

## THE BEGINNING OF THE END OF THE GENERIC PREEMPTION DEFENSE

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State product liability statutes generally permit a plaintiff to file suit against a product manufacturer alleging design, manufacturing, and warnings defects. By the nature of the product, absent a discreet manufacturing issue, a pharmaceutical product liability case is almost always a failure to warn case. Under the Federal Food, Drug and Cosmetic Act (“FDCA”)<sup>1</sup>, no manufacturer may sell a new drug in interstate commerce before obtaining FDA approval, which includes submission and approval of the precise language the manufacturer proposes to use in the drug’s labeling.<sup>2</sup>

### The Near Demise of the Preemption Defense for Innovator Drugs

Last year, in *Wyeth v. Levine*, 555 U.S. \_\_\_, 129 S.Ct. 1187, 173 L.Ed. 2d 51 (2009), the United States Supreme Court significantly decreased the ability of a drug manufacturer to successfully defeat state law failure to warn claims using the implied preemption defense.<sup>3</sup> Before *Levine*, drug manufacturers argued that state law claims alleging that different or additional language should have been used in a drug’s labeling necessarily conflict with the FDA regulatory approval scheme requiring pre-approval of the drug’s labeling language. Drug manufacturers argued that because of this conflict: 1) compliance with both the federal regulations and the state laws was impossible; and 2) state law claims hindered the accomplishment of Congress’s dual objectives for the FDCA of both protecting and promoting the public health by ensuring that safe and effective drugs are made available to the public. Thus, said the manufacturers, state law claims had to yield.

In *Levine*, the Supreme Court disagreed and refused to preempt the plaintiff’s state law tort claim that Phenergan Injection contained inadequate warnings

about the risk of IV push administration of the drug. *Levine*, 129 S.Ct. at 1196-99. First, the Court reasoned that it was not impossible for the defendant to strengthen its warning without FDA approval because the “CBE” or “Changes Being Effected” regulation<sup>4</sup> allowed the defendant to implement a labeling change to add or strengthen a warning before the FDA approved it, and then seek subsequent approval. *Id.* at 1199. Absent clear evidence in the regulatory record that the FDA did or would reject a stronger warning as to the specific risk at issue, the Supreme Court found no merit in Wyeth’s claim of “impossibility.” *Id.* Second, the Court ruled that state law failure to warn claims do not stand as an obstacle to Congress’s objectives for the FDCA in that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness. *Id.* So, the defense is still viable, but likely only in very narrow circumstances.

### The Distinction Between Innovator and Generic Drug Approval

*Levine*, however, involved an innovator drug, not a generic drug. The applicable FDA regulatory schemes for the approval of an innovator, as opposed to generic, drugs are different. The applicant seeking approval of an innovator drug must submit a New Drug Application (“NDA”) that demonstrates, after significant and costly studies and tests, that the drug is safe and effective.<sup>5</sup> Pursuant to the 1984 Hatch-Waxman Amendments,<sup>6</sup> generic drug manufacturers need only submit an Abbreviated New Drug Application (“ANDA”) demonstrating that the generic drug is bioequivalent to a drug that has already been found safe and effective.<sup>7</sup> Thus, approval is easier and more economical for generic drugs, which allows for generic drugs to be

<sup>1</sup> 21 U.S.C. § 301 et seq.

<sup>2</sup> 21 U.S.C. § 355(a); 21 U.S.C. § 355(b)(1)(F); 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. 314.50(e)(2)(ii); 21 C.F.R. § 314.94(a)(8)(ii).

<sup>3</sup> The doctrine of preemption originates from the Supremacy Clause of the United States Constitution, which provides that the “Constitution, and the laws of the United States which shall be made in Pursuance thereof ... shall be the supreme Law of the Land.” U.S. CONST. art. VI, cl. 2. The Supremacy Clause invalidates state laws that “interfere with, or are contrary to, federal law.” *Hillsborough County v. Automated Med. Labs.*, 471 U.S. 707, 712 (1985) (quoting *Gibbons v. Ogden*, 22 U.S. 1 (1824)). Implied conflict preemption, just one of the several existing types of preemption, occurs when “state law is nullified to the extent that it actually conflicts with federal law,” even though Congress has not displaced all state law in that area. *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 261 (3d Cir. 2008) (quoting *Hillsborough*, 471 U.S. at 713); see also *English v. General Elec. Co.*, 496 U.S. 72, 78-79 (1990).

