Legal Backgrounder

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GENERIC DRUGS AND PREEMPTION IN THE WAKE OF *WYETH v. LEVINE*

by

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In *Wyeth v. Levine,* the United Supreme Court held that failure-to-warn claims against brand name drug manufacturers were not automatically preempted by the federal Food, Drug and Cosmetic Act (FDCA) simply by virtue of the fact that the Food and Drug Administration (FDA) had approved the drug's labeling. 129 S. Ct. 1187 (2009). In the past year, several courts have applied *Levine* in the generic drug context coming down on both sides of the issue;[1] the majority have concluded that the federal regulatory regime governing generic pharmaceuticals does not preempt state-law failure-to-warn claims against generic drug manufacturers.[2]

Many commentators have read these decisions broadly and maintain that *Levine* forecloses future preemption arguments by generic manufacturers. They are mistaken. Although *Levine* has made it more difficult for generics to succeed on preemption grounds in certain jurisdictions, these decisions do not make preemption impossible. In this LEGAL BACKGROUNDER, we examine the continuing viability of a preemption defense in pharmaceutical product liability cases alleging the defective labeling of generic drugs in the wake of *Levine.*[3]

The FDCA does not expressly preempt product liability claims against generic drug manufacturers. Instead, courts have found that there is implied preemption: (1) where it is impossible for the manufacturer to comply with both the federal law requiring an FDA-approved label and any state-law claim seeking to require additional warnings; and (2) when state law stands as an obstacle to the accomplishment and execution of the full purposes of Congress.

A proper understanding of the issue requires a brief examination of the regulatory framework governing pharmaceutical products under which preemption decisions are made and a review of the *Levine* decision.

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[1]Since *Levine*, two Circuit Courts have addressed the issue and concluded that there is no preemption in generic drug cases. *DeMahy v. Actevis*, __ F.3d __ (5th Cir. 2010); *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009). The generic manufacturers recently filed a petition for certiorari to the United States Supreme Court in *Pliva, Inc. et al. v. Mensing*, No. 09-993.

[2]Several district courts have considered the issue post-*Levine*. Compare *Bartlett v. Mut. Pharm., Co., Inc.,* 659 F. Supp. 2d 279 (D.N.H. 2009) (finding no preemption of state-law failure-to-warn claims brought against generics); *Stacel v. Teva Pharm.*, 620 F. Supp. 2d 899 (N.D. Ill. 2009) (same); *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009) (same) to *Morris v. Wyeth, Inc.*, 582 F. Supp. 2d 861 (W.D. Ky. 2008), *aff'd* 2009 WL 424590 (W.D. Ky. Feb. 20, 2009), *aff'd* 2009 WL 736200 (W.D. Ky. Mar. 4, 2009) (granting generic manufacturers' motion to dismiss based on federal conflict preemption despite *Levine* because generic drug makers cannot unilaterally heighten label warnings under the Changes Being Effected or CBE procedure); *Wilson v. Pliva, Inc.*, 640 F. Supp. 2d 879 (W.D. Ky. 2009) (same). Appeals involving materially identical preemption claims are now pending in the Sixth Circuit in *Morris v. Wyeth, Inc. et al,* No. 09-5509; *Smith v. Wyeth, Inc. et al,* No. 09-5460; and *Wilson v. Pliva, Inc. et al.*, No. 09-5466; the Fifth Circuit in *Pustejovsky v. Pliva, Inc.,* No. 09-10983, and yet another is pending Ninth Circuit in *Gaeta v. Perrigo Pharms. Co.*, No. 09-15001.

[3]Virtually every court to have considered the issue prior to the Supreme Court's *Levine* decision held because the FDA prohibited generic companies from adding any warning to its generic labeling that differed from the brand-name's labeling, plaintiff's claims created an impermissible conflict with, and posed an obstacle to, congressional objectives applicable to generic drug manufacturers under the FDCA.

