Pharmacovigilance in a post-Wyeth v. Levine world
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Background
On March 4, 2009, the U.S. Supreme Court decided Wyeth v. Levine and found that approval of a drug label by the Food and Drug Administration (FDA) does not give rise to-the defense of federal preemption to shield the brand drug manufacturer from failure-to-warn claims. A year later, written opinions from courts throughout the country demonstrate the impact of the Wyeth v. Levine decision in lawsuits against brand and generic drug manufacturers on the issue of preemption. To put it simply, in the aftermath of Wyeth v. Levine, the possibility of the defense of federal preemption is no longer available to brand manufacturers, and it is evident that most courts are extending the holding of Wyeth v. Levine to foreclose preemption to generic drug manufacturers.

The expanding law also makes it clear that Wyeth v. Levine has impacted pharmacovigilance, the science and activities related to the detection, assessment, understanding and prevention of adverse effects or other drug-related problems.

Overview
This article will review Wyeth and some of the significant court decisions to examine how Wyeth has impacted and will likely continue to impact brand and generic drug manufacturers. Finally, we will conclude by briefly touching on:

- Wyeth’s impact on the development of warnings and labels
- Trends in product liability litigation related to pharmacovigilance
- The relationship between pharmacovigilance and product liability litigation
- Risk management recommendations
- The need for “transparency” throughout a company’s operations

I. What is preemption and why has it been in the news?

A. What is preemption and how is the affirmative defense applied?

The preemption doctrine comes from the Supremacy Clause of the U.S. Constitution, which provides that the “Constitution and the laws of the United States shall be the supreme law of the land … anything in the constitutions or laws of any State to the contrary notwithstanding.” This means that any federal law or a regulation of a federal agency may supersede state law in three ways. Express preemption arises when a federal statute or regulation specifically provides that the federal enactment supersedes or preempts state law. Implied field preemption arises in instances where the state law occupies a field that is reserved for federal regulation. Implied field preemption arises where the scheme of the federal law or regulation is so pervasive that it is reasonable to infer that Congress left no room for the states to supplement the federal law. Implied conflict preemption arises when state law actually conflicts with federal law and it is impossible for a private party to comply with both state and federal requirements, or when the state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.

B. Why has preemption been in the news?

Wyeth and other manufacturers battled state court lawsuits for years, arguing preemption should be afforded to the brand manufacturer of prescription drugs. In February 2008, the Supreme Court issued its decision in Reigel v. Medtronic, finding Congress had expressly preempted state tort law claims against medical device manufacturers whose devices are approved
under the more rigorous statutory scheme of 21 U.S.C. § 360k(a). Following the Reigel decision, many of us on the defense side were hopeful preemption would be extended to brand prescription drug manufacturers for failure-to-warn claims in the pending case of Wyeth v. Levine, based on the argument that the FDA had approved Wyeth’s labeling. However, on March 4, 2009, the Supreme Court decision in Wyeth v. Levine made it clear that the defense of federal preemption is not available to brand drug manufacturers.

II. What was the Supreme Court’s reasoning in Wyeth v. Levine?

A review of the legal precedent and recent cases, including Wyeth v. Levine, is instructive as to how the Supreme Court came to its conclusion that a brand prescription drug manufacturer cannot avail itself of the preemption defense. In order to determine if preemption applies, the courts must make a determination about whether Congress intended to occupy the field.

A. History of federal regulation

Congress enacted the first significant public health law in 1906. (Federal Food and Drugs Act, ch. 3915, 34 Stat. 768.) The act prohibited the manufacture or interstate shipment of adulterated or misbranded drugs and supplemented protections for consumers that were already regulated by state regulation and state common law liability. In the 1930s Congress enacted the Federal Food, Drug, and Cosmetic Act (FDCA) (ch.675, 52 Stat. 1040, as amended, 21 U.S.C. § 301 et seq.) out of increased concern about unsafe drugs and fraudulent marketing. The act provided for premarket approval of new drugs and required every manufacturer of a new drug to submit a new drug application (NDA), inclusive of reports about investigations and specimens of proposed labeling to the FDA for review. The act also prohibited a manufacturer from distributing the new drug until the FDA approved the new drug application. The FDA could also reject an application if it determined the drug unsafe for use as labeled, although if the agency failed to act, the application became effective 60 days after the filing. FDCA, §505(c), 52 Stat. 1052.