<sup>4</sup> 21 C.F.R. §314.70(c)(6)(iii).

<sup>5</sup> 21 U.S.C. § 355(b)(1)(A).

<sup>6</sup> The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

<sup>7</sup> 21 U.S.C. § 355(j)(2)(A)(iv).

made available to the public cheaper and more quickly. Key to the “generic preemption” defense is the requirement that the generic drug applicant also show, in a side by side comparison format, that the proposed labeling for the generic drug is “the same as” the approved labeling for the innovator drug.<sup>8</sup>

These differences in the regulatory approval schemes give rise to different preemption arguments for generic drug manufacturers than those arguments made by innovator manufacturers, which were rejected by the Supreme Court in *Levine*. In a nutshell, generic drug manufacturers have argued that, per the federal regulations, they cannot change the warning label because the applicable regulations require a generic drug label to be “the same as” the innovator drug label. Thus, to find them liable under state law for not changing the label creates a direct conflict between state law and federal law, and compliance with both is indeed impossible. Further, generic drug manufacturers have argued that requiring them to propose labeling changes would necessitate them having to engage in time consuming, expensive testing of their drugs, which would defeat Congress’s objective of bringing low cost generic drugs to market quickly.

Prior to *Levine*, generic drug manufacturers made these arguments with mixed success among the lower courts, and they continue to do so post-*Levine* in the hopes that the outcome for generic preemption might be different – and better – than the outcome for innovator preemption. But a pair of recent decisions from the federal appellate courts seem to signal a similar beginning to the end of the generic preemption defense.

### The Eighth Circuit Mensing Decision

In November 2009, the Eighth Circuit Court of Appeals became the first federal appellate court to address the generic preemption defense. Relying heavily on the recognition of the *Levine* Court that the content of the label is the responsibility of the manufacturer at all times (both before and after approval), the Court held that the regulatory requirements for changing drug labeling, or at least bringing labeling change issues to the FDA’s attention, apply to generic drug, as well as innovator drug, manufacturers. *Mensing v. Wyeth, Inc., et al.*, 588 F.3d 603 (8th Cir. 2009). In *Mensing*, the plaintiff brought state law failure to warn claims against the manufacturers of both the innovator drug Reglan® and various generic metoclopramide manufacturers. The

District Court for the District of Minnesota dismissed Mensing’s claims against the generic manufacturers and held that requiring generic metoclopramide manufacturers to deviate from the approved language of the Reglan® label created an impermissible conflict with federal law. *Id.* at 604. In this case, the generic manufacturers argued that they were prohibited from implementing a unilateral label change without prior FDA approval through the CBE process. *Id.* at 608. However, the Court declined to rule on this issue.. Instead, the Eighth Circuit reversed and held that the generic manufacturers could have at least proposed a label change for consideration by the FDA through the prior FDA approval process used for most labeling changes. *Id.* The Court emphasized that “[t]he regulatory framework makes clear that a generic manufacturer must take steps to warn its customers when it learns it may be marketing an unsafe drug.” *Id.* at 608-09. The Court held that generic manufactures are not permitted to simply ensure that their labels are identical to the brand name label. *Id.* (holding that “§201.57(e) does not permit generic manufacturers passively to accept the inadequacy of their drug’s label as they market and profit from it.”).

The Court noted that commentary by the FDA published contemporaneously with the Hatch-Waxman Amendments “supports the requirement that at a minimum a generic manufacturer should alert the agency to any new safety hazard associated with its products.” *Id.* at 609. Specifically, the FDA stated: “After approval of an ANDA, if an ANDA holder [a generic manufacturer] believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.” *Id.* (citing 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992) (emphasis supplied)). Additionally, the Court reasoned that 21 C.F.R. § 314.98 requires that generic manufacturers follow the same post marketing record keeping and reporting of adverse drug experiences as the innovator manufacturers presumably with the expectation that generic manufacturers will initiate label changes and not just merely make changes to match those initiated by the innovator manufacturer. *Id.* The Court also pointed out that, in addition to proposing labeling changes, generic manufacturers could suggest that the FDA send out warning letters to health care professionals. *Id.* at 610.

