Adverse Reaction Without a Remedy

By Steven F. Casey and David A. Lester

Most consumers decide whether to buy a brand-name or generic drug based on one of two considerations–price or myths regarding quality. Few, if any, give thought as to whether their choice will affect their ability to pursue a claim against the manufacturer in the event they suffer an adverse reaction to the drug. However, after recent decisions by the United States Supreme Court, consumers who purchase generic drugs may have no avenue to pursue claims against generic drug manufacturers for failing to warn about potential adverse effects of drugs. To comprehend how a consumer could possibly suffer an adverse drug reaction and be left without a legal remedy, it is helpful to review a bit of the history of drug regulations in the United States.

History

The Food, Drugs, and Cosmetics Act ("FDCA") can trace its roots back to the Pure Foods and Drugs Act of 1906.[1] From 1906 to 1962, drugs were reviewed and approved only for safety.[2] During this time, a generic version of a brand name drug could be approved based upon the submission of a "paper" new drug application, which contained published scientific and medical literature demonstrating that the drug was safe.[3] The FDCA was amended in 1962 to require drug companies to show that their drugs were effective through clinical trials.[4] The amended FDCA contained no provision by which companies could gain approval of a generic version of a brand-name drug in an abbreviated process.[5] The generic drug companies were hesitant to invest the time and expense required for clinical trials and, as a result, by 1984, there were 150 drugs whose patents had expired but for which there was no generic drug equivalent.[6] In fact, only 35 percent of the top-selling drugs with expired patents had generic equivalents.[7]

By the early 1980s, as the availability of generic drugs declined, the average price for prescription drugs increased.[8] The Food and Drug Administration ("FDA") began considering the possibility of implementing new regulations that would allow abbreviated new drug applications for generic drugs.[9] Instead, Congress intervened and passed the Drug Price Competition and Patent Term Restoration Act of 1984, better known as the Hatch-Waxman amendments to the FDCA.[10] The amendments sought to balance two competing objectives:

- Encourage competition from generic drugs and

- Continue to provide incentives for brand-name drug companies to develop new drugs.[11]

The Hatch-Waxman amendments preserved the incentive for brand-name companies to invest in research to develop new drugs by increasing the patent exclusivity period for new drugs.[12] The amendments also allowed brand-name drug companies to obtain patent extensions for a period of time equal to the time the drug spent in clinical trials, so that the brand-name drug company could reap the financial benefits from its new drug for the entire patent term.[13]

The amendments streamlined the process for approving generic drugs by requiring only that manufacturers demonstrate bioequivalence to an already-approved drug through the submission of an abbreviated new drug application.[14] Bioequivalence means that the active ingredient in the generic drug is absorbed at the same rate and to the same extent as the active ingredient in the brand-name drug.[15] The tests required to prove bioequivalence are much less costly than those required to prove safety and efficacy.[16] The amendments also require that generic drug companies label their drugs with the same label that is approved for their brand-name equivalent.[17] The amendments further allowed generic drug companies to submit abbreviated drug applications before the expiration of the brand-name drug's patent.[18] This change alone shortened the average time between the expiration of a brand-name drug's patent and the entry of generic versions into the market from three years to three months.[19]

There is no doubt that the Hatch-Waxman amendments achieved the goal of increasing competition from generic drug manufacturers. In 1983, generic drugs accounted for 13 percent of the prescription drug market.[20] In 2010, generic drugs accounted for 78 percent of all drugs sold in the United States.[21] Today, on average, more than 80 percent of a brand's prescription volume is replaced by generics within six months of patent expiration[22]

Pharmaceutical Litigation After Hatch-Waxman

As long as there have been prescription drugs on the market, there have been patients who suffered adverse reactions from taking those drugs. Accordingly, litigation has been a part of the pharmaceutical industry for as long as it has been around. Some adverse reactions are foreseeable and drug companies warn of those potential reactions in their labels and warnings. Sometimes, there are reactions that were not discovered in clinical trials. Over the years, plaintiffs have asserted claims against pharmaceutical companies based upon countless theories of liability, but most claims have included some variation of a common law failure to warn claim.