In Wyeth, the Supreme Court explained that while Congress enlarged the FDA’s powers to “protect the public health” and “assure the safety, effectiveness, and reliability of drugs,” it also took care to preserve state law. In fact, the 1962 amendments added a saving clause specifying that a provision of state law would only be invalidated upon a “direct and positive conflict” with the FDCA. Significantly, suits under state common law have continued to be filed unabated despite FDA regulation. Even more significant, when Congress enacted an express preemption provision for medical devices in 1976 (§521, 90 Stat. 574; codified at 21 U.S.C. §360k (a)), it declined to enact such a provision for prescription drugs.

In 1984, Congress created a mechanism enabling generic drug manufacturers to obtain approval through an abbreviated new drug application (ANDA) process. Under the provisions of the Drug Price Competition and Patent Restoration Act of 1984, PL 98-417, more commonly known as the “Hatch-Waxman Act,” a generic manufacturer is not required to prove that its product is safe and effective, only that the product is “bioequivalent” to the brand name, or “listed,” product. Generally speaking, a drug is considered “bioequivalent” if the rate and extent of absorption of the generic product is not significantly different from that of the brand product. 21 U.S.C. § 355 (j)(8)(B). The conditions of use and warning for the generic versions of the product must be identical to those for the brand-name product. 21 U.S.C. § 355 (j)(2)(A).

Prior to Wyeth v. Levine, generic drug manufacturers vehemently argued the ANDA requirement that the labeling of the generic drug be identical to the brand label created grounds for preemption, because the generic drug manufacturer could not comply with federal law requiring generic labeling to be identical to the brand labeling and also be subjected to state law
claims that its labeling was inadequate. Post *Wyeth v. Levine*, the majority of decisions around the country hold that drug manufacturers, including generic manufacturers, are responsible for crafting an adequate label and ensuring that their warnings remain adequate as long as the drug is on the market. This responsibility is directly tied to the drug manufacturer’s obligations related to pharmacovigilance.

In 2007, Congress amended the FDCA again (121 Stat. 823) and for the first time granted the FDA statutory authority to require a manufacturer to change its drug label based on safety information that becomes available after a drug’s initial approval. (§ 901(a)) A manufacturer is required to revise labeling to include additional warning information as soon as there is reasonable evidence of an association of a serious hazard. (21 C.F.R. § 201.80(e)) The Supreme Court in *Wyeth* noted that the amendment did not contain a provision that required the FDA to preapprove all changes to drug labels, but instead adopted a rule of construction to make it clear that manufacturers remain responsible for updating their labels. (121 Stat. 925-926.) The manufacturer may change a product’s labeling after providing the FDA with notice of the change, and the manufacturer can then effect the labeling change prior to actual FDA approval under the provisions of 21 C.F.R. §314.70(c), which is referred to as the “change being effected” (CBE) provision. The CBE may be utilized only 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. 21 C.F.R. §§ 314.70(c)(6)(iii), (C).

### B. *Wyeth v. Levine*, 129 S.Ct. 1187 (March 4, 2009)

In *Wyeth v. Levine*, the plaintiff received an intravenous injection of Phenergan, which is a brand drug manufactured by Wyeth. However, the drug entered Levine’s artery and she developed gangrene, resulting in the amputation of a forearm. She sued in Vermont state court, alleging Wyeth had failed to provide an adequate warning about the significant risks associated with administering Phenergan by intravenous injection. The Vermont jury found Levine’s injury would not have occurred if Phenergan’s label had an adequate warning and awarded in favor of the plaintiff. The trial court refused to overturn the jury’s verdict, denying Wyeth’s argument that the plaintiff’s failure-to-warn claims were preempted by federal law because the labeling had been approved by the federal FDA.

In the U.S. Supreme Court, Wyeth argued that the state law claims were preempted because it was impossible for Wyeth to comply with both the state law duties underlying those claims and its federal labeling duties. The preemption argument was rejected. The Supreme Court noted that, although a manufacturer generally may change a drug label only after the FDA approves a supplemental application, the agency’s “changes being effected” (CBE), regulation permits certain preapproval labeling changes that add or strengthen a warning to improve drug safety. Pursuant to the CBE regulation, Wyeth could have unilaterally added a stronger warning about intravenous administration and there was no evidence that the FDA would have rejected such a labeling change.

