ADVISEN Productivity & Insight for Insurance Professionals

LEXINGTON INSURANCE
CHARTIS

Preemption and REMS: Evolving Risk Landscape for Generic Drug Manufacturers

Executive Summary

The U.S. Supreme Court's 2009 decision in *Wyeth v. Levine* has thrust a spotlight on the preemption doctrine in the pharmaceutical sector. Dubbed as "the blockbuster business case of the century,"[1] the Supreme Court ruled against the drug maker Wyeth, holding that pharmaceutical companies can be held liable for harm from medicines that carry warnings approved by U.S. Food and Drug Administration (FDA). The ruling is seen as a major defeat that could have long-lasting repercussions on the application of the preemption defense in product liability claims asserted against drug manufacturers. Amid uncertainties with respect to whether preemption will effectively shield drug manufacturers from liability, drug manufacturers are also facing stiffer regulatory hurdles and costs stemming from increased federal management initiatives such as Risk Evaluation and Mitigation Strategies (REMS). Implementation of effective risk management practices and procedures are key strategies for minimizing liability.

Understanding the Preemption Doctrine

When drafting the United States Constitution, the framers saw the need for a strong federal government in certain domains. As a result, the U.S. legal structure is composed of two parallel levels – the federal level and the state level.

The preemption doctrine is rooted in the Supremacy Clause found in Article VI, paragraph two of the Constitution, which states 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 where federal laws exist, similar laws of the fifty states must conform or risk being preempted. Congressional intent is the touchstone of analysis when courts consider preemption.

Although the distinction between federal and state authority was intended to be clearly delineated, and despite the fact that the two levels have separate judicial systems, overlaps and conflicts sometimes occur. When this happens, generally federal law displaces, or preempts, state law regardless of whether the conflicting laws come from courts, legislatures or administrative agencies.

Three types of preemption are recognized by the courts. The first type is express exemption, which applies when a federal statute explicitly states that it preempts state law. The second is implied preemption, which arises when the structure and purpose of federal law shows the intent of Congress to preempt state law. The third type is conflict preemption, which occurs when a conflict exists between federal and state law.

Congress has preempted state regulation in a number of industries including financial, automotive, air transportation, employment, rail freight service, and telecommunication. In certain industries such as the pharmaceutical sector, federal regulations are particularly specific, especially in the labeling of drugs. The pharmaceutical industry has long considered FDA standards as the final word.

[1] "Justices Weigh Effect of FDA Approval of Drug Labels on Suits in State Courts," *The New York Times*, November 3, 2008.

Preemption in the Pharmaceutical Industry

Federal law requires drug manufacturers to obtain approval for their products from the FDA prior to marketing. As a regulatory agency, the FDA is tasked with ensuring that drugs reaching consumers are safe and effective. Before a new drug is introduced into the market, it undergoes a lengthy and stringent evaluation process. FDA requirements for branded and generic drugs are distinct.

For pharmaceutical companies seeking to introduce new or branded drugs, the filing of a New Drug Application (NDA) is required. In the NDA, the applicant must include a comprehensive and complete report of research, clinical trials, and investigations conducted to prove that the drug is safe and effective. Another requirement is the submission of a proposed drug label. While the FDA sets forth requirements about the form and subject matter of the label, drug manufacturers propose the content of drug labels based on clinical information. Several edits and revisions between the FDA and the drug company may occur before the final language of a drug label is approved.

Generic drugs are subject to separate statutory requirements. Rather than an NDA, manufacturers of generic drugs are required to submit an Abbreviated New Drug Application (ANDA). This type of application has less demanding requirements in response to Congress' recognition that generic drugs should not go through as costly and time-consuming a process as has already occurred for their name-brand equivalents. For ANDA, manufacturers of generic drugs are required to establish bioequivalence between the generic and branded drug identified in the ANDA. The FDA defines bioequivalence as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." The generic drug manufacturer also is required to duplicate the branded drug's label in order for an ANDA to be approved.

