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Here We Go Again: The Fosamax Preemption Saga Continues

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For the second time, the U.S. Court of Appeals for the Third Circuit vacated the U.S. District Court for the District of New Jersey's judgment that plaintiffs' state law failure-to-warn claims in the Fosamax litigation were preempted under federal law. *See In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 118 F.4th 322 (3d Cir. 2024) (Fosamax II). The Third Circuit found that the court erred because it gave "too little weight to the required presumption against pre-emption" and improperly determined that the Food and Drug Administration informed Merck that it would disapprove a label change. Unless the Third Circuit's decision is reversed, this decision revives hundreds of cases, many of which have been dormant since at least 2017.

Background

Fosamax is an FDA-approved medication prescribed to treat and prevent osteoporosis in postmenopausal women. At the time of approval, the label did not warn of the risk of atypical femoral fractures even though Merck was aware of the "theoretical risk" of them. In 2008, after receiving additional evidence, Merck submitted a prior approval supplement (PAS) to update the label. A PAS requires FDA approval before label changes can be made. Merck proposed adding information related to "low-energy femoral shaft fracture" in the Adverse Reactions section and additional information in the Precautions section focusing on the association between Fosamax and stress fractures.

In 2009, the FDA responded to the PAS with a complete response letter (CRL). A CRL sets forth the deficiencies identified by FDA and reflects FDA's complete review of the submitted data. *Id.* at *331 (citing 21 C.F.R. § 314.110(a)(1) and (2)). In the CRL, FDA approved the Adverse Reactions changes, but rejected the Precautions changes. FDA determined that Merck's justification was "inadequate" because the "[i]dentification of 'stress fractures' may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature" and the "[d]iscussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and post-marketing adverse event reporting." *Id.* at 335. FDA also informed Merck that it could resubmit the PAS to address FDA's concerns. Merck withdrew its PAS and updated the Adverse Reactions section through the Changes Being Effected (CBE) process. *Id.* at 336-37; *see* 21 C.F.R. §314.70(c)(6)(iii)(A) (permitting changes without FDA approval where there is "newly acquired information" about "evidence of a causal association" that will "add or strengthen a ... warning").

In September 2010, an FDA Task Force found that there was evidence of femoral shaft fractures with long-term bisphosphonate use and recommended changing bisphosphonate labels. In October 2010, FDA announced that it would require all bisphosphonate labels to include the risk of atypical femoral fractures. In January 2011, Merck added FDA's proposed language, nearly verbatim, to the Precautions section of the Fosamax label.

Fosamax Litigation

More than 500 plaintiffs allege that they suffered atypical femoral fractures between 1999 and 2010. Their claims were consolidated in an MDL, in the U.S. District Court for the District of New Jersey. In 2013, the first bellwether trial resulted in a defense verdict. Following the verdict, the court determined that plaintiffs' failure-to-warn claims were preempted and entered an order to show cause as to why all cases in the MDL alleging injuries prior to the Task Report should not be dismissed on preemption grounds. *Id.* at 337-38 (citing *In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 951 F. Supp. 2d 695, 701, 703-04 (D.N.J. 2013)). The court concluded that Merck was entitled to judgment because plaintiffs failed to show cause why their claims were not preempted.

On appeal, the Third Circuit reversed, vacated and remanded. *Id*. at 338 (citing *In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 852 F. 3d 268, 271, 293 (3d Cir. 2017) (Fosamax I)). In Fosamax I, the Third Circuit interpreted the Supreme Court's "clear evidence" standard from *Wyeth v. Levine*, 555 U.S. 555 (2009), to be akin to an evidentiary standard. Based on *Wyeth*, the Third Circuit reasoned that the Supreme Court intended to establish a standard of proof and that a preemption defense required the factfinder to conclude that it was highly probable that FDA would not have approved a label change. The Third Circuit also concluded that it was a question of fact for the jury to determine whether the FDA would have rejected a proposed label change. Merck sought review by the Supreme Court.

