

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),¹ no manufacturer may sell a new drug in interstate commerce before obtaining the U.S. Food and Drug Administration's (FDA's) approval of that drug, which includes submission and approval of the precise language that the manufacturer proposes to use in the drug's labeling.²

The Near Demise of the Preemption Defense for Innovator Drugs

Last year, in *Wyeth v. Levine*,³ the U.S. Supreme Court significantly decreased the ability of a drug manufacturer to successfully defeat state law failure to warn claims using the implied preemption defense.⁴ Before *Levine*, drug manufacturers argued that state law claims that different or additional language should have been used in a drug's labeling necessarily conflict with the FDA regulatory approval scheme under which the labeling language was previously approved. Drug manufacturers argued that because of this conflict: (1) compliance with both the federal regulations and the state laws was impossible; and (2) the state law claims were an obstacle to the accomplishment of Congress' 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 plaintiff's state law tort claim that Phenergan Injection contained inadequate warnings about the risk of IV push administration of the drug.⁵ First, the court reasoned that it was not impossible for Wyeth to strengthen its warning without FDA approval because the Changes Being Effected (CBE) regulation⁶ allowed Wyeth to implement a labeling change to add or strengthen a warning before the FDA has approved it, and then seek subsequent approval.⁷ 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."⁸ Second, the court ruled that state law failure to warn claims do not stand as an obstacle to Congress' objectives for the FDCA in that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.⁹ So, the defense is still viable, but likely only in narrow circumstances.



The Distinction Between Innovator and Generic Drug Approval

However, *Levine* involved an innovator drug, not a generic drug. The regulatory schemes that are applicable for the approval of innovator differ from those for the generic drugs. The applicant seeking approval of an innovator drug must submit a New Drug Application (NDA) that demonstrates, after significant, costly studies and tests, that the drug is safe and effective.¹⁰ Pursuant to the 1984 Hatch-Waxman Amendments,¹¹ 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.¹² Thus, approval is easier and more economical, and generic drugs can be made available to the public cheaper and more quickly. Key to the "generic preemption" defense is the requirement that the generic drug applicant must 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.¹³

These differences in the regulatory approval schemes give rise to different generic preemption arguments than those arguments made by innovator manufacturers and rejected by the Supreme Court in *Levine*. In a nutshell, generic 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 manufacturers have argued that requiring them to propose labeling changes would necessitate them having to engage in time-consuming, expensive testing of their drugs, and would thus defeat Congress' objective of bringing low-cost generic drugs to market quickly.

Prior to *Levine*, generic manufacturers had been making these arguments with mixed success among the lower courts, and they continued to do so after *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 seems to signal a similar beginning to the end of the generic preemption defense.

The Eighth Circuit *Mensing* Decision

In November 2009, the Eighth Circuit became the first federal appellate court to address the generic preemption defense. Relying heavily on the *Levine* decision's recognition of the central premise 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 changes issues to the FDA's attention, apply to manufacturers of generic drugs as well as innovator drugs.¹⁴ *Mensing* brought state law failure to warn claims against the manufacturers of both the innovator drug Reglan® and various generic metoclopramide manufacturers. The U.S. District Court for the District of Minnesota dismissed *Mensing's* claims against the generic manufacturers, holding that requiring generic metoclopramide manufacturers to deviate from the approved language of the Reglan® label created an impermissible conflict with federal law.¹⁵

The generic manufacturers argued that they were prohibited from implementing a unilateral label change without prior FDA approval through the CBE process.¹⁶ The court declined to decide whether generic manufacturers could unilaterally enhance a label warning through the CBE procedure. The Eighth Circuit nonetheless reversed, holding that the generic defendants could have at least proposed a label change for consideration by the FDA through the prior FDA approval process used for most labeling changes.¹⁷ 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.”¹⁸ The court held that generic manufacturers are not

permitted to simply ensure that their labels are identical to the brand name label.¹⁹

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.”²⁰ Specifically, the FDA stated that, “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.”²¹ 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 name-brand manufacturers presumably with the expectation that generic manufacturers will initiate label changes and not merely make changes to match those initiated by the name-brand manufacturer.²² The court also pointed out that in addition to proposing labeling changes, generic manufacturers could suggest that the FDA send out warning letters to healthcare professionals.²³

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.²⁴ 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.²⁵ The court found that no such evidence was offered by the generic defendants.²⁶

The Eighth Circuit also rejected the generic defendants' 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.²⁷ 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 that generic manufacturers are already required to collect, per the regulations.²⁸

The Fifth Circuit *Demahy* Decision

In January 2010, the Fifth Circuit followed the Eighth Circuit in holding that failure to warn claims against a generic manufacturer



are not, per se, preempted by the federal regulatory scheme governing generic pharmaceuticals.²⁹ Demahy sued Actavis, a manufacturer of a generic form metoclopramide.³⁰ The Fifth Circuit affirmed the U.S. District Court for the Eastern District of Louisiana's denial of Actavis' motion to dismiss the state law failure to warn claims as preempted.

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.³¹ The court pointed out that although per the FDCA the generic drug's labeling must conform to the innovator's label at the time that the drug is being approved, the statutory scheme is silent on the issue of the "sameness" of the labeling after the ANDA is granted.³² In looking at the applicable regulations, however, the court 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.³³ 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.³⁴

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.³⁵ 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.³⁶ 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.³⁷

Conclusion

As the *Demahy* court noted, seven out of every ten prescriptions filled these days is filled with a generic drug.³⁸ With generic manufacturers enjoying a large and still increasing market share, the courts appear unwilling to hold that a generic manufacturer can benefit from the research and development efforts of the innovator drug and the warning label that those efforts produce, but then avoid liability for any inadequacies in that label. 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 does not appear to be carrying the day with the federal appellate courts. More decisions on this issue are poised to be issued in the coming months. Expect similar holdings, which will continue to signal the demise of the generic preemption defense.

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1 21 U.S.C. § 301 *et seq.*

2 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).

3 129 S.Ct. 1187 (2009).

4 The doctrine of preemption originates from the Supremacy Clause of the U.S. 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 several types of preemption that exist, arises 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).

5 *Levine*, 129 S.Ct. at 1196-99.

6 21 C.F.R. § 314.70(c)(6)(iii).

7 *Id.* at 1199.

8 *Id.*

9 *Id.*

10 21 U.S.C. § 355(b)(1)(A).

11 The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

12 21 U.S.C. § 355(j)(2)(A)(iv).

13 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(i) through (iv).

14 *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009).

15 *Id.* at 604.

16 *Id.* at 608.

17 *Id.*

18 *Id.* at 608-09.

19 *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.").

20 *Id.* at 609.

21 *Id.* (citing 57 Fed. Reg. 17950, 17961 cmt. 40 (Apr. 28, 1992) (emphasis supplied)).

22 *Id.*

23 *Id.* at 610.

24 *Id.* at 610.

25 *Id.* at 611.

26 *Id.*

27 *Id.* at 611-12.

28 *Id.*

29 *Demahy v. Actavis, Inc.*, No. 08-31204, 2010 WL 46513 (5th Cir. Jan. 8, 2010).

30 *Id.* at *1.

31 *Id.* at *2.

32 *Id.* at *4.

33 *Id.* at *5.

34 *Id.* at *6.

35 *Id.* at *7.

36 *Id.* at *10-11.

37 *Id.* at *14-15.

38 *Id.* at *2.

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