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PREEMPTION

PHARMACEUTICALS

Two recent cases, *Seufert v. Merck* and *Cerveny v. Aventis*, illustrate when federal law preempts state product liability failure to warn claims, attorney Diane E. Lifton and law student Danielle Rosen say. A showing that the FDA reviewed ''the science of the alleged causal association between the drug and the specific risk at issue, post-product use, remains the key to a successful preemption defense,'' the authors say.

Seufert v. Merck and *Cerveny v. Aventis*: The Intersection of Science And Federal Preemption in Pharmaceutical Product Liability Litigation

BY DIANE E. LIFTON AND DANIELLE ROSEN

In *Wyeth v. Levine*, 555 U.S. 555, 571 (2009), the Supreme Court declined to find federal preemption of a state law product liability failure to warn claim in the absence of ''clear evidence'' that the FDA would have rejected the warning sought by the plaintiff. As reiterated by two recent cases, *Seufert v. Merck* and *Cerveny v. Aventis*, the hypothetical question of what the FDA would have done can be answered with evidence that the FDA (1) considered the specific risk plaintiff claims the manufacturer should have warned of in its drug product labeling; (2) examined whether the science establishes the existence of a causal association between the drug and that risk and found it lacking; and (3) continued to approve the product (or related products) without changes to the label with respect to that risk. *Seufert v. Merck Sharpe & Dohme Corp.*, No. 13cv2169, 2016 BL 227777 (S.D. Cal. May 11, 2016), *appeal docketed*, No. 16-55853 (9th Cir. Jun. 15, 2016); *Cerveny v. Aventis, Inc.*, No. 2:14-CV-00545, 2016 BL 80932 (D. Utah Mar. 16, 2016), *appeal docketed*, No. 16-4050 (10th Cir. Apr. 13, 2016).

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As courts now recognize, the clear evidence standard does not require a showing that the drug manufacturer proposed the warning sought by a plaintiff, only to have the FDA reject it.

In *Seufert v. Merck*, plaintiffs claimed that Merck failed to warn that Ongylza and Kombiglyze—both incretin mimetics—increased the risk of pancreatic cancer. Plaintiffs consumed Ongylza and Kombiglyze for treatment of type 2 diabetes and had all developed pancreatic cancer during or soon after their ingestion of the drugs. As in an earlier case involving the same class of drugs, *In re Incretin-Based Therapies Prods. Liab. Litig.*, the factual and regulatory record revealed a number of instances in which the FDA considered the issue of a potential causal connection between the drug and

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the risk of pancreatic cancer and conducted a comprehensive review of the underlying science, without making any changes to the label. First, in 2009, the FDA had considered the risk in connection with adverse event reports it received concerning incretin mimetics, and found any causal link to be indeterminate. The FDA sought no label changes in connection with that review.

Next, in April of 2012, the FDA received a citizen petition for Victoza®, also an incretin mimetic, claiming that the drug posed an increased risk for pancreatic cancer and seeking withdrawal of the FDA's approval. While that citizen petition remained under review, in March of 2013, the FDA issued a drug safety communication notifying the public that it was evaluating unpublished reports from academic researchers regarding incretin mimetics and potential risks of pancreatitis and pancreatic cancer. In June of 2013, however, the FDA participated in a workshop where an FDA supervisory toxicologist stated affirmatively that there was no association between incretin mimetics and pancreatic cancer. In February of 2014, the FDA published an assessment in the New England Journal of Medicine (''NEJM''), providing an ''independent and comprehensive review of pancreatic cancer risk[,]'' which denied any causal association between incretin mimetics and pancreatic cancer. One month later, the FDA formally rejected the 2012 Victoza citizen petition. 2016 BL 227777, Slip op. at 6.

In September of 2014, the FDA reviewed concerns regarding Saxenda®, another incretin mimetic, and the risk of pancreatic cancer. In its briefing, the FDA cited its February 27, 2014 NEJM publication and stated that the connection between incretin mimetics and pancreatic cancer was inconclusive. After September of 2014, the FDA approved other incretin-based therapies without any reference to pancreatic cancer in their labels.

