer a number of dental problems including osteonecrosis of the jaw (henceforth, "ONJ"), a condition in which a portion of the jaw bone essentially dies. On March 28, 2008, the Plaintiffs filed the instant suit, alleging

that Zometa caused Nancy Guenther to suffer ONJ, and that Novartis failed to, *inter alia*, provide proper warning of that risk. Nancy Guenther asserted claims against Novartis based on strict liability (Count I), negligent manufacturing (Count II), failure to warn (Count III), breach of express warranty (Count IV), and breach of implied warranty (Count V). Her husband, Donald Guenther, filed a claim for loss of consortium (Count VI). The case was transferred to a multidistrict litigation panel in May 2008 and remanded to this Court in September 2012.

II. Legal Standard

Broadly speaking, a motion in limine may be defined as a request, generally made before a trial has begun, "to exclude anticipated prejudicial evidence before it is actually offered." *Luce v. United States*, 469 U.S. 38, 40 n.2 (1984). Although in limine rulings are not binding on a trial court and remain subject to reconsideration during the trial itself, *id.* at 41-42, motions in limine provide notice to the trial judge of the movant's position so as to avoid the introduction of damaging evidence, which may irretrievably affect the fairness of the trial, *Stewart v. Hooters of America, Inc.*, 2007 WL 1752873 (M.D.Fla. June 18, 2007). A pretrial motion in limine may also have the salutary effect of reducing the number of interruptions during the trial itself. *Bradley v. Pittsburgh Bd. of Educ.*, 913 F.2d 1064, 1069 (3d Cir. 1990).

While the list is not exhaustive, courts generally recognize that a motion in limine is proper where:

> (1) the trial court has directed that evidentiary issue be resolved before trial; (2) the evidentiary material is highly prejudicial or inflammatory and would risk mistrial if not previously addressed by the trial court; (3) the evidentiary issue is significant and unresolved under the existing law; (4) the evidentiary issue involves a significant number of witnesses or substantial volume of material making it more economical to have the issue resolved in advance of the trial so as to save time and resources of all concerned; or (5) the party does not wish to object to the evidence in the presence of the

> jury and thereby preserves the issue for appellate review by obtaining an unfavorable ruling via a pretrial motion in limine.

75 Am. Jur. 2d Trial § 39.

Unless the evidence is clearly inadmissible on all possible grounds, evidentiary rulings should be deferred until trial so that questions of foundation, relevancy, and potential prejudice may be resolved in proper context. *See generally* 21 FED. PRAC. AND PROC. EVIDENCE § 5037.10 (2d ed.). A ruling in limine does not "relieve a party from the responsibility of making objections, raising motions to strike or making formal offers of proof during the course of trial." *Thweatt v. Ontko*, 814 F.2d 1466, 1470 (10th Cir.1987).

III. Analysis

A. "Notice" Evidence

According to Novartis, the Zometa package insert was revised in September 2003 to include information about ONJ. Novartis seeks to exclude several items of evidence that, in the Plaintiffs' view, tend to suggest that Novartis knew or should have known about a connection between Zometa and ONJ prior to May 2002, when Nancy Guenther began taking the drug.

1. Gotcher and Jee article

The first such item involves a study in which rats were given a bisphosonate to see if it would reduce periodontal bone loss. Some of the rats developed exposed jaw bones during the study, the results of which were published in 1981 by Gotcher and Jee. The Plaintiffs argue, *inter alia*, that knowledge of the study should have led Novartis to look for (and therefore discover) jaw bone problems developing during the clinical trials of Zometa (and a predecessor bisphosphonate, "Aredia"), resulting in proper warnings about the risk of ONJ being provided to Nancy Guenther when she was considering whether to take Zometa in 2002.