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Marketing of Brand-Name and Generic Drugs Is Governed by Detailed Federal Regulations. Under the FDCA, before any new drug can be marketed, drug manufacturers must obtain Food and Drug Administration (FDA) approval. 21 U.S.C. § 355. To obtain approval, the first applicant to market a drug (the pioneer or innovator drug) must submit a New Drug Application (NDA) to the FDA that demonstrates the drug's safety and efficacy for its intended use. 21 U.S.C. § 355(b)(1). The NDA must include "specimens of the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1)(F); *see also* 21 C.F.R. § 314.50(c)(2)(i). The FDA considers evidence submitted by the applicant as well as other relevant scientific information to determine whether the label is accurate, truthful, and adequate. 21 C.F.R. § 201.80(e). Based on the known scientific evidence, appropriate warnings are drafted that identify established risks while avoiding inadequately substantiated risks, the mention of which could improperly deter use of the drug and deprive individuals who could benefit from the drug. *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996). When the FDA approves an NDA for an innovator drug, it also approves the precise final version of drug labeling. 21 C.F.R. §§ 314.50(e)(2)(ii), 314.105(b). After the NDA is approved, any subsequent major change in labeling requires a supplement to an application and approval by the FDA. 21 C.F.R. §§ 314.70(b), (c), 314.71. Brand name manufacturers may make moderate labeling changes, including strengthening of a warning based on newly acquired evidence, *without* prior agency approval through the use of the "changes being effected"(CBE) procedure. 21 C.F.R. § 314.70(c)(6)(iii)(A)-(D).

Once the innovator drug has been approved for sale, a drug manufacturer may seek approval under the FDCA to market a generic form of that drug by submitting an Abbreviated New Drug Application (ANDA). Under this simplified process, the manufacturer is not required to show independent clinical evidence of efficacy or safety. 21 U.S.C. § 355(j). The manufacturer must simply demonstrate that the generic drug generally has the same active ingredients as the innovator drug and is bioequivalent to that drug. 21 U.S.C. § 355(j)(2)(A)(ii), (iv). The applicant must also "show that the labeling proposed for the [generic] drug is the same as the labeling proposed for the [innovator] drug . . . ." 21 U.S.C. § 355(j)(2)(A)(v); *see also* 21 C.F.R. §§ 314.94(a)(8), 314.127(a)(7). As a condition of approval, the FDA requires the generic drug to use labeling that is virtually identical to the approved labeling for the innovator drug. The only labeling changes permitted to be made are changes to reflect a different manufacturer or that the generic drug has "a different active ingredient" or a different "route of administration, dosage form, or strength" from the innovator drug. 21 U.S.C. § 355(j)(2)(A), (j)(2)(C). There is an on-going debate as to whether generic drug manufacturers may unilaterally change labeling language post-approval where there has been no change to the labeling of the listed drug.[4]

The FDCA prohibits the manufacture and distribution of any misbranded drug. 21 U.S.C. § 352(a). A drug is unlawfully misbranded when its labeling is false or misleading in any way, does not provide adequate directions for use or adequate warnings against any use dangerous to health, or when an applicant fails to maintain labeling in compliance with the requirements of the FDCA. 21 U.S.C. § 331(a), (b), and (k); 21 U.S.C. § 352(a), (f) and (j); 21 U.S.C. § 321(p).

Wyeth v. Levine. In *Wyeth v. Levine,* the Supreme Court eliminated the availability of across-the-board, automatic preemption for state-law failure-to-warn claims against brand-name drug manufactures. Douglas G. Smith, *Preemption after Levine*, 70 OHIO STATE L.J. 6 (2010). In that case, Diane Levine was treated with Wyeth's drug Phenergan for nausea following a migraine headache. *Levine*, 129 S. Ct. at 1191. She initially received the medication via intramuscular injection. *Id.* at 1190. After the first injection failed, she received a second injection, which was administered via an "IV-push" method of administration. *Id*. at 1191. Levine's forearm was amputated after she developed gangrene as a result of improper administration of the drug. *Ibid*.

She filed suit in Vermont state court alleging that Wyeth had failed to adequately warn of the hazards associated with IV-push administration of the drug. *Levine*, 129 S. Ct. at 1191. Phenergan's label contained a warning about the hazards of intrarterial injections. But it did not specifically contain a warning or instruction "concerning the preferred use of an intravenous infusion set" versus IV-push for administration of the drug.[5]

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[4]FDA's approval of an ANDA may be withdrawn if FDA finds that the labeling for the generic drug "is no longer consistent with that for the listed drug referred to in the [ANDA]." 21 C.F.R. §314.150(b)(10). *See also* ANDA Regs., 57 Fed. Reg. at 17970 (agreeing with comment that provision should be added to withdraw ANDA where ANDA holder fails to modify label to match changes to listed drug's labeling).