The court called the above set of facts ''unprecedented,'' and granted defendants' motion for summary judgment, concluding that federal law preempted plaintiffs' state law failure to warn claim based on the absence of a warning regarding pancreatic cancer in the labeling for Ongykza and Kombiglyze. 2016 BL 227777, Slip op. at 11. The *Seufert* court found that the FDA's ''repeated review of pancreatic safety, coupled with its consistent conclusion that product labeling adequately reflected the state of scientific data,'' demonstrated that if Merck had requested a warning regarding pancreatic cancer on Ongykza and Kombiglyze, the FDA would have rejected it. *Id.* at 14. The court found that ''the most persuasive evidence'' in support of preemption in fact was the FDA's February 27, 2014 NEJM publication because the FDA's independent review was based on a broader data set than would be available to a manufacturer submitting a proposed label change. *Id.* at 10. The court rejected plaintiffs' argument that the FDA's acknowledgement that it had not arrived at a ''final conclusion'' regarding pancreatic cancer risk and incretin mimetics weighed against preemption, stating that while ''[t]he scientific discoveries of tomorrow may redefine our understanding of the safety and efficacy of prescription drugs[,]'' science is always evolving, thus ''arguments challenging the finality of the FDA's conclusions are not persuasive.'' *Id.* at 12.

The *Seufert* court further rejected plaintiffs' argument that the regulatory record could not demonstrate clear evidence of preemption because the FDA did not consider and reject specific warning language when it considered the risk of pancreatic cancer. The court expressly found that Merck did not need to submit a pancreatic cancer labeling change to establish conflict preemption. In so doing, the *Seufert* court found plaintiffs' reliance on *Wyeth v. Levine* and *Gaeta v. Perrigo Pharmaceuticals* inapposite, and recognized that courts should determine whether the FDA had considered the relevant risk, rather than specific warning language. In *Wyeth v. Levine*, the FDA had paid little to no attention to the IV push method of administrating the drug Phenergan, which was the issue in plaintiff's failure to warn claim. *Wyeth*, 555 U.S. at 572. In *Gaeta*, the FDA reviewed general safety of ibuprofen and did not specifically consider the risk of hepatoxicity, the warning for which was what plaintiffs were seeking. *Gaeta v. Perrigo Pharm. Co.*, 630 F.3d 1225, 1236-37 (9th Cir. 2011), *vacated sub nom. L. Perrigo Co. v. Gaeta*, 132 S. Ct. 497 (2011)). Although the courts had not found preemption in either *Wyeth* or *Gaeta*, there was only limited evidence in those cases that the FDA had considered the specific risks raised by plaintiffs. By contrast, in the record before the *Seufert* court, the FDA had indeed considered pancreatic cancer, the same risk plaintiffs claimed defendants failed to include in their product warnings.

The record in *Seufert* was compelling, making clear that preemption can be a defense even in the absence of the manufacturer or any other entity submitting a specific proposed warning to the FDA and the FDA rejecting it. When such a warning is proposed, however, such as through a citizen petition, the FDA's review of the science of the alleged causal association between the drug and the specific risk at issue, post-product use, remains the key to a successful preemption defense.

In *Cerveny v. Aventis*, plaintiffs brought state law claims for strict liability and negligent failure to warn in connection with plaintiff Victoria Cerveny's use of the fertility drug Clomid®, arguing that the Clomid labeling should have included a warning regarding the possibility of birth defects in connection with use of the drug prior to pregnancy. Plaintiff contended that Clomid remained in her body during conception and early development of fetal organs, impairing the biosynthesis of cholesterol, in turn causing her son's birth defects. She alleged that had she known of the risk, she would not have taken the drug. Defendant Aventis moved for summary judgment on federal preemption grounds, arguing that the FDA's denial of a citizen petition seeking essentially the same warning—which came 15 years after plaintiff ingested the drug and was based on a thorough review of the science—constituted clear evidence that the FDA would have rejected such a warning had Aventis presented it back in 1992.