Both brand name and generic pharmaceutical companies have also experimented with many theories in defending against failure to warn claims. For most of the past generation, the "learned intermediary doctrine" was an industry favorite.[23] Under the learned intermediary doctrine, a pharmaceutical company cannot be held liable for a patient's adverse reaction to its drug if the patient's physician was aware that the possibility of such a reaction existed.[24] In other words, the doctrine shifts liability from the pharmaceutical company who had no interaction with the patient to the physician, who knew the patient's medical history, physical condition and other medications the plaintiff was taking.[25] Today, some variation of the learned intermediary doctrine has been adopted by 48 states.[26]

In the past few years, however, new theories of defense have arisen in the pharmaceutical industry that led to landmark decisions from the Supreme Court of the United States. Brand-name drug companies began arguing that plaintiffs could not maintain failure to warn claims against them because it was the FDA, not the drug companies, who had the ultimate say as to what is, and what is not, contained in drug labels and warnings. Generic drug companies argued that plaintiffs could not maintain failure to warn claims against them for two reasons: first, because the Hatch-Waxman amendments require them to use the same labels and warnings on their drugs as are used on the brand-name equivalent; and, second, because neither the FDCA nor FDA regulations provide a mechanism by which the generic manufacturers could amend the labels or warnings. The Supreme Court addressed the brand-name drug companies' labeling defense in *Wyeth v. Levine*[27] and the generic drug companies' labeling defense in *PLIVA, Inc. v. Mensing*.[28]

Wyeth v. Levine

In April 2000, Diane Levine, a professional musician in Vermont, suffered a severe migraine headache and associated nausea.[29] She went to a local clinic, where she was treated with intramuscular injections of Demerol, for the headache, and Phenergan, for the nausea.[30] The injections did not relieve Levine's headache and she returned to the clinic, where she was again treated with Demerol and Phenergan, this time through an intravenous push injection.[31]

Wyeth produces Phenergan.[32] At the time Levine was treated, the drug's labeling identifies intramuscular injection as the preferred method of administration.[33] The package insert warned in at least four places that adverse reactions, including gangrene, can result from exposure of Phenergan to arterial blood.[34] In fact, the FDA had reviewed Wyeth's labeling for Phenergan three years before Levine's treatment and, during that review, ordered Wyeth to maintain its gangrene warning.[35]

As you could probably guess, the healthcare provider who had given Levine the injection of Phenergan inadvertently injected it into her artery rather than her vein.[36] Levine developed gangrene in her arm, which she ultimately had to have amputated. Levine sued the clinic and healthcare providers for malpractice and settled those claims for $700,000.[37] She then sued Wyeth in Vermont state court, asserting that Wyeth had inadequately warned of the dangers of injecting Phenergan into an artery.[38]

Wyeth's expert testified that Wyeth should have contraindicated intravenous injection of Phenergan on the drug's labeling even though the FDA never required such a contraindication.[39] Wyeth moved for summary judgment, arguing that the plaintiff's state law failure-to-warn claims were preempted by federal law.[40] Wyeth explained that the FDA dictated the warnings that were included in the Phenergan labeling and argued that state law could not require Wyeth to provide different warnings.[41] The trial court rejected Wyeth's argument and a jury awarded Levine a verdict for $7,400,000.[42]

Wyeth appealed the verdict to the Vermont Supreme Court.[43] Wyeth reiterated its argument that it could not comply

with its federal duty to distribute Phenergan only under the precise labeling approved by the FDA and its Vermont common law duty to give different warnings.[44] The Vermont Supreme Court was unpersuaded and affirmed the jury verdict.[45]

Wyeth petitioned the Supreme Court of the United States for a writ of certiorari.[46] The Supreme Court issued its opinion in March 2010, rejecting Wyeth's preemption argument in a six-to-three decision.[47] The Court explained that the FDA's "changes being effected" ("CBE") regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon the filing of a supplemental application with the FDA and it need not wait for FDA approval.[48] The Court went on to explain that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market."[49]

After the Supreme Court's decision in *Wyeth v. Levine*, most legal scholars concluded that the preemption argument was dead in the pharmaceutical failure to warn context. Needless to say, very few people foresaw the Court's decision in *Mensing*.

PLIVA, Inc. v. Mensing

A year after its decision in *Wyeth v. Levine*, the Supreme Court addressed the generic drug manufacturer's preemption argument in *PLIVA, Inc. v. Mensing*.[50] The plaintiff in *Mensing* was prescribed metoclopramide, the generic form of the brand-name drug Reglan.[51] At the time the plaintiff was initially prescribed metoclopramide, the warning label stated that "tardive dyskinesia . . . may develop in patients treated with metoclopramide," and the drug's package insert added that "[t]herapy for longer than 12 weeks has not been evaluated and cannot be recommended."[52] In 2004, the warning label was changed to read "[t]herapy should not exceed 12 weeks in duration."[53] The label was once again strengthened in 2009 when the FDA ordered a black-box warning stating that "[t]reatment with metoclopramide can cause tardive dyskinesia, a serious movement disorder that is often irreversible. . . . Treatment with metoclopramide for longer than 12 weeks should be avoided in all but rare cases."[54] After taking the drug as prescribed for several years, the plaintiff developed tardive dyskinesia[55] and filed suit against the generic manufacturers and the manufacturers of the brand-name equivalents, alleging that the manufacturers failed to warn of the effects of long-term use of metoclopramide.[56]

