For Generic Drug Manufacturers

Viability of the Federal Preemption Defense Post-*Levine*

By Sharon L. Caffrey, Alan Klein and Paul M. da Costa

The defense is consistent with both federal legislation and regulatory judgment that brand, rather than generic, drug companies should initiate label changes.

The U.S. Supreme Court's recent decision in *Wyeth v. Levine*, No. 06-1249, 555 U.S. __ (Mar. 4, 2009), in affirming a Vermont state court jury verdict against Wyeth, held that the plaintiff's state law-based failure to warn claims were not preempted. This decision was the first time that the Supreme Court addressed whether federal preemption could serve as a complete defense to state law-based claims in pharmaceutical product liability cases. Although the *Levine* opinion is clearly precedential in cases involving brand drug manufacturers, it does not necessarily preclude generic drug manufacturers from asserting a federal preemption defense. This article discusses the viability of an implied preemption defense for generic drug manufacturers following the Supreme Court's rejection of Wyeth's conflict and obstacle preemption arguments in *Levine*.

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Wyeth's Implied Preemption Arguments

Wyeth argued to the U.S. Supreme Court that a plaintiff's state law-based claims should be dismissed because of implied preemption. Specifically, Wyeth asserted that it would have been impossible to comply with labeling requirements as determined by a state court jury and conflicting federal requirements governed by the Food and Drug Administration's (FDA) regulations. Additionally, Wyeth argued that a state trial court's verdict rejecting the adequacy of federally approved drug label warnings obstructed the purposes of Congress.

Wyeth's Conflict and Obstacle Preemption Arguments Rejected

The foundation of the Supreme Court's decision against federal preemption was "two cornerstones" of preemption jurisprudence. First, the majority highlighted that "'the purpose of Congress is the ultimate touchstone in every pre-emption case.'" *Id.* (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). Based upon a review of the legislative history of the federal regulation of pharmaceuticals, the Court concluded that there is not and has never been any Congressional intent to preempt state law in pharmaceutical product liability lit-

igation. In support of its conclusion, the Court noted that despite ample opportunities, Congress has never enacted an express preemption provision in regulating prescription drugs, although it has enacted this type of provision in regulating medical devices. The second "cornerstone" relied upon by the Court was the presumption against preemption in instances in which Congress has legislated in a field traditionally occupied by the states, such as the health and safety of their citizens.

The Court's rejection of Wyeth's contention that state law-based failure to warn claims are federally preempted on the basis of conflict preemption was based upon the FDA's "Changes Being Effected" (CBE) regulation, 21 C.F.R. §314.70(c)(6)(iii). In particular, the majority held that this regulation gave Wyeth the ability to comply with both federal and state law requirements so that Wyeth could have unilaterally strengthened its drug's warnings, subject to subsequent FDA approval. Furthermore, the Court found that using the CBE process would not have been considered a misbranding of Wyeth's drug by the FDA. The Court also noted that the ultimate authority remained with the FDA to reject any labeling changes made by a drug manufacturer under the CBE regulation. Vital to the Court's decision was that it had no evidence in *Levine* that the FDA would have rejected stronger warnings.

Wyeth's obstacle preemption argument was also dismissed by the Court. The majority held that Congress "did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness." *Id.* In rejecting Wyeth's assertion that it would obstruct congressional purposes embodied in the Food, Drug, and Cosmetic Act (FDCA) and the FDA's pharmaceutical regulations if a drug manufacturer had to comply with additional warnings beyond those required by the FDA, the Court emphasized that Congress has not enacted an express preemption provision in regulating prescription drugs. In addition, Wyeth rooted its obstacle preemption argument in part on an FDA policy pronouncement favoring preemption in a 2006 preamble to amended labeling regulations. Although the 2006 preamble supported federal preemption of state law-based failure to warn claims, the majority declined to give the 2006 preamble deference because of the FDA's failure to provide states or interested parties with notice or an opportunity to comment on the preamble.

The Federal Regulatory Scheme for Generic Drugs

In 1984, Congress enacted the Hatch-Waxman Act (Act), 21 U.S.C. 355(j), to allow for the approval of generic drugs without additional clinical trials beyond those performed by the drug's innovator or brand manufacturer. Congress' primary purpose in enacting this legislation was to increase the availability of inexpensive generic drugs. Under the Act, an abbreviated new drug application (ANDA) must establish that the generic drug is identical to the listed drug with respect to (1) route of administration, (2) active ingredients, (3) strength, (4) dosage form, and (5) conditions of use recommended in the labeling. *See* 21 U.S.C. §355(j). Thus, the FDA will only approve an ANDA application if the generic drug is "the same as a listed drug." *See* 21 C.F.R. §314.1.

In accordance with the Act, the FDA also mandates that a generic drug manufacturer submitting an ANDA provide "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug…." 21 U.S.C. 355(j)(2)(A)(v). The FDA's regulations define "same as" to mean "identical." 21 C.F.R. §314.92(a)(1).