[5]There had been some proposals for revision of the label. *Id.* at 1192. But the issue of IV-push administration came up only intermittently and was not the subject of extensive discussion with the FDA. *Ibid.* In 1981 and again in 1988, Wyeth proposed changing

Wyeth filed an unsuccessful motion for summary judgment arguing that FDA's labeling requirements preempted Levine's claim because it was impossible for the company to comply with any state-law duty to modify the Phenergan label to include stronger warnings about the risks of IV-push administration without violating its labeling duties under the FDCA since the FDA was aware of the risks of the IV-push method of administration and had specifically ordered Wyeth to continue using a label that lacked such warnings. *Levine,* 129 S.Ct. at 1193. The trial court disagreed. *Id.* at 1192. After a five-day trial, a jury awarded Levine $7,400,000. *Id.* at 1204. The Vermont Supreme Court agreed with the trial court that this was not a particularly good case for application of the preemption doctrine because the FDA record did not adequately demonstrate that the agency had thoroughly considered this issue of IV-push administration in approving the wording in the label.

The Supreme Court upheld the Vermont high court's decision, ruling that FDA's drug labeling judgments, and specifically, its approval of the label for Phenergan, did not preempt state-law tort claims alleging inadequate warning. *Id.* at 1204. In holding FDA's approval of Phenergan did not bar Levine's claims, the majority decision noted that Wyeth could have unilaterally strengthened the label's warning without prior agency approval through the use of the CBE procedure. *Id.* at 1196-99. The Court's decision focused on the lack of evidence suggesting that the FDA considered and rejected a stronger warning concerning IV-push administration, leading the majority to reject Wyeth's argument that compliance with both federal and state law was impossible. *Ibid*.

The Court also rejected the contention that the jury's verdict established an obstacle to the purposes and objective of the FDA's federal drug labeling regulation authority.[6] In reaching this conclusion, the majority held (1) there was no evidence of congressional intent to proscribe state-law tort claims, and (2) the Court would not grant deference to the FDA's most recent pronouncements on preemption.

Although the Court rejected Wyeth's preemption arguments, the decision does not eliminate preemption in every product liability case. Instead, the decision leaves the door open to the continued application of the preemption defense in other failure-to-warn cases against brand-name drug makers in certain cases.[7] For example, the Court suggested that failure-to-warn claims will be preempted when the FDA has specifically considered the particular risks at issue and has determined that the product's labeling adequately warns of those risks. Additionally, the decision acknowledges that state-law fraud-on-the-FDA claims remain preempted under *Buckman Co. v. Plaintiffs' Legal Committee.* 531 U.S. 341 (2001).

Post-Levine Cases Rejecting Preemption in the Generic Drug Context. Since *Levine*, a majority of courts have held that the FDCA does not preempt state-law failure-to-warn claims brought against generic drug makers. In *Mensing v. Wyeth*, the U.S. Court of Appeals for the Eighth Circuit ruled that the federal regulatory regime governing generics does not provide for preemption of state-law failure-to-warn claims against generic drug manufacturers. 588 F.3d 603 (8th Cir. 2009). Shortly thereafter, the Fifth Circuit reached the same conclusion in *Demahy v. Actavis, Inc.* In both cases, plaintiffs claimed they developed tardive dyskinesia, an irreversible neurological condition, after long-term use of metoclopramide, a generic version of Wyeth's drug Reglan, to treat acid reflux. Both argued that the generic manufacturers should be held liable because the companies: (1) failed to warn of the serious risks associated with long-term use of the drug; (2) failed to request a labeling change revision with the FDA under the CBE provisions of the FDCA; and (3) failed to report safety information directly to the medical community.

In response, generic drug manufacturers argued plaintiffs' claims were preempted for two reasons. First, it was impossible to add the warnings required by plaintiffs without violating federal law because the FDA prohibits generic companies from unilaterally adding any additional warning to its generic labeling that differs

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the package insert to include warnings relating to IV-push administration of Phenergan. *Ibid.* Revised labeling was not used and the FDA later directed Wyeth to "retain verbiage in [the] current label." *Ibid.*

[6] *Id.* at 1199-1204.

[7] This view finds support in the Court's treatment of the preemption issue in *Colacicco v. Apotex Inc.* In *Colacicco*, the Third Circuit ruled that, where the FDA has specifically rejected the need for an additional warning regarding the risk of suicide in patients taking antidepressants, plaintiff's claims challenging the absence of additional warnings were preempted. 521 F.3d 253 (3d Cir. 2008), *vacated,* __ U.S. __, 129 S. Ct. 1578 (2009). After accepting the case for review, the Supreme Court did not summarily reverse the Third Circuit's decision after *Levine*. Instead, the Court remanded the case back to the Third Circuit "for further consideration" in light of its decision in *Levine.*

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from the brand-name's labeling. Second, plaintiffs' claims created an impermissible conflict with, and posed an obstacle to, congressional objectives applicable to generic drug manufacturers under the FDCA.