The generic and brand-name manufacturers moved to dismiss the plaintiff's claims, arguing that federal statutes and FDA regulations preempted the plaintiff's state law claims.[57] The generic companies argued that they were required to label the metcolopramide they produce with the same warnings that are required for Reglan, the brand-name form of the

drug.[58] The brand-name companies argued that they owed no duty to warn consumers of the risks associated with taking the generic forms of their drugs.[59] The district court agreed and dismissed the case.[60] On appeal, the Eighth Circuit affirmed the district court's dismissal of the brand-name manufacturers, but reversed the dismissal of the generic manufacturers.[61] The Eighth Circuit found that the FDA regulations provided mechanisms by which the generic manufacturers could propose changes for their labels.[62] The generic manufacturers appealed the Eight Circuit's ruling.[63]

On appeal, the Supreme Court noted that a conflict between state and federal law exists, making it impossible for a private party to comply with both state and federal law requirements.[64] In such situations, state law must give way.[65] The Supreme Court found that a conflict exists between state law failure-to-warn claims asserted in the *Mensing* case and the Hatch-Waxman amendments to the FDCA.[66] Specifically, the Court found that, under the Hatch-Waxman amendments, a generic manufacturer seeking approval to produce a generic form of a brand-name drug must show that the drug it wishes to produce is equivalent to an already-produced brand-name drug and that the safety and efficacy labeling it proposes is the same as that already approved for the brand-name drug.[67] Therefore, the Court reasoned, the generic drug manufacturers could not comply with the Hatch-Waxman amendments and provide the strengthened warnings that the plaintiffs contended were required, because the generic manufacturers had no ability to change their labels.[68]

In reaching this decision, the Court specifically rejected the Eighth Circuit's reasoning that the generic manufacturers could have satisfied the state law warning requirements by proposing label changes to the FDA.[69] The Court explained that state law demanded a safer label, not communication between the manufacturer and the FDA.[70] Therefore, even if the generic manufacturers had proposed label changes to the FDA, they could not have compelled the FDA to approve such changes.[71] In such a circumstance, if the generic manufacturers' suggested label changes had not been approved, the generic manufacturers would still be in violation of state law.[72]

The Supreme Court further noted that if the plaintiff had taken Reglan rather than metoclopramide, her claims would not have been preempted. The Court acknowledged that, from the plaintiff's perspective, the finding of preemption in this case but not in *Wyeth v. Levine* makes little sense.[73] The Court noted, however, that Congress enacted meaningfully different statutory schemes to govern generic manufacturers than it did to govern brand-name manufacturers.[74] The Court concluded that those different statutes and regulations lead to different preemption results and noted that Congress and the FDA have the authority to change the law and regulations if they so desire.[75] Until Congress or the FDA adopts such changes, plaintiffs will not be able to maintain state law failure to warn claims against the manufacturers of generic drugs.[76]

Failure-to-Warn Claims After *Wyeth* and *Mensing*

After the *Wyeth* and *Mensing* decisions, it would be easy to conclude that consumers who suffer adverse reactions from taking a generic drug are left without a legal remedy to compensate them for their injury. That could be true, but plaintiffs have pursued an alternate theory of liability which would compel a different result.

This alternate theory was first advanced in *Conte v. Wyeth, Inc.*, a 2008 California case.[77] In that case, the plaintiff developed tardive dyskinesia after taking metoclopramide for almost four years.[78] He sued Wyeth, the manufacturer of Reglan–the brand name version of metoclopramide–and three manufacturers of generic metoclopramide, alleging that the defendants should have known of a widespread tendency among physicians to mistakenly prescribe metoclopramide for periods longer than that called for in the labeling because the label allegedly understated the risks of extended treatment with metoclopramide[79] It was undisputed that the plaintiff only ingested generic metoclopramide, not Reglan.[80] His claims against Wyeth were premised on misrepresentation in Wyeth's labeling of Reglan and in a monograph on Reglan it provided for the *Physician's Desk Reference*.[81] The trial court entered summary judgment in favor of the defendants and the plaintiff appealed.[82]

On appeal, the California Court of Appeals held that it is very likely that a doctor would rely on Wyeth's Reglan product information when prescribing generic metoclopramide.[83] Based on this logic, the California Court of Appeals reversed the trial court's entry of summary judgment and held that a brand-name manufacturer could be held liable for its failure to warn consumers of generic drugs of the adverse reactions they could suffer from ingesting a generic version of the brand-name manufacturer's drug.[84]