Zometa contains nitrogen. Clodronate -- the bisphosphonate administered during the rat study chronicled by Gotcher and Jee – does not. Because of this distinction, Novartis argues that the study should be excluded as it would not put one on notice of a possible association between Zometa and ONJ. However, Novartis offers nothing other than its own assertion that the results of a study of the effects of a nitrogen-free bisphosphonate have no relevance when one is considering the potential hazards of a nitrogen-containing bisphosphonate.

Novartis also notes that the article was published in 1981, long before the events at issue in this case, and that the study involved rats rather than humans. At best, these arguments go to the weight that one ought to assign to the Gotcher and Jee article, rather than its admissibility.

2. Phossy Jaw

Through the 19th and early 20th centuries, workers exposed to white phosphorus (commonly used in match factories of the time) sometimes developed a condition known as "phossy jaw" in which, among other things, jaw bone tissue would rot and die. As with the Gotcher and Jee article, the Plaintiffs seek to introduce evidence regarding phossy jaw to argue that Novartis should have been on notice, prior to conducting the clinical trials of Aredia and Zometa, of a potential link between phosphorus-containing compounds and jaw problems. Novartis argues that such evidence would be irrelevant because of the differences in the chemical composition of white phosphorus and Zometa. Again, however, Novartis offers nothing other than its bare assertion that the compounds are sufficiently dissimilar as to render such evidence irrelevant.

Novartis also asserts that the report prepared by one of the Plaintiffs' experts, Dr. Robert Marx, does not address phossy jaw. Because of this, Novartis argues that Marx should be precluded from offering testimony about the condition. However, while the Marx report does not

contain any references to phossy jaw in the section detailing the opinions he intends to express, it does cite to at least two articles with "phossy jaw" in their titles. More importantly, Marx was deposed at some length in the instant case on the topic, including references to an article he had recently submitted for publication describing what he saw as similarities between phossy jaw and ONJ. (Doc. 172-2 at 7-8). Novartis has not shown that Marx is unqualified to discuss the purported similarities between phossy jaw and ONJ or that the company will suffer any prejudice if Marx is permitted to do so.

3. Osteopetrosis

Osteopetrosis is a genetic disorder that results in bones becoming harder and more dense. Osteopetrosis typically impairs the proper functioning of osteoclasts, a type of bone cell that removes bone tissue. Zometa also inhibits osteoclasts. Because of this, the Plaintiffs argue that Novartis should have been on notice that Zometa could cause conditions such as ONJ. Novartis points out that one of the Plaintiffs' own experts has testified that osteopetrosis and ONJ are two "totally different" disease processes, Doc. 162 at 6, and argues that any evidence about osteopetrosis is irrelevant. However, the Plaintiffs are not arguing that the processes are the same, and therefore there is no basis to conclude that evidence about osteopetrosis would be irrelevant when assessing the potential hazards that might result from a drug that impairs the functioning of osteoclasts.

B. FDA-controlled issues

1. Black Box warning

Novartis expects the Plaintiffs to argue that it should have added a so-called "black box" warning – a bolded statement that appears in a black box at the beginning of a drug label with the heading "WARNING." Novartis argues that it was prohibited by law from doing so without prior

FDA approval, and that the Plaintiffs have no evidence that the FDA would have granted a request by Novartis to do so. Novartis points to an FDA statement in the Federal Register that, "to ensure the significance of boxed warnings in drug labeling, they are permitted only when specifically required by FDA." 44 Fed. Reg. 37434, 37448 (June 26, 1979).

The Plaintiffs do not directly respond to this point. Rather, they assert that all of the failure-to-warn arguments in this case are controlled by *Wyeth v. Levine*, 555 U.S. 555 (2009). *Levine* involved Phenergan, an antinausea drug that can be administered intravenously but which causes gangrene if it enters a patient's artery. *Id.* at 559. Of the two methods by which Phenergan can be administered intravenously – the "IV-push" method and the "IV-drip" method – the former was found to present a much higher risk of the drug entering an artery. *Id*. at 560. The plaintiff in *Levine* received Phenergan by the IV-push method; the Phenergan entered one of the plaintiff's arteries, causing gangrene that resulted in the amputation of the plaintiff's arm at the forearm. *Id.* at 599.