Importantly, the Supreme Court noted that Wyeth’s cramped reading of the CBE regulation and its broad assertion that unilaterally changing the Phenergan label would have violated federal law governing unauthorized distribution and misbranding of drugs were based on the fundamental misunderstanding that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. It is a central premise of the FDCA and the FDA’s regulations that the manufacturer bears responsibility for the content of its label at all times.

### III. Evolving case law in the aftermath of *Wyeth v. Levine*

#### A. Brand prescription drug manufacturers owe no duty to plaintiffs consuming generic products (majority of state jurisdictions)


In *Moretti v. Wyeth*, the plaintiff was diagnosed with a neurological disorder called tardive dyskinesia after she consumed generic metoclopramide. She sued Wyeth, the brand manufacturer of Reglan (metoclopramide), alleging fraud and
misrepresentation. The Nevada court granted Wyeth’s motion for summary judgment and held that a brand manufacturer has no duty to warn about the risks associated with their competitors’ generic drugs.


In *Morris v. Wyeth, Inc., et al.*, the Louisiana court held that the brand prescription drug manufacturer may not be held liable under the law of Louisiana for the warning provided by a generic manufacturer.

**Schrock v. Wyeth et al., 601 F. Supp. 2d 1262, 1267 (W.D. Okla. 2009)**

In *Schrock v. Wyeth et al.*, the plaintiff sued the brand manufacturer, Wyeth, as well as generic manufacturers for failure to warn after she developed tardive dyskinesia following her consumption of generic metoclopramide. In granting Wyeth’s motion for summary judgment, the court noted that twenty-four courts in fourteen different states have rejected the assertion that a brand prescription drug manufacturer has a duty to warn about a product it did not manufacture.

**B. No preemption afforded to generic drug manufacturers, and generic drug manufacturers have a duty to warn**

**Schrock v. Wyeth et al., 601 F. Supp. 2d 1262 (W.D. Okla. 2009)**

In *Schrock v. Wyeth et al.*, the plaintiff sued the brand manufacturer, Wyeth, as well as generic manufacturers for failure to warn after she developed tardive dyskinesia following her consumption of generic metoclopramide. The court cited *Wyeth v. Levine* in denying the generic drug manufacturers’ motion to dismiss based on federal preemption, e.g., that it could not comply with state laws and comply with federal law requiring its labeling to be the same as the brand drug labeling.

**Stacel v. Teva Pharmaceuticals, 620 F. Supp.2nd 899 (N.D. IL 2009)**

In *Stacel v. Teva Pharmaceuticals*, the plaintiff sued the generic manufacturer, claiming her drug-induced lupus was caused by minocycline. She claimed negligent failure to warn, fraud and misrepresentation. Teva moved to dismiss based on preemption under the FDCA (ANDA), arguing its labeling must be the same as the label of the brand prescription drug manufacturer and that CBE “change being effected” provisions of 21 C.F.R. § 314.70 do not apply to manufacturers of generic drugs. The court disagreed and denied Teva’s request for preemption and the motion to dismiss, finding key parts of the Supreme Court’s decision in *Wyeth v. Levine* applicable to generic manufacturers. Citing to *Wyeth v. Levine*, the Stacel court noted:

First, the [Supreme] Court noted that when Congress amended the FDCA in 1982 to expand the FDA’s powers to protect the public health and to assure the safety, effectiveness, and reliability of drugs, Congress expressly found that state-law claims should not be preempted except for incidents of ‘direct and positive conflict’ with the FDCA. Subsequent amendments continued to affirm this position. ‘[T]hrough many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulations that the manufacturer bears responsibility for the content of its label at all times.’ Manufacturers are ‘charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.’ [21 C.F.R. § 201.80(e) requires manufacturers to revise labels to include additional warning information ‘as soon as there is reasonable evidence of an association of a serious hazard with a drug.] Although the FDA could subsequently reject the amended label, the [Supreme] Court was unpersuaded by the argument that manufacturers ran the risk of being accused of having ‘misbranded’ their products by utilizing the CBE process. … The [Supreme] Court also observed that the manufacturer’s argument would leave injured parties with no remedy, for injured parties have no cause of action under the FDCA. Although Congress has the authority to eliminate certain remedies if it chooses to do so, the [Supreme] Court assumed Congress ‘determined that widely available state rights of action
provide appropriate relief for injured consumers.’ Congress was aware of state tort remedies and chose not to foreclose them.