In *Merck Sharp & Dohme v. Albrecht*, 587 U.S. 299 (2019), the Supreme Court vacated and remanded Fosamax I. The court clarified that "clear evidence" is not an evidentiary standard; it refers to the quality of the evidence presented. Rather, "clear evidence" is [1] "evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law and [2] that the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." The court further noted that the only agency actions that can determine whether a claim is preempted are those actions taken pursuant to FDA's congressionally delegated authority, including the issuance of a CRL. The court observed that because the CBE process permits label changes without prior FDA approval, a manufacturer will not ordinarily be able to demonstrate that there was an actual conflict between state and federal law and that it is impossible to comply with both laws. The court also found that the preemption determination was a matter of law for the court to decide.

On remand, the Third Circuit directed the district court to decide whether plaintiffs' state law claims were preempted under the *Albrecht* standards. Fosamax II, 118 F.4th at 341. In 2022, the district court determined that Merck had satisfied the *Albrecht* two-prong test. As to the first prong, plaintiffs' claims were preempted because Merck fully informed the FDA of the basis for its proposed warning. Merck provided FDA with formal safety updates, periodic emails, and submitted a PAS, which fully informed FDA of the numerous risks associated with long-term Fosamax use and the reasons for its proposed label change.

As to the second prong, the court determined that FDA formally informed Merck that it would reject any warning in the Precautions section. Although the CRL gave rise to different inferences as to why FDA rejected the proposed change, the court considered Merck's communications with FDA and concluded that the CRL rejected the change because FDA doubted that there was a causal association between bisphosphonate use and atypical femoral fractures. The court determined that in light of 21 U.S.C. § 355(o), which requires FDA to tell drug manufacturers if the agency "becomes aware of new information" that should be included in a drug's label, it was improbable that FDA declined the change or failed to propose a different solution, if FDA had sufficient causal evidence linking bisphosphonates to atypical femoral fractures, which exposed patients to harm. Lastly, the court rejected plaintiffs' argument that Merck could have amended the Precautions section through the CBE process after FDA rejected Merck's PAS because there was no "newly acquired information" which was required to submit a CBE amendment.

Third Circuit's Ruling

On appeal, the Third Circuit determined that it would review the court's overall preemption conclusion de novo but would apply the clear-error standard to "any subsidiary factual determinations." As to the first prong, the Third Circuit determined, based on the clear error standard, that the court did not err and agreed that "Merck 'clearly and fully informed the FDA of the panoply of risks associated with long-term Fosamax use and the justifications for its proposed label change.'" The Third Circuit rejected plaintiffs' argument that Merck failed to provide FDA with available and relevant information concerning atypical femoral fractures. The Third Circuit also rejected plaintiffs' argument that Merck failed to demonstrate by clear evidence that FDA prohibited it from adding a warning required by state law.

As to the second prong, however, the Third Circuit reviewed the issue *de novo* and found that Merck had not shown that FDA would have rejected all warnings that satisfied state law. The Third Circuit maintained that the court failed to read FDA's CRL in a way that disfavored preemption and carried out Congress's intent to permit preemption only when it was "abundantly clear" that it was impossible to comply with both federal and state law. According to the Third Circuit, the Supreme Court established a "very high bar" for impossibility preemption in labeling cases, and Merck failed to show that federal law, including FDA actions, prohibited any and all warnings that satisfied state law. Accordingly, the Third Circuit determined the court erred because FDA had not clearly rejected Merck's proposed warning in a way that demonstrated that no label change would have been appropriate at the time of Merck's PAS.

The Third Circuit also rejected Merck's argument that FDA would have required a label change pursuant to 21 U.S.C. § 355(o)(4)(A) if it "becomes aware of new information" that "should be included in the labeling." The Third Circuit reasoned that while the FDA received information concerning a new risk of atypical femoral fractures when it issued its May 2009 CRL, the FDA had not yet determined whether a change to the Precautions section was justified. However, after the Task Force report in September 2010, the FDA decided it did have enough information and used its authority to require a label change. The Third Circuit also noted that "[w]hether it seems fair or not, the FDA can take its time, but Merck is responsible 'for the content of its label at all times.'"

Conclusion

More than 10 years have elapsed between the district court's judgment that plaintiffs' failure to warn claims were preempted and the Fosamax II decision. On Nov. 19, 2024, the Third Circuit denied Merck's petition for rehearing and remanded to the district court. How plaintiffs' counsel and defense counsel respond to this decision and whether the Supreme Court decides to intervene for a second time remain to be seen.

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The opinions expressed in this article are those of the authors and not necessarily those of the firm or its clients.