Post-NDA or ANDA approval, the labeling requirements for branded and generic drugs are also different. Branded drug manufacturers are required to revise or modify a label "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a casual association with a drug...." This is known as the Changes Being Effected (CBE) regulation, under which manufacturers of branded drugs may revise or modify drug labels to strengthen a contraindication or warning without obtaining prior approval from the FDA for the content of the revised or modified drug label. The FDA has ultimate authority to approve or reject these labeling changes, so drug makers often consult with the FDA before making changes, and is meant for emergency situations.

Generic drug manufacturers, however, do not have the same autonomy. They are not permitted to unilaterally revise or modify their drug labels without prior FDA approval. Oftentimes, generic drug manufacturers do not have all the information on adverse effects needed to suggest changes, as most of the customer usage data is held by the branded drug makers in the earlier drug-lifecycle years.

Following an NDA or an ANDA approval, the FDA reserves the right to recall a drug's approval for a number of reasons, including deficient labeling and imminent hazard to public health.

For years, drug companies considered federal regulations through the FDA as the ultimate rule, paying little attention to state regulations. Drug companies, in fact, considered federal preemption as an absolute defense in pharmaceutical litigation. This picture was significantly altered by the landmark decision in *Wyeth v. Levine*. "For failure-to-warn cases," explains James Clair, associate at law firm Bivona & Cohen, P.C., "the federal preemption defense is definitely at risk, and perhaps will cease to be available."

Changing the Course for Federal Preemption

Wyeth v. Levine took center stage when the Supreme Court ruled against Wyeth, holding that pharmaceutical companies can be held liable for harm from medicines that carry warnings approved by the FDA. By a 6-to-3 vote, the Supreme Court ruled that the FDA's labeling approval does not preempt state law and shield companies from damages in liability claims. The case was dubbed as "the blockbuster business case of the century" by *The New York Times*.[2] Pharmaceutical industry observers saw the ruling as a major defeat for the pharmaceutical industry with respect to the application of the preemption doctrine as an insurmountable defense against product liability claims brought under state law.

Wyeth v. Levine considered whether federal laws preempted a state common-law damage suit for injuries caused by a prescription drug. Specifically, the Supreme Court was asked to decide "whether the prescription drug labeling judgments imposed on manufacturers by the [FDA]…preempt state-law product liability claims."

Facts of the Case

In the spring of 2000, Vermont-based musician Diana Levine suffered a particularly bad episode of migraine-related nausea. She visited the Northeast Washington County Community Health, Inc. where she was injected with Phenergan, an anti-nausea drug manufactured by Wyeth. She received two injections. The first was administered by intramuscular injection. After the injection, Levine's nausea continued, and she received a second dose by a method known as "IV push," which was a direct intravenous injection into her arm.

During the second injection, Phenergan was inadvertently injected directly into an artery. As a result, Levine suffered severe tissue deterioration and gangrene in her arm. After several weeks, her hand and forearm were amputated, leaving Levine unable to continue her work as a musician.

Levine sued for negligence and failure-to-warn, alleging that Wyeth's inadequate warning of the known dangers of direct intravenous injection of Phenergan caused her injuries. The pharmaceutical giant argued that the claims were preempted by the Federal Food, Drug and Cosmetic Act (FDCA), since Phenergan's label was approved by the FDA and changing it to conform to state law would have violated superseding federal labeling regulations.

In 2005, the trial court jury found in favor of Levine on both claims and awarded her $2.4 million in economic damages and $5 million in noneconomic damages. The case was taken to the Vermont State Supreme Court, which upheld the trial court's ruling in a 4-1 decision.

The U.S. Supreme Court granted certiorari in 2008 on the issue of conflict preemption. In its ruling, the Court found that while federal law requires that every prescription drug label be approved by FDA, the CBE regulation permits certain preapproval changes to strengthen a drug's warning. Without clear evidence that the FDA would not have approved the specific label change at issue, the Court ruled that it was not impossible for Wyeth to comply with both the federal and state requirements.

