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Generic Drug Manufacturers Post-ANDA Approval Duties With Reference To Labeling Changes: Viability of Federal Preemption Defense Post-*Levine*

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The U.S. Supreme Court's decision in *Wyeth v. Levine*, 129 S.Ct. 1187 (2009), found that plaintiffs' state-law based failure-to-warn claims were not preempted in the context of drugs manufactured by innovator manufacturers. The *Levine* decision, however, left unanswered the question of whether its findings are applicable in the context of claims brought against generic drug manufacturers. Accordingly, while the *Levine* decision is precedential in cases involving brand drug manufacturers, it does not necessarily forecast an identical holding when plaintiffs' claims are directed at generic drug manufacturers.

In *Levine*, the court rejected Wyeth's federal preemption defense largely based upon the Food and Drug Administration's (FDA) Changes Being Effected (CBE) regulation, 21 C.F.R. § 314.70(c)(6)(iii). Specifically, the court held that the CBE regulation afforded Wyeth the ability to comply with both federal and state law requirements; and that Wyeth could have unilaterally strengthened its drug's warnings, subject to subsequent FDA approval. That Wyeth had submitted proposed changes that the FDA had not acted upon was of no moment.

Although not considered by the Court in *Levine*, it is undisputed that distinct regulatory schemes exist for generic and innovator 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 the necessity of clinical trials beyond those previously performed by the drug innovator. Pursuant to the Act, an abbreviated new drug application (ANDA) must establish that the generic drug is identical to the reference 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). The FDA approves an ANDA application only if the generic drug is "the same as a listed drug." *See* 21 C.F.R. § 314.1. The FDA has defined "same as" to mean "identical." 21 C.F.R. § 314.92(a)(1). Generic drugs' labeling must also remain the "same as" the innovator drug post-ANDA approval. The FDA has advised that generic drug manufacturers have a responsibility to monitor the brand

drug's labeling and update their own labels accordingly. *Guidance for Industry: Revising ANDA Labeling Following Revision of the RLD Labeling*, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (May 2000).

Generics Manufacturers and the CBE Process

Although the Court in *Levine* concluded that brand drug manufacturers can utilize the CBE process to effectuate labeling changes prior to FDA approval, the *Levine* opinion did not address whether generic drug manufacturers can avail themselves of the CBE process. Generic drug manufacturers, however, are uniquely situated to argue that the CBE regulation does not apply to them. Most recently, in August 2008, the FDA published a final rule entitled "Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices," addressing the CBE process and attempting to codify the FDA's position in regard to when a labeling change may be made in advance of FDA review and approval. 73 Fed. Reg. 49603 (Aug. 22, 2008). The proposed final rule provides explicit support for 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 (January 16, 2008). Particularly, the FDA stated that the proposed amendment to the CBE regulation only applies to brand drug manufacturers insofar as it stated that "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 brand name drug. *See* 21 C.F.R. § 314.150(b)(10); *see also* 57 Fed. Reg. 17950, 17953, and 17961." *Id.* at n. 1. In an amicus brief filed in *Colacicco v. Apotex, Inc.*, No. 05-CV-05500-MMB, 432 F.Supp. 2d 514 (E.D. Pa. 2006), the FDA stated that "there is no statutory or regulatory provision permitting the [generic] manufacturer to make a labeling change to its generic drug without prior FDA approval. To the contrary, a generic manufacturer is required to conform to the approved labeling for the listed drug." Br. of the United States as *Amicus Curiae* at 6, *Colacicco v. Apotex, Inc.*, 432 F.Supp. 2d 514 (E.D. Pa. 2006) (No. 05-CV-05500-MMB) (*Colaccico Amicus* Br.). The proposition that a generic drug manufacturer cannot alter its labeling absent prior FDA approval is also supported in federal statute and regulation. 21 U.S.C. §§ 355(j)(2)(A)-(C); 21 C.F.R. § 314.150(b)(10).

There is further evidence that the CBE process is inapplicable to generic drug manufacturers and that they may not add new warnings to the labeling approved for the innovator drug manufacturer. Specifically, the CBE regulation (21 C.F.R. § 314.70(c)) is contained in Subpart B. As explained by the FDA in its same amicus brief in *Colacicco*, "[a]lthough Subpart C contains a provision requiring applicants to 'comply with the requirements of §

314.70 and 314.71 regarding submission of supplemental applications and other changes to an approved abbreviated application,' 21 C.F.R. § 314.97, that provision does not modify the requirement that the drug label for a generic drug must be the same as the label for the approved innovator drug (with limited exceptions not relevant here." Any ambiguity in the regulatory text has been clarified by the FDA, which explained at the time of promulgation that the regulations do not authorize generic drug manufacturers to add new warnings to the approved labeling for the innovator drug. *See* 57 Fed. Reg. at 17961, 17953, 17955 (Apr. 28, 1992). *Colacicco Amicus* Br., p. 8, n. 4

Post-ANDA Approval Pharmacovigilance and Procedures

Although generic drug manufacturers arguably cannot avail themselves of the CBE regulation, they do, of course, maintain a duty to apprise the FDA of new safety information that could serve as the basis for a labeling change. The *Levine* decision emphasized that all drug manufacturers — not the FDA — bear the primary responsibility to maintain labeling that is consistent with safe and effective use of the drug. Accordingly, generics manufacturers must remain vigilant in their post-ANDA approval pharmacovigilance efforts. In particular, if a generic drug manufacturer believes additional safety information might be warranted in its drug's labeling, the manufacturer should contact the FDA with "adequate supporting information." 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992). The FDA must consider the proposed additional information and make a determination whether the labeling for the generic and the reference listed drug should be revised. *Id.* Generic drug manufacturers also have the same responsibilities as brand drug manufacturers when it comes to post-marketing reporting of adverse drug events and record keeping. 21 C.F.R. § 314.98; *see also* 21 C.F.R. § 314.80. The vast majority of labeling changes, however, are considered "major changes," and the procedure for effectuating a "major change" requires FDA approval prior to modifying the labeling. 21 U.S.C. § 356a(c)(1); 21 C.F.R. § 314.70(b)(2)(v)(A). While a generic manufacturer can propose a label change through the prior approval process, the reality is that it will likely be the brand manufacturer that is in the best position to evaluate the available data to determine if a labeling change is potentially needed. Accordingly, the brand manufacturers will usually initiate the "major change" process, and generic manufacturers will be bound by the FDA's ultimate decision.

In the aftermath of the *Levine* decision, generic drug manufacturers still have two viable paths of seeking dismissal of plaintiffs' claims on federal preemption grounds. As explained above, generic drug manufacturers have unique arguments to combat the Court's finding that the CBE regulation offers the ability to comply with both federal and state-law requirements since it is not clear that generic drug manufacturers can avail themselves of

the CBE process. Second, generic drug manufacturers, like brand drug manufacturers, may still assert federal preemption defense arguments based upon the "absence of clear evidence" standard established in *Levine*. To that end, both generic and brand drug manufacturers can still successfully make federal preemption arguments if they are able to prove through record evidence that the labeling change allegedly required was either outright rejected by the FDA, or the FDA would not have agreed to require the manufacturer to change their labeling to include the plaintiffs' proposed language.

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