The Phenergan label at the time warned of the dangers of gangrene and amputation if the drug entered an artery. *Id.* at 559-60. Despite this, the plaintiff argued that the label was insufficient, rendering the product defective, because it failed to instruct clinicians to use the IV-drip method rather than the IV-push method so as to minimize the chance that the drug would enter an artery. *Id.* at 560. The drug manufacturer argued that the warning language had been approved by the FDA and therefore any state law failure-to-warn claim was preempted by federal law. *Id.* The plaintiff prevailed at trial and on appeal. *Id.* at 562-63. The United States Supreme Court granted certiorari to answer the question of "whether FDA drug labeling judgments preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use." *Id.* at 563.

Before the Supreme Court, the drug manufacturer made two pre-emption arguments: first, that the company could not comply with its state law duty to add a warning to the label without violating federal law that required FDA approval of drug labels (thereby running afoul of federal law prohibiting misbranding of drugs); and second, that recognition of such a state law duty would create an unacceptable obstacle to Congress's objectives by substituting a lay jury's opinion about drug labeling for the expert judgment of the FDA. *Id.* at 563-64 (citing *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982) and *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941)).

The *Levine* Court rejected both arguments. As to the first point, the court found that while label changes generally cannot be made without FDA approval, the FDA's "changes being effected" ("CBE") regulation permitted manufacturers to make preapproval changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *Id.* at 568 (citing C.F.R. §§314.70(c)(6)(iii)(A), (C)). The court also noted that drug manufacturers, rather than the FDA, remain primarily responsible for drug labels. *Id.* at 1197-98. The court noted that the FDA retained the authority to reject labeling changes, but absent clear evidence that the FDA would not have approved a change to the Phenergan label, the court would not find that it was impossible for the manufacturer to abide by both federal and state law. *Id.* at 571.

As to the second point, the court found that the refusal, by Congress, to provide a federal remedy for consumers harmed by unsafe or ineffective drugs suggested that Congress thought that widely available state rights of action provided appropriate relief – a conclusion bolstered by the fact that Congress had enacted an express pre-emption provision as to state tort claims involving medical devices, but not in regard to such claims involving prescription drugs. *Id.* at 574-75. The

court also rejected FDA statements (taken from the preamble of a 2006 FDA regulation governing the content and format of prescription drug labels) that the Food, Drug and Cosmetics Act ("FDCA"), 21 U.S.C. §301 *et seq.*, establishes both a floor and a ceiling for such labels, so that FDA approval preempts conflicting or contrary state law, and that state law failure-to-warn claims threatened the FDA's statutorily prescribed role as the expert federal agency responsible for evaluating and regulating drugs. *Id.* at 575-76.

Novartis argues that a number of arguments it expects the Plaintiffs to make in this case are preempted because they conflict with the FDA's regulatory authority over the marketing of prescription drugs. (Doc. 162 at 7). However, the two cases primarily cited by Novartis for this proposition -- *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 133 S.Ct. 2466 (2013) *and PLIVA, Inc. v. Mensing*, 131 S.Ct. 2567 (2011) -- are inapposite because they involve manufacturers of generic drugs, who do not possess the ability to alter drug labels through the CBE regulations (or otherwise). The Supreme Court itself described the holding of *PLIVA* as being that "failure to warn claims against *generic* manufacturers are pre-empted by the FDCA's prohibition on changes to generic drug labels". *Bartlett*, 133 S.Ct. at 2472 (emphasis added). Novartis relies upon some out-of-context language to suggest that *Bartlett* expanded this pre-emption to encompass all failure-to-warn claims, not just those against manufacturers of generic drugs. However, a review of the opinion demonstrates that the FDCA's prohibition on label alterations by generic drug manufacturers was as central to the decision in that case as it was in *PLIVA*. In addition, the Court notes that Novartis is unable to point to any authority – case law, treatise, or otherwise – suggesting that *Bartlett* altered the legal landscape in regard to failure-to-warn claims against manufacturers of name-brand prescription drugs.