In March 2009, the Court issued its 6-3 opinion in favor of Levine. In conclusion, the Court said that when the risk of gangrene from IV-push administration of Phenergan became apparent, Wyeth had a state-law duty to provide a warning that adequately described the risk, and the CBE regulation permitted Wyeth to unilaterally provide such warning. Therefore, Wyeth could comply with both state and federal law. Moreover, the Court underscored that "the manufacturer bears responsibility for the content of its label at all times."

[2] Ibid.

Significance of the Case

Wyeth v. Levine's significance lies in the fact that it presented an answer to the question of whether a drug manufacturer who has complied with the FDA's drug labeling requirements can still be liable under a product liability claim based on state common-law principles on the ground that its drug label was inadequate. The Supreme Court's decision in this case was closely watched by many because it provided an opportunity for the Court to clarify the federal preemption doctrine.

The Aftermath

Many saw the decision in *Wyeth v. Levine* as a closing of the door on preemption. Observers say that the decision will effectively limit the ability of drug manufacturers to use preemption as a defense in failure-to-warn pharmaceutical product liability claims. Moreover, it increased name-brand manufacturers' litigation exposure and raised concerns for generic manufacturers.

Immediately after the decision was rendered, district courts that had previously granted temporary stays pending the outcome of *Levine* took up the issue and ruled against preemption. A few days after handing down the decision on *Levine*, the Supreme Court granted certiorari in *Pennsylvania Employee Benefit Trust Fund v. Zeneca Inc. and Colacicco v Apotex Inc*. – two cases which specifically upheld the preemption defense. The Court remanded both cases to the Third Circuit for further consideration in light of the *Levine* decision.

Federal courts subsequently denied federal preemption to the following cases, principally based on *Wyeth v. Levine*: *Dobbs v. Wyeth Pharmaceuticals, Miller v. Smithkline Beecham Corp., Mason v. Smithkline Corp., Demahy v. Actavis, Mensing v. Wyeth, In re Prempro Products*, and *In Re Pharmaceutical Industry Average Wholesale Price Litigation*.

With these recent developments, drug companies can expect defense costs, and possibly damages, to go up in failure-to-warn cases since they now have to make drug warnings compliant across fifty states.

Impact on Generic Drug Manufacturers

In *Mensing v. Wyeth*, the Eighth Circuit Court of Appeals reversed a district court's pre-*Levine* finding of preemption based upon the Supreme Court's decision in *Levine*. The Court found that although FDA regulations prohibit generic applicants from unilaterally making label changes, the generic drug maker involved in this case "could have at least proposed a label change that the FDA could receive and impose uniformly." This means that generic drug manufacturers must comply with state labeling regulations, as well as the FDA's CBE process. In this case, the Court determined that federal law does not preempt failure-to-warn claims against generic manufacturers; and that name-brand manufacturers cannot be held liable for allegedly inadequate warnings on a generic drug label, where the plaintiff never used the brand name product. The decision is significant because it represents the first federal appellate court to apply the rationale of *Wyeth v. Levine* to generic drug manufacturers.

In another case, *Demahy v. Actavis*, the Fifth Circuit Court of Appeals ruled that while the statutes require generic drug manufacturers to use the name-brand drug's label initially, as in the *Mensing v. Wyeth* case, the generic drug manufacturer could have proposed a label change to the FDA. The generic drug maker, according to the Court, could have also suggested to the FDA a "Dear Doctor" letter, which are letters warning healthcare professionals about possible adverse effects associated with use of a drug, also requiring FDA approval because such letters fit the FDA's broad definition of labeling. It was decided in this case that while Congress intended generic drug makers to have the same label as branded drugs when applying for the ANDA, the law "is silent as to the manufacturer's obligations after the ANDA is granted." These two cases are indicative of a trend toward increased liability for generic drug

manufacturers, as it was ruled that preemption does not apply to them because federal law does not prevent them from pursuing FDA approval of label changes.