The Eighth Circuit disagreed. The court concluded that generic manufacturers failed to show it was impossible to add warnings regarding the risks of developing tardive dyskinesia and comply with federal law because generic manufacturers could have (1) proposed a label change for both brand-name and generic drugs through the prior approval process, or, alternatively, (2) requested that the FDA send out a warning letter to health care professionals. 588 F.3d at 608-610. The Court refused to address whether generic manufacturers could unilaterally change labeling without prior FDA approval through the CBE procedure.[8]

The court also rejected defendants' argument that imposing such a duty on generic manufacturers would stand as an obstacle to the purposes and objective of the FDA's federal drug labeling regulation authority because it would require expensive clinical studies, thwarting the goal of the Hatch-Waxman Amendments to bring low cost generic drugs to market quickly. *Id.* at 1199-1204. In reaching this conclusion, the court reasoned that generic manufacturers were already required by federal law to collect and report adverse drug events. By presenting this information to the FDA, the generic manufacturers could presumably have substantiated a request to change the label without the need to conduct expensive studies.

Like the Eight Circuit, the Fifth Circuit rejected the generic drug manufacturers' preemption argument, albeit for slightly different reasons. In addition to submitting a supplemental application and requesting that the FDA send out warning letters to physicians, the court maintained that generic manufacturers could make unilateral changes through the CBE process. Several district courts have reached similar conclusions.[9]

Post-Levine Cases Supporting Preemption in the Generic Drug Context. Two courts have reached the opposite conclusion. In *Morris v. Wyeth, Inc.*, another Reglan case, the Western District of Kentucky denied plaintiffs' motion for reconsideration in light of *Levine* after concluding for a second time that plaintiffs' state-law failure-to-warn claims against generic drug makers were preempted because they conflicted with the federal regulation of generic drug labeling. 582 F. Supp. 2d 861 (W.D. Ky 2008), *motion for reconsideration denied* 642 F. Supp. 2d 677 (W.D. Ky 2009). In reaching this conclusion, the court rejected *DeMahy* based upon its conclusion that CBE procedures are not available to generic drug makers. 642 F. Supp. 2d at 683-87.

The Northern District of California reached a similar conclusion in *Gaeta v. Perrigo Pharmaceuticals Co.* There the court denied plaintiffs' motion for reconsideration finding that federal law preempted their failure-to-warn claim because generic manufacturers could not comply with heightened state-law warning label requirements without running afoul of FDA regulations requiring generic drug labels to conform to the approved labeling for the listed drug. 2009 WL 4250690 at *1. In reaching this conclusion, the court rejected plaintiffs' argument that *Levine* required a different result. The court explained that the drug at issue in *Levine* was a brand-name drug, not a generic drug. As the FDA and several courts have recognized, generic manufacturers do not have the same duty to add and strengthen warnings as do brand-name manufacturers under the CBE procedure.

Conclusion. There is a rapidly growing split of authority among courts as to whether FDA regulation of generic drug labeling preempts state-law failure-to-warn claims. Until the Supreme Court definitively decides the issue, generic drug manufacturers should anticipate increased product liability litigation and continue to assert the defense. Although *Levine* arguably makes it more difficult to succeed under a preemption defense in future cases, it should not preclude continued application of the doctrine in those cases where the FDA has specifically considered the particular risks at issue and has determined that the product's labeling adequately warns of those risks. Likewise, state-law fraud-on-the-FDA claims against generic drug manufacturers should also remain preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001).

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[8] *Id.* at 608. At least one other court, post *Levine,* has also refused to address whether generic manufacturers can make use of the CBE procedure to unilaterally change labeling. *Weilbrenner, supra,* No. 7:08-CV-23 (M.D.Ga Mar. 10, 2010).

[9] *Bartlett, supra,* 659 F. Supp. 2d at 295-302 (finding generic makers may use CBE procedure to add warnings without prior FDA approval per 21 C.F.R. §314.97); *Stacel, supra*, 620 F. Supp. 2d at 905-06 (same); *Kellogg, supra*, 612 F. Supp. 2d at 441 (same).