Demahy v. Actavis, Inc., 593 F.3d 428 (5th Cir. 2010)

In Demahy v. Actavis, Inc., the plaintiff developed tardive dyskinesia after consuming a generic form of Reglan, metoclopramide, manufactured by Actavis. She sued Actavis for failure-to-warn. The issue on appeal was whether the federal regulatory regime governing pharmaceuticals preempts state law failure to warn claims against generic drug manufacturers. Like Teva in the Stacel case, Actavis argued preemption should apply because ANDA provisions required its labeling be the same as the brand drug manufacturer’s. The plaintiff argued that she did not allege that Actavis was liable under state law for failure to adequately warn at the time the FDA approved the ANDA. Rather, the plaintiff sought to hold Actavis liable for failing to take steps to change the label after the ANDA approval in order to provide adequate warning once additional risks emerged and, while Congress clearly intended the generic drug labeling to be identical to the brand drug’s when seeking ANDA approval, the statutory scheme “is silent as to the manufacturer’s obligations after ANDA is granted.” Hence, the plaintiff argued Actavis could have complied with FDA regulations and state law by using the “changes being effected” federal regulatory scheme [21 C.F.R. § 314.70 (c) (6)(iii)(A)], “prior [FDA] approval process” [21 C.F.R. § 314.70 (b)(2)(v)(A), or by directly warning doctors through a “Dear Doctor” letter [21 C.F.R. § 314.70 (b) (2); 21 C.F.R. §§ 202.1; 44 Fed.Reg. 37434, 37447 (June 26, 1979); 21 U.S.C. § 355-1(i)(2)].

In Demahy, the appellate court affirmed the trial court’s ruling that the plaintiff’s claims were not preempted and noted:

> Of the three avenues for complying with both state and federal law that Demahy identifies – the CBE process, the prior approval process, and letters sent directly to healthcare providers – each shares the same fundamental attributes: the manufacturer bears primary responsibility for maintaining its label consistent with safe and effective use of its product; when reports indicate that a label requires revision, the manufacturer must alert the FDA and provide supporting scientific data; and the FDA then makes the decision whether such a labeling change is supported by science. Even though with the CBE process, the decision is made after the label has been changed, the key feature remains: the FDA is still the final arbiter of labeling changes, while the manufacturer retains primary responsibility for the content of its label. The federal interest is in maintaining safe and effective labeling that is consistent across name brand and generic bioequivalent versions of the same drug. Who prompts the FDA to consider necessary changes to that shared label is immaterial.”

Other cases where preemption has been denied to generic drug manufacturers:


Cases where preemption has been applied:


IV. Pharmacovigilance has arrived

In *Forst v. SmithKline Beecham Corp.*, Gary and Bonita Forst sued GlaxoSmithKline (GSK), the brand manufacturer of Paxil CR, alleging negligence, *negligent pharmacovigilance* and strict liability for failure to warn related to the adequacy of its warnings, after Gary attempted suicide two weeks after he began using the drug. The plaintiffs asserted the labeling did not have any specific warnings regarding an increased risk of suicidality caused by Paxil itself.

GSK filed a motion for summary judgment, arguing it owed no duty to warn about possible adverse effects, as no causal link had been established between Paxil and increased suicidality in patients over age 24. GSK’s motion was denied in its entirety after the plaintiffs submitted evidence that Dr. Russell Katz of the FDA stated that Paxil’s clinical trial data showed “causality,” and the plaintiffs pointed to GSK’s own 2006 analysis of its previous clinical trial data that demonstrated a patient on Paxil was six times more likely to attempt suicide as one on a placebo. The court opined that GSK was not insulated from the plaintiffs’ failure-to-warn claims because the FDA did not require enhanced warnings.

In response to GSK’s assertion that its product carried FDA-approved labeling and additional warnings would have violated federal law, the court specified that drug manufacturers have an affirmative duty to add new warnings to drug labels as soon as there is reasonable evidence of an association of a serious hazard with the drug and that a causal relationship need not have been proved. 21 C.F.R. § 201.80. Thus GSK had a duty to update its labeling to warn against the enhanced risk.