There are exceptions to the requirement that ANDA applicants maintain labeling identical to the listed or brand drug's labeling. With the FDA's approval, a generic drug manufacturer may submit an ANDA that does not mirror the label of the listed drug "in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients." *See* 21 C.F.R. §314.93. Exceptions, however, are relatively rare and do not detract from the principal maxim that ANDA applicants must have labeling identical to the listed drugs.

Inapplicability of the CBE Process to Generic Drug Manufacturers

Although the Court in *Levine* concluded that brand drug manufacturers can utilize the CBE process to effectuate labeling changes prior to FDA approval, the CBE regulation does not apply to generic drug manufacturers. Most recently, in August 2008, the FDA published a final rule in the Federal Register entitled "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices," addressing the CBE process and codifying the FDA's position about when a labeling change may be made in advance of FDA review and approval. *See* 73 Fed. Reg. 49603–49609. Publication of the final rule followed notice and a lengthy comment period. During the public comment period, the FDA received approximately 20 comments from various interested parties, including individuals, consumer advocacy groups, pharmaceutical companies, trade associations, law firms, law professors and members of Congress, none of which addressed the applicability of the CBE regulation to generic drug manufacturers.

The final rule codifies the FDA's view that generic drug manufacturers are not permitted to utilize the CBE process to implement a labeling change. *See* 73 Fed. Reg. 2848. Specifically, the FDA stated that the proposed amendment to the CBE regulation only applies to brand drug manufacturers: "CBE changes are not available for generic drugs approved under an abbreviated new drug application under 21 U.S.C. 355(j). To the contrary, a generic drug manufacturer is required to conform to the approved labeling for the listed drug. *See* 21 C.F.R. §314.150(b)(10); *see also* 57 FR 17950, 17953, and 17961." *Id.* at n.1.

Federal and State Court Decisions Vary on Whether Failure to Warn Claims against Generic Drug Manufacturers Are Preempted

Prior to the Supreme Court's decision in *Levine*, several federal and state courts addressed whether generic drug manufacturers could invoke federal preemption as a defense to plaintiffs' state law-based product liability claims. An analysis of these decisions reveals varying interpretations of the CBE regulation.

In *Gaeta v. Perrigo Pharmaceuticals Co.*, 562 F. Supp. 2d 1091 (N.D. Cal., Nov. 9, 2007), the court held that the plaintiffs' claims were preempted by the FDCA insofar as the generic drug manufacturer's ANDA would be jeopardized if additional warnings were required by state law or state

court juries, since the generic drug's labeling would no longer be the "same as" the listed drug's labeling. Similarly, the District Court of Minnesota concluded that the CBE regulation did not permit a generic drug manufacturer to unilaterally change a product label so that it differs from the label for the corresponding brand drug. *Mensing v. Wyeth, Inc.*, 562 F. Supp. 2d 1056 (D. Minn. 2008). Other courts have subscribed to this view. *Masterson v. Apotex Corp.*, 2008 U.S. Dist. LEXIS 60238 (S.D. Fla. Aug. 7, 2008); *Bolin v. SmithKline Beecham*, 2008 U.S. Dist. LEXIS 60241 (S.D. Fla. Aug. 7, 2008); *Valerio v. SmithKline Beecham*, 2008 U.S. Dist. LEXIS 60242 (S.D. Fla. Aug. 7, 2008); *Morris v. Wyeth, Inc.*, 2008 U.S. Dist. LEXIS 87734 (W.D. Ky. Oct. 24, 2008); *Smith v. Wyeth, Inc.*, 2008 U.S. Dist. LEXIS 87684 (W.D. Ky. Oct. 24, 2008) and *Wilson v. Wyeth, Inc.*, 2008 U.S. Dist. LEXIS 87726 (W.D. Ky. Oct. 24, 2008). The trial courts in all of these cases have concluded that a plaintiff's failure to warn claims are preempted by federal law insofar as generic drug manufacturers may not unilaterally strengthen or otherwise modify their drug labels in the absence of FDA approval.

Specifically, the FDA stated that the proposed amendment to the CBE regulation only applies to brand drug manufacturers.

Additional federal and state courts have held the contrary, finding no preemption of claims against generic drug companies. Since the Supreme Court's decision in *Levine*, the Northern District of Illinois refused to grant a generic drug manufacturer's motion to dismiss based on an argument that the FDCA preempted the plaintiff's state law based failure-to-warn claims. The District Court in *Stacel v. Teva Pharmaceuticals, USA et al.*, 2009 WL 703274 (N.D. Ill., Mar. 16, 2009), rejected the generic manufacturer's federal preemption defense as a matter of law. Although Judge Joan B. Gottschall recognized that the Supreme Court's decision in *Levine* was not directly controlling in the context of claims against generic drug manufacturers, she did find that key portions of the majority's analysis were applicable. *Id.* at 4. Specifically, Judge Gottschall held that "[i]f generic manufacturers can utilize the CBE, then the logic of *Levine* is directly applicable." *Id.* at 5. Even though the CBE regulations are located in Subpart B of Part 314, which is generally applicable to innovator, brand name drug applications and not the abbreviated applications filed with the FDA by generics, the court concluded that section 314.97 located within Subpart C requires a generic drug manufacturer submitting an abbreviated application to comply with CBE regulations. *Id.* Furthermore, in refusing to give deference to the FDA's statements in its 2008 proposed rule amending the CBE regulations disclaiming that the regulations were applicable to generics, Judge Gottschall found that the FDA's statements did not contradict Congress' understanding that state law failure to warn actions "lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times." *Id.* at 7. (quoting *Levine*, 555 U.S. at 12.) The court, however, afforded the generic drug defendant another opportunity to assert the preemption defense at a later stage in the case following the completion of discovery. *Id.*