The district court closely evaluated the factual and regulatory record, including the sequence of ingestion, initiation of litigation, and FDA consideration and rejection of the comparable warning. Plaintiff had taken Clomid from September 1992 through October of 1992. In November of the same year, plaintiff discovered she was pregnant, and her son was subsequently born without the first and fifth digits on his left hand, and a congenital dislocation of his left elbow. In 2014, the plaintiff brought suit, arguing that her son's birth defects were the result of Clomid remaining in her body when she became pregnant.

In 2007, fifteen years after the plaintiff had taken the drug, a California personal injury attorney submitted a

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citizen petition to the FDA requesting a warning of a risk of birth defects when Clomid is ingested prior to pregnancy. The petition was supplemented five times with scientific data. In 2009, the FDA denied the petition, and in the same year, petitioner filed for reconsideration. In 2010, the petition for reconsideration was supplemented with more scientific data, but in 2012, the FDA rejected it again. On October 22, 2012, the FDA approved a label for the drug that did not contain a warning suggesting an association between Clomid use prior to pregnancy and birth defects. Rather, the 2012 label included an affirmative statement in the Precautions section that available scientific data did not show any cause and effect relationship between use of the drug prior to pregnancy and any increased risk of birth defects.

On this factual and regulatory record, the court granted the defendant drug company's motion for summary judgment, finding that the FDA's rejection of the citizen petition, which came fifteen years after the plaintiff's injury and had cited the identical studies proffered by the plaintiff in support of her argument, constituted clear evidence that the FDA would have rejected such a warning if the manufacturer had proposed it. Although not sufficient to find preemption standing on its own, the court further found it ''dispositive'' that in addition to rejecting the citizen petition, the FDA ''has consistently approved Clomid labeling that includes affirmative rejections of the [p]laintiffs' theories.'' 2016 BL 80932, Slip op. at 10. The *Cerveny* court used several key preemption cases as ''guideposts'' from which to gauge the evidentiary strength of the citizen petition as clear evidence, noting that the clear evidence rule does not require that the manufacturer itself attempt to apply the warning suggested by the plaintiff. *See, e.g.*, *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1275-77 (W.D. Okla. 2011) (finding that a rejection of a changes being effected submission does not constitute the only way a manufacturer can satisfy Levine's ''clear evidence'' standard).

The *Cerveny* court carefully contrasted the factual record before it with post-*Levine* preemption jurisprudence involving the FDA's rejections of citizen petitions that predated the plaintiff's injury—where courts consistently have held that such rejections do not constitute clear evidence of what the FDA would have done with respect to a plaintiff's proposed warning. In *Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1117 (W.D. Wash. 2014), for example, the court found that the FDA's rejection of three citizen petitions several years prior to plaintiff's ingestion of the drug and suicide, where additional studies had been conducted in the five-year gap between the final rejection and the death — did not constitute clear evidence that the FDA would have rejected plaintiff's proposed warning. Similarly, in *Dorsett v. Andoz*, 699 F. Supp. 2d 1142, 1157 (C.D. Cal. 2010), FDA rejection of citizen petitions from the 1990s did not constitute clear evidence that the FDA would have rejected the same warning in 2004.

The *Cerveny* court also emphasized the importance of a factual record showing that the FDA based its rejection of the citizen petition on its substance—namely a lack of scientific evidence—not merely its form. A rejection based on form will not suffice. For example, in *Hunt v. McNeil Consumer Healthcare*,6 F. Supp. 3d 694, 699-701 (E.D. La. 2014), the court found that the FDA's refusal to grant citizen petitions seeking to add the terms ''Stevens-Johnson Syndrome (SJS)'' and ''Toxic Epidermal Necrolysis (TEN)'' to the warnings did not constitute clear evidence that the FDA would have rejected plaintiff's proposed warning, because the FDA did not specifically reject the substance of the warnings sought by plaintiff. Moreover, new safety information had become available between the date of FDA's rejection of the citizen petition and plaintiff's ingestion of ibuprofen. *Hunt*, 6 F. Supp. 3d at 701; *see also Reckis v. Johnson & Johnson*, 471 Mass. 272, 288-89 (Mass. 2015) (finding FDA's rejection of citizen petition that requested a heightened warning on children's non-prescription Motrin for SJS and TEN as a matter of wording—not for a lack of scientific basis—did not constitute clear evidence that the FDA would have rejected the substance of a heightened warning); *but see In re Fosamax (Alendronate Sodium) Products Liability Litigation*, 951 F. Supp.2d 695 (D.N.J. 2013) (finding that clear evidence existed that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to plaintiff's femur fracture, and that FDA based its rejection of Defendant's proposed label on the absence of supporting data, not on language).