Despite the foregoing, the Plaintiffs never directly dispute Novartis's contention that the FDA regulations preclude a manufacturer from adding a black box warning without preapproval. Accordingly, the Plaintiffs will not be permitted to argue at trial that Novartis should have done so. Nevertheless, evidence bearing on the issue of potential black box warnings may be relevant to, *inter alia*, the sorts of warnings that Novartis could have added without preapproval. Accordingly, such evidence is not necessarily inadmissible.

2. Dosing/duration of use and comparison with Aredia

Novartis argues that the Plaintiffs should be precluded from arguing that the company should have altered Zometa's label to reduce the recommended frequency of infusions or to recommend a limit on the total number of doses or months of treatment. Novartis argues that

> Prior FDA approval is required, inter alia, for any change that "has a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product." 21 C.F.R. § 314.70(b).

(Doc. 162). However, contrary to Novartis's statement, prior FDA approval is not required for "any change" that has such an effect, but rather for "any change in the drug substance, drug product, production process, quality controls, equipment, or facilities" that does so. 21 C.F.R. §314.70(b)(1). In this case, the Plaintiffs appear to be arguing that Novartis should have altered the label to add a warning about dosage and administration – which is explicitly permitted, without prior approval, under 21 C.F.R. § 314.70(c)(6)(iii)(C).[1] *Levine*, 555 U.S. at 568.

Along the same lines, Novartis objects to any argument by the Plaintiffs that Zometa's label should have included a warning that Aredia was safer than Zometa. Novartis argues that, per

[1]This citation is to the current version of the regulation. At the time Nancy Guenther was taking Zometa, the same provision could be found at 21 C.F.R. § 314.70(C)(2)(iii). (Doc. 175-8 at 2).

21 C.F.R. § 314.126(b), comparisons to other drugs on drug labels must be supported by "substantial evidence derived from adequate and well-controlled studies as defined in §314.126(b)," and that there are no studies showing that Aredia is superior to Zometa. The Plaintiffs argue that there were comparative studies of Zometa and Aredia, because Novartis referenced Aredia as a control during the Zometa trials, and the Zometa label already describes Zometa as not inferior to Aredia for use by breast cancer patients. (Doc. 175 at 10). The Plaintiffs then argue that "[w]hen Novartis had indications that Aredia's safety profile on [ONJ] was better than Zometa's … it had *carte blanche* through the CBE to say so on the label." (Doc. 175 at 10). However, having "indications" that one drug is safer than another is a far cry from having "adequate and well-controlled studies" reaching that conclusion, which the Plaintiffs appear to admit is the applicable standard. At this juncture, the Court does not know enough about the comparison(s) to be made or the evidence backing them to reach a final conclusion. But it appears that the Plaintiffs' evidence would not satisfy the standard established by 21 C.F.R. §314.126(b).

3. Challenge to formatting

Because the FDA regulates the format of prescription drug labels, 21 C.F.R. § 201.57(d), Novartis argues that the Plaintiffs should be barred from arguing that the company should have formatted the Zometa label differently, such as by moving the ONJ warning to a different section. However, the FDA also regulates the content of such labels and drug manufacturers can add warning language, and it makes no sense to hold the formatting sacrosanct where the actual content is not. The CBE regulations that permit manufacturers to add or strengthen warnings impose no limitations on the formatting of such warnings. *See* 21 C.F.R. § 314.70(c)(6)(iii)(A).

4. Failure to report to the FDA

Novartis argues that the Plaintiffs should be barred from contending that the company violated FDA regulatory requirements by failing to report some information about ONJ to the agency. Novartis argues that such arguments are constitutionally preempted. The Plaintiffs offer no response to this argument. The question of whether certain information was reported to the FDA may still be relevant here, but the Plaintiffs will not be permitted to argue that Novartis violated FDA regulations by withholding information from the agency.