Prior to the *Levine* decision, other courts had also found that generics are not entitled to the protection of the Supremacy Clause barring failure to warn claims. Although *in dicta*, the U.S. Court of Appeals for the Fourth Circuit posited that a generic drug manufacturer may change its product's labeling through the CBE process. *Foster v. American Home Products Corp.*, 29 F.3d 165 (4th Cir. 1994). The Fourth Circuit's decision in *Foster* has served as the basis of other federal and state court decisions against preemption. *See Goldych v. Ely Lily and Co.*, 2006 U.S. Dist. LEXIS 49616 (N.D. NY. Jul. 19, 2006); *Sharp v. Leichus*, 2006 WL 515532 (Fla. Cir. Ct. 2006).

For instance, the presumption against preemption was found to trump preemption by the Southern District of Alabama in *Barnhill v. Teva Pharmaceuticals USA, Inc.*, 2007 U.S. Dist. LEXIS 44718 (S.D. Ala. Apr. 24, 2007). In *Laisure-Radke v. Par Pharmaceutical, Inc.*, 2006 U.S. Dist. LEXIS 57158 (W.D. Wash. Mar. 29, 2006), the court concluded that the FDA requirement that a generic drug manufacturer have labeling that is the "same as" the brand drug did not prevent the generic drug manufacturer from changing its label after its ANDA had been approved. Likewise, in *McKenney v. Purepac Pharmaceutical Co.*, 167 Cal. App. 4th 72 (Cal. App. 2008), the court found no basis in the federal statutory scheme to distinguish between a generic drug and a brand drug manufacturer's ability to strengthen product labeling. *See also Kelly v. Wyeth, Inc.*, 22 Mass. L. Rep. 384 (Mass. Sup. 2007); *Barhoum v. Barr Pharmaceuticals, Inc.*, (N.J. Super., L. Div., Aug. 1, 2008).

Some courts have concluded that generic drug manufacturers may add additional warnings through the CBE process if they have new information about health risks from their drugs. *Kellogg v. Wyeth, Inc.*, 2008 U.S. Dist. LEXIS 104073 (D. Vt. Dec. 17, 2008); *Demahy v. Wyeth, Inc.*, 2008 U.S. Dist. LEXIS 87014 (E.D. La. Oct. 28, 2008); *Swicegood v. Pliva, Inc.*, 543 F. Supp. 2d 1351 (N.D. Ga. 2008).

Preemption as a Defense for Generic Drug Manufacturers Post-*Levine*

Although the Supreme Court rejected Wyeth's implied preemption defense arguments because, in part, the CBE process permitted Wyeth to comply with both federal and state law, the preemption defense may remain a viable option for generic drug manufacturers.

The FDA's most recent statement on this issue unequivocally specifies that generic drug manufacturers cannot use the CBE process to strengthen drug warnings. Current FDA regulations, including 2008 CBE regulatory amendments, require generic drug manufacturers to maintain labeling that is the "same as" the listed drug's labeling. Once a generic drug manufacturer has received marketing approval, it cannot alter a drug's labeling without risking FDA enforcement action and the agency's withdrawal of its ANDA.

Placing the responsibility on the brand manufacturer to initiate label changes is likely attributable to the historically more

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complete record that a brand manufacturer, patent holder and drug innovator have about a product, due to lengthy clinical trials and extensive post-approval marketing activities, compared with the generic manufacturer. The brand manufacturer, with years of clinical trials experience and the receipt and evaluation of adverse event reports, is in a significantly better position than its generic counterparts to appreciate the necessity of strengthening product warnings.

Unlike the "preemption preamble" considered and rejected in *Levine*, the FDA's newest CBE regulations were enacted after notice and an ample comment period. For this reason, one could argue that the factors that precluded the Supreme Court from deferring to the FDA's 2006 regulatory preamble are not applicable to the agency's 2008 CBE regulation amendments. The traditional deference that courts have extended to federal agencies in interpreting and applying their own regulations should apply here, thereby bolstering generic drug manufacturers' preemption claims.

In the absence of evidence that a generic drug manufacturer withheld important safety information from the FDA either before or after ANDA approval, the preemption defense remains a viable option for generic drug manufacturers, and it is consistent with both the purposes of the Hatch-Waxman Act and the FDA's experience-based judgment that brand rather than generic drug companies should initiate label changes.