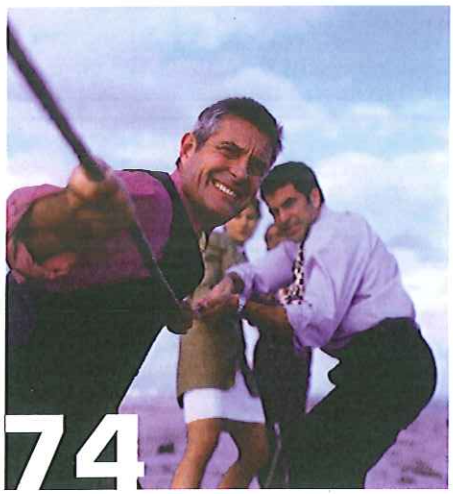
While this may seem to be an incredible result, remember that the FDA regulations impose a duty on the brand-name manufacturer to provide an adequate label and to ensure that its warnings remain adequate as long as the drug is on the market. Generic manufacturers, on the other hand, must label their drugs with the exact language found on the brand-name drug's label. Even so, a number of courts have rejected the reasoning of *Conte*.[85] The Alabama Supreme Court has yet to weigh in on the *Conte* theory of liability, though the question is currently before it in question certified by the United States District Court for the Middle District of Alabama, in *Wyeth, Inc. v. Danny Weeks*.[86]

Conclusion

At this point, it is difficult to predict how liability for adverse reactions to generic drugs will be apportioned. It seems unlikely that Congress and the Courts will allow generic manufacturers to remain immune from suit in failure to warn claims forever. The FDA or Congress may impose a duty on generic manufacturers to seek changes for their labels when they become aware of adverse events that are not discussed in their warnings. In any event, this area of the law has witnessed extraordinary changes in the past few years and there is no indication that the evolution is close to an end. | AL

Endnotes

1. Food and Drug Administration, History, *http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm* (October 30, 2011).
2. Mossinghoff, Gerald J., "Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process," *Food and Drug Law Journal* (1999): 187.
3. *Id.*
4. *Id.*
5. *Id.*
6. *Id.*
7. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," *http://www.cbo.gov/doc.cfm?index=655&type=0* (July 1998).
8. Mossinghoff, Gerald J., "Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process," *Food and Drug Law Journal* (1999): 187.
9. *Id.*
10. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," *http://www.cbo.gov/doc.cfm?index=655&type=0* (July 1998).
11. *Id.*
12. *Id.*
13. *Id.*
14. *Id.*
15. *Id.*
16. *Id.*
17. *Id.*
18. *Id.*
19. *Id.*
20. *Id.*
21. IMS Institute for Healthcare Informatics, "U.S. Spending on Medicines Grew 2.3 Percent in 2010, to $307.4 Billion," *http://www.imshealth.com/portal/site/ims/menuitem.d248e29c86589c9c30e81c033208c22a/?vgnextoid=1648679328d6f210VgnVCM100000ed152ca2RCRD&vgnextchannel=4eb65890d33ee210VgnVCM10000071812ca2RCRD&vgnextfmt=default* (Apr. 19, 2011).
22. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," *http://www.cbo.gov/doc.cfm?index=655&type=0* (July 1998).
23. *In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 806 (E.D. Tex. 2002).
24. *Id.*
25. *Id.*
26. *Id.*
27. *Wyeth v. Levine*, 555 U.S. 555, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (2009).
28. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 180 L. Ed. 2d 580 (2011).
29. *Wyeth v. Levine*, 555 U.S. 555, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (2009).
30. *Id.*
31. *Id.*
32. *Id.*
33. *Id.*
34. *Id.*
35. *Id.*
36. *Id.*
37. *Id.*
38. *Id.*
39. *Id.*
40. *Id.*
41. *Id.*
42. *Id.*
43. *Id.*
44. *Id.*
45. *Id.*
46. *Id.*
47. *Id.*
48. *Id.*
49. *Id.*
50. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 180 L. Ed. 2d 580 (2011).
51. *Id.*
52. *Id.*
53. *Id.*
54. *Id.*
55. *Id.*
56. *Id.*
57. *Id.*
58. *Id.*
59. *Id.*
60. *Id.*
61. *Id.*
62. *Id.*
63. *Id.*
64. *Id.*
65. *Id.*
66. *Id.*
67. *Id.*
68. *Id.*
69. *Id.*
70. *Id.*
71. *Id.*
72. *Id.*
73. *Id.*
74. *Id.*
75. *Id.*
76. *Id.*
77. *Conte v. Wyeth, Inc.*, 168 Cal. App. 4th 89 (Cal. App. 2008).
78. *Id.*
79. *Id.*
80. *Id.*
81. *Id.*
82. *Id.*
83. *Id.*
84. *Id.*
85. *See, e.g., Mosley v. Wyeth, Inc.*, 719 F. Supp. 2d 1340 (S.D. Ala. 2010).
86. *Wyeth, Inc. v. Danny Weeks*, Alabama Supreme Court, Case Number 1101397.



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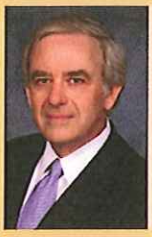

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