C. Expanded Scope Arguments

1. Invasive procedures and the learned intermediary doctrine

Plaintiffs in other Aredia and Zometa cases have argued that Novartis had a duty to warn that patients should avoid invasive dental procedures while undergoing treatment with those drugs. Novartis argues that the Plaintiffs should not be permitted to make that argument in this case, as Nancy Guenther did not undergo any such procedures while on Zometa, and therefore any failure to provide such a warning could not have harmed her. Novartis also contends that its obligation under the learned intermediary doctrine was only to warn prescribing physicians of the dangers associated with Zometa, and that the Plaintiff should be barred from arguing that it was obligated to warn other medical professionals in addition to prescribing physicians.

In response to both of these arguments, the Plaintiffs (without explanation) direct the Court's attention to two district court opinions: *Mahaney v. Novartis Pharms. Corp.*, 835 F.Supp.2d 299 (W.D.Ky. 2011) and *Hogan v. Novartis Pharms. Corp.*, 2011 WL 1533467 (April 24, 2011). In these cases, the courts adopted the position espoused by the Restatement (Third) of Torts that drug manufacturers are obligated to notify not only prescribing physicians but also

"other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings."[2] *See, e.g.*, *Hogan* at *10.

Although the decisions cited by the Plaintiffs seem to represent the prevailing trend in regard to the scope of the learned intermediary doctrine, neither applies or even refers to Florida or Georgia law. Novartis cites to Georgia and Florida cases in which the courts have stated that a drug manufacturer's duty under the learned intermediary doctrine is limited to an obligation to warn prescribing physicians. *See, e.g.*, *Bryant v. Hoffmann-La Roche, Inc.*, 585 S.E.2d 723, 730 (Ga. App. 2003) (stating that "[W]here prescription drugs are concerned, the manufacturer's duty to warn is limited to an obligation to advise the prescribing physician of any potential dangers that may result from the drug's use."). However, in the cases cited by Novartis, the court was considering either (1) whether the drug manufacturer had a duty to warn the *patient* in addition to the prescribing physician or (2) whether the text of the warning provided by the manufacturer to the prescribing physician was sufficient to discharge its duty. Thus, none of the cases cited by the parties address the particular issue of whether, under Georgia or Florida law, the learned intermediary doctrine requires warnings to medical professionals outside of the class of

[2] More specifically, the pertinent passage from the Third Restatement provides as follows:

> A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to … prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings.

Restatement (Third) of Torts: Prod. Liab. § 6 (1998).

prescribing physicians. This Court has also been unable to locate a decision by a Georgia court or a Florida court explicitly addressing the issue.

No party in this diversity case has suggested that Georgia differs from Florida in regard to substantive tort law. Accordingly, for simplicity's sake, the Court will assume that Florida substantive tort law will be applied in this case. As no Florida appellate court has addressed the topic, this Court must attempt to divine whether the Supreme Court of Florida would adopt the Third Restatement's version of the learned intermediary doctrine or restrict the doctrine's application to warnings to prescribing physicians. *See Fritz v. Standard Sec. Life Ins. Co.*, 676 F.2d 1356, 1358 (11th Cir. 1982) ("[I]n the absence of controlling state precedent, we must discern how the Florida Supreme Court would rule if presented with the issue.").

The Court concludes that the Florida Supreme Court would apply the Third Restatement's version of the doctrine. While Florida has not yet adopted the Third Restatement,[3] Florida courts have adopted some portions of it. *See, e.g., Kohler v. Marcotte*, 907 So. 2d 596 (Fla. 3d DCA 2005) (adopting component parts doctrine of Restatement (Third) of Torts: Product Liability § 5). As noted above, it appears that when courts outside of Florida have confronted the issue, they have tended to adopt the version of the learned intermediary doctrine set forth in the Third Restatement rather than the more restrictive version advocated by Novartis. And the Court notes that the very first court to recognize the learned intermediary doctrine in Florida held that its application could require a warning to others besides prescribing physicians:

> A manufacturer of a dangerous commodity, such as a drug, does have a duty to warn but when the commodity is a prescription drug we hold that this duty to warn is fulfilled by an adequate warning given to those members of the medical community lawfully authorized to prescribe, dispense and administer prescription drugs.