V.  Trends in product liability litigation related to pharmacovigilance

A.  What is pharmacovigilance?

Pharmacovigilance relates to collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients about adverse effects of medications, with a view toward identifying new information about hazards associated with medicines and preventing harm to patients.

Pharmacovigilance is concerned with instances of adverse drug reaction (ADR). An ADR is officially described as: “A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.”

B.  What is the relationship between pharmacovigilance and product liability litigation?

In product liability litigation, plaintiff attorneys continue to ask the following questions: “What did the company know?” “When did the company know?” “How long did it take for the company to take remedial action?” Why do they ask these questions? Simple, they are looking for any delay to take action. Delayed action is the recipe for big plaintiff verdicts. *Wyeth v. Levine* and its progeny make it clear that brand and generic drug companies bear primary responsibility for drug labeling at all times, and that there is a mechanism in place to provide notice to the FDA and initiate labeling changes prior to obtaining FDA approval. In the world of litigation, according to the developing case law, there are fewer and fewer valid excuses for failing to act, and a company must be able to document its actions.

In the world of eDiscovery, the documentation of pharmacovigilance is becoming very expensive. Prescription drug companies are required to exercise pharmacovigilance from the inception throughout the life of the drug. If documentation does not exist, plaintiff attorneys will argue the drug company failed to take adequate steps to monitor safety and to provide sufficient warnings. If sued, a drug company should expect that plaintiff attorneys will seek documentation about operating procedures related to receipt of information about adverse events, and adverse event investigation, reporting and analysis, as well as follow up action.

The case of *Forst v. GlaxoSmithKline* is a good example. In that case, the plaintiff actually sued for negligent pharmacovigilance in addition to inadequate warnings. The plaintiff attempted suicide on March 17, 2004, as a result of taking Paxil, an antidepressant that made him even more depressed. The plaintiff sought and obtained discovery about similar adverse events as far back as 1989. The plaintiff was able to defeat GSK’s motion for summary judgment by, among other things, demonstrating that GSK’s own 2006 analysis of its previous clinical trial data demonstrated a patient on Paxil was six times as...
likely to attempt suicide as one on a placebo. This type of evidence is powerful if submitted to a jury by a plaintiff seeking compensatory and punitive damages.

VI. Risk management recommendations

We should expect to see more lawsuits alleging negligent pharmacovigilance. In order to successfully defend such claims, pharmaceutical companies will need to make sure that routine pharmacovigilance activities include:

A. Adverse reaction/event collection and single case processing
   - Maintenance of validated database for centralized collection, permanent retention and retrieval of post-marketing spontaneous reports
   - Real time medical review of all post-marketing adverse reaction reports
   - Follow-up of appropriate cases
   - Preparation and electronic submission of case reports to regulatory authorities

B. Post-marketing signal detection
   - Periodic review of line listings for suspected adverse reactions
   - Signal detection methodology appropriate to the drug and number of cases
   - Surveillance of post-marketing risks based on assessment and evaluation of collected adverse reaction data
   - Routine review of the worldwide scientific literature based on safety literature searches performed on a weekly basis

C. Aggregate reports
   - Preparation of reports for health authorities, including Periodic Safety Update Reports and equivalent safety summaries
   - Ad hoc safety reports or interim reports on specific topics as requested by the FDA, and other regulatory authorities or as dictated by signal detection activities

D. Continuous oversight of safety
   - Continuous monitoring and management of the safety profile and benefit risk balance of marketed products
   - Activities as a result of pharmacovigilance issues including labeling updates, assessment of need for risk minimization measures and communication with the FDA and other regulatory authorities as appropriate

VII. The need for “transparency” throughout a company’s operations

A manufacturer should understand that, once a matter gets into a litigation arena, the rules for discovery are broad and courts are liberal in allowing plaintiffs access to information. There is no hiding the ball. A manufacturer can demonstrate transparency in its operations by developing and encouraging a culture of candor, a culture where there are no secrets. There needs to be an understanding that there is no containment of truth and that all actions and directives need to be a demonstration of the philosophy of candor. In other words, there should be open documentation of all activities related to the compliance with regulatory obligations. At trial, a manufacturer must be able to demonstrate its willingness to share information and the actual sharing of information to stakeholders (the FDA, doctors, medical community) in a timely fashion.

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