The *Cerveny* court further noted the importance to its preemption analysis of a record of FDA basing its rejection of a citizen petition on the state of the science at some time after the plaintiff's ingestion of the drug, as illustrated in *In re Incretin-Based Therapies Prods. Liab. Litig*. In a similar fact pattern to *Seufert v. Merck*, plaintiffs in that case alleged that defendants failed to warn that four prescription drugs approved in 2005 for the treatment of type 2 diabetes caused or increased the risk of pancreatic cancer. *In re Incretin*, 142 F. Supp. 3d at 1112. Defendants argued they could not reference pancreatic cancer in the label and comply with FDA regulations. As was the case in *Seufert*, the court determined that the FDA independent review, its assessment in the NEJM, its rejection of a citizen petition, and its subsequent approval of other incretin mimetics all constituted clear evidence that the drug manufacturer was federally preempted from including the warning proffered by the plaintiffs. *Id.* at 1121-24. Again, the timing of the FDA's rejection of a causal link after the plaintiff's use of the product, suggesting that FDA would have rejected a warning of the risk earlier when the science was even less developed, was critical. *See also Gentile v. Biogen Idec, Inc.*, 2016 BL 258563 (Mass. Super. July 25, 2016) and *Christison v. Biogen Idec Inc.*, *No. 2:11-CV-01140-DN-DBP* (D. Utah Aug. 5, 2016) (citing *Rheinfrank v. Abbott Labs., Inc.*, 119 F. Supp. 3d 749, 766-67 (S.D. Ohio 2015) (clear evidence standard satisfied where FDA rejection of warning based on review of the science post-ingestion), *reconsideration denied*, 137 F. Supp. 3d 1035 (S.D. Ohio 2015)).

Although *Seufert* and *Cerveny* are currently on appeal to the Ninth Circuit and Tenth Circuit, respectively, both cases suggest that a regulatory record reflecting the FDA's review of the science regarding the risk at issue, without a label change, ultimately can result in a finding that the FDA would have rejected plaintiffs' proposed warning, and, thus, that federal law preempts plaintiffs' state law product liability failure to warn claim. Factors to consider in evaluating the strength of the factual and regulatory record for a federal conflict preemption defense include:

1. FDA Rejection of Same Warning: Whether the FDA rejected a request from any party seeking the same warning plaintiff contends the drug label should have included;

2. FDA Consideration of Same Risk: If the FDA has not considered the precise warning, whether the FDA considered the risk plaintiff claims the manufacturer needs to warn about;

3. FDA Review of Science and Rejection of Causal Link: If the FDA has considered the risk, whether in doing so the FDA independently reviewed the available scientific evidence and rejected the proposed association between the drug and the specific risk;

4. Timing of Rejection Post-Use: Whether the FDA's consideration of the available scientific evidence, and/or the rejection of the proposed association between the drug and a specific risk, took place at some point in time *after* the plaintiff's ingestion of the drug; and

5. Subsequent Approval Without Additional Warning: Whether the FDA subsequently approved labeling for the drug, or the same type of drug, that did not include the proposed warning.

No one can predict with certainty whether a court will find that federal law preempts state law product liability failure to warn claims in a given case. As further illustrated by *Gentile v. Biogen* and *Christison v. Biogen*, courts continue to make clear that a regulatory and factual record of the FDA considering the science and rejecting a causal association between the drug and the risk at issue, conducted after plaintiff's ingestion of the drug, can lead a court to conclude that the answer to the hypothetical *Wyeth v. Levine* question is a ''yes'' — the FDA indeed would have rejected the warning had the manufacturer proposed it.

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