[3] *See, e.g., Liggett Group, Inc. v. Davis*, 973 So. 2d 467, 473 (Fla. 4th DCA 2007).

Buckner v. Allergan Pharmaceuticals, Inc., 400 So. 2d 820, 822 (Fla. 5th DCA 1981). In enumerating the medical professionals that drug manufacturers were obliged to warn, the *Buckner* court relied on sections of the Florida Statutes that "evidence[d] legislated public policy to rely on physicians and pharmacists protect the consuming public from injury by product use when the product is a prescription drug." *Id.* at 822 n.3.

To the extent that this may be relevant at trial, the Plaintiffs will be permitted to argue that the learned intermediary doctrine obligated Novartis to provide warnings to medical professionals other than prescribing physicians.

2. Promotional material not seen by the prescribers, and the PDR

Novartis seeks to preclude evidence and argument about Zometa promotional material that was not seen by the oncologist who initially prescribed the drug to Nancy Guenther. Novartis makes the same argument in regard to the Physicians' Desk Reference, a collection of package inserts. Novartis contends that such material cannot be relevant to the instant case. *See also In re Seroquel Prods. Liabl. Litig.*, 2009 WL 223140 at *4 (M.D.Fla. Jan. 30, 2009) (Baker, M.J.) (barring admission of Seroquel promotional letters where there was no evidence the letters had been seen by prescribing physician). The Plaintiffs argue only that the Court "should await the event at trial." Of course, all of the Court's *in limine* rulings are subject to reconsideration in light of developments at trial. Nonetheless, on this record, the Court sees no basis for admitting this evidence or allowing such arguments.

3. Duty to warn beyond Zometa Package Insert

Novartis complains that the Plaintiffs may seek to argue that the company should have provided warnings about ONJ in various ways beyond the Zometa package insert itself, such as by putting warnings in promotional letters or via the PDR. Novartis contends that such arguments

would run afoul of case law providing (under both Georgia and Florida law) that a drug manufacturer fulfills its duty to warn the learned intermediary by way of package inserts accompanying its products. *See, e.g.*, *Guarino v. Wyeth*, 719 F.3d 1245, 1250 (11th Cir. 2013). But Novartis reads these cases too narrowly. They hold that a drug manufacturer can satisfy its obligation by way of such package inserts, but they do not hold that package inserts are the *only* way to do so. With Novartis arguing that the FDA would have stymied any effort to provide additional warnings in the Zometa package insert, the company's ability to provide warnings via other channels appears likely to be relevant.

4. Subsequent Remedial Measures

Novartis asserts that the Plaintiffs should be barred from discussing changes that were made to the Zometa label in 2007 or later, after Nancy Guenther stopped the Zometa treatment. Novartis argues that the changes are subsequent remedial measures and therefore inadmissible under F.R.E. 407. The Plaintiffs again only assert that the Court should await developments at trial. In the absence of knowledge as to what label changes are at issue here, the Court is unable to

conclude that they constitute subsequent remedial measures so that Rule 407 applies. However, this appears likely to be the case.

IV. Conclusion

In consideration of the foregoing, it is hereby

ORDERED AND ADJUDGED that the Motion in Limine (Doc. 162) is **GRANTED IN PART AND DENIED IN PART,** as set forth above.

DONE and **ORDERED** in Orlando, Florida on August 29, 2013.

GREGORY A. PRESNELL
UNITED STATES DISTRICT JUDGE

Copies furnished to:

Counsel of Record
Unrepresented Parties