<sup>8</sup> 21 U.S.C. §355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(i) through (iv).

Again taking a cue from the *Levine* decision, the Eighth Circuit noted that uncertainty about the FDA's acceptance or rejection of a proposed labeling change makes preemption, in general, less likely. *Id.* at 610. Accordingly, "[t]o support preemption the generic defendants must show the likelihood of FDA inaction" in order to establish that they cannot fulfill a state law duty to warn and comply with the FDCA. *Id.* at 611. The Court found that no such evidence was offered by the generic manufacturers in the *Mensing* case. *Id.*

The Eighth Circuit also rejected the generic manufacturer's argument that state law failure to warn claims are preempted because they obstruct the goal of the Hatch-Waxman Amendments to bring low cost generic drugs to market quickly. *Id.* at 611-12. The Court held that generic manufacturers need "scientific substantiation" to support a proposed labeling change and noted that this substantiation need not consist of additional, expensive studies. Rather, the Court pointed out, that the substantiation could come in the form of adverse drug experiences, which generic manufacturers are already required, per the regulations, to collect. *Id.*

### The Fifth Circuit *Demahy* Decision

In January 2010, the Fifth Circuit followed the Eighth Circuit in holding that state law failure to warn claims against generic manufacturers are not, per se, preempted by the federal regulatory scheme. *Demahy v. Actavis, Inc.*, 593 F.3d 428 (5<sup>th</sup> Cir. 2010). In this case, Demahy filed suit against Actavis, a manufacturer of a generic form metoclopramide. *Id.* at \*430. The Fifth Circuit affirmed the Louisiana District Court's denial of Actavis' motion to dismiss the state law failure to warn claims under the preemption doctrine.

The Court initially emphasized the presumption against preemption and focused as well on the distinction between what the regulations say about the "sameness" of content of the generic and innovator labeling at approval as opposed to after approval. *Id.* at \*431-435. The Court pointed out that although, per the FDCA, the generic drug's labeling must conform to the innovator's label when the drug is approved, the statutory scheme is silent on the issue of the "sameness" of the labeling after the ANDA is granted. *Id.* at \*436. In looking at the applicable regulations, however, the Court again held that post approval, generic manufacturers – just like innovator manufacturers – are required to ensure that the labeling accurately reflects

evidence of the risks associated with the drug. *Id.* at \*437-438. The Court noted that the regulation authorizing withdrawal of the approval of a generic drug if its labeling is no longer consistent with that of the innovator was not meant to prohibit a generic manufacturer from attempting to strengthen its label, but was instead implemented to give the FDA a weapon to ensure that generic manufacturers change (i.e., update) their labels to mirror changes proposed and made by the innovators. *Id.* at \*438-439.

The Court held that it was not impossible for Actavis to comply with both federal and state law regarding the warnings supplied, saying it is, at best, uncertain whether the CBE regulation available to innovator manufacturers can also be used by generic manufacturers. *Id.* at \*445-446. Furthermore, like the Eighth Circuit, the Fifth Circuit held that Actavis could have used the normal prior FDA approval process to propose a labeling change regarding the warning at issue and/or that Actavis could have, again with prior FDA approval, sent a "Dear Doctor" letter notifying healthcare professionals of the risks at issue. *Id.* The Fifth Circuit similarly also rejected the idea that requiring generic manufacturers to bear liability for inadequacies in the drug labeling obstructs the goals of the FDCA saying that the most important goal of the FDA is to make sure drugs are indeed safe and effective. *Id.* at \*447-449.

### Conclusion

As the *Demahy* Court noted, 7 out of every 10 prescriptions are filled with generic drugs. *Demahy*, 593 F.3d at 432. With generic manufacturers enjoying a large and still increasing market share, the Courts appear unwilling to hold that generic manufacturers can benefit from the research and development efforts by innovator manufacturers, and the warning labels that those efforts produce, but then avoid liability for any inadequacies in those labels. The opposing argument that subjecting generic manufacturers to as much regulatory responsibility/ liability for labeling as innovator manufacturers increases the time and expense of bringing generic drugs to market has, so far, been unpersuasive with the federal appellate courts. While more decisions on this issue are poised to be issued in the coming months, we can expect similar holdings which will continue to signal the demise of the generic preemption defense. ⚖️