The defendants in both of these cases have filed petitions for writ of certiorari with the U.S. Supreme Court, and many believe the Court will accept at least one case, and perhaps combine the two cases. However, upon invitation by the Court, the U.S. government filed a brief in *Mensing* in which it argues the Supreme Court should not grant certiorari in that case. The government's position reduces but does not eliminate the likelihood that the Supreme Court will grant certiorari. The government argued that: (a) the Eight Circuit Court of Appeals' decision in *Mensing* was correct on the important issue that federal law did not preempt state failure-to-warn law applied to generic drug manufacturers; (b) because *Mensing* was decided at the pretrial stage, it was not a suitable vehicle for a full consideration of the federal preemption issues raised by the generic drug manufacturers; (c) federal law requires a manufacturer to take steps to update its labeling, and a State may impose a similar duty; and (d) there is no conflict among the different circuit courts of appeals on the federal preemption issue as presented in *Mensing*. The government has not filed a brief in *Demahy.* At some time, the Supreme Court will hear an appeal that will likely settle the argument of federal preemption for generic drug manufacturers in failure-to-warn cases, particularly since the *Levine* decision hinged on the CBE obligations of branded drug makers. Lower court decisions are likely in limbo until this issue is resolved, particularly cases involving generic manufacturers. "Providing clarity on this important issue is an impetus for the Supreme Court to accept these cases," suggests James Clair.

The Supreme Court could decide that the CBE obligations apply to generic drug makers, which is unlikely given that FDA regulations are mostly explicit in this regard. The Court, however, could decide as the circuit courts have that the obligations of proposing major label changes and Dear Doctor letters apply to generic drug makers as well. The trend throughout all courts, from district courts up through the Supreme Court, appears to be a "presumption against preemption, unless preemption is expressed or at least very strong," explains James Clair.

With these developments, generic companies would vigilantly have to monitor adverse-impact results and safety studies conducted on any drug that they sell in the market. The increasing liability for generic pharmaceutical companies might also force some companies to conduct safety and efficacy testing, which would certainly entail significant costs.

Generic drug companies also will have to invest in establishing procedures that will allow them to monitor drug-related laws across all 50 states. This additional regulatory burden, both monitoring regulatory changes and complying with them, will result in a disproportionate strain on small generic drug companies, perhaps diminishing their imprint in the pharmaceutical industry. Ultimately, this will defeat Congress's goal of promoting affordable drugs. As Dr. John Parente, Senior Science Advisor for Lexington Insurance, notes "profit margins for generic drug makers are a fraction of their branded counterparts. Much of the additional costs will ultimately be passed onto consumers by way of increased drug prices."

Adding a Layer of Complexity to the Landscape

As if handling the preemption issue is not enough, generic drug companies are also faced with the additional burdens posed by the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Signed into law in September 2007, FDAAA provides the FDA with expanded authority. Some of the new provisions gave FDA the authority to:

- require post-approval studies or clinical trials to assess a known or serious risk, or to learn more about a hypothetical serious risk;
- require that new safety information be added to the product labeling; and
- require that companies submit REMS when deemed necessary to ensure that the product's benefits outweigh the risks.

Among the 11 titles under FDAAA, Title IX ("Enhanced Authorities Regarding Post-market Safety of Drugs") is expected to have the most impact on generic drugs. This title includes various programs intended to improve the post-market safety of drugs, including giving the FDA authority to impose REMS for any branded and generic drug at any stage of the product lifecycle. REMS are emerging regulatory requirements for all drug companies that include managing known or potentially serious risks associated with pharmaceutical products.

A post-marketing safety surveillance tool, REMS is being referred to by industry observers as the most significant change in U.S. drug regulation history in many years. Proposed REMS may include a medication guide, a communication plan, an implementation plan, Elements to Assure Safe Use (EASU), and a timetable for submission of assessments. It can range from periodic assessments of a product's post-marketing safety profile to strict limitations on prescribing.

If the FDA requires REMS, a drug company is given 120 days to submit proposed REMS for a marketed drug. For a new drug, manufacturers must include the proposed REMS as part of its NDA submission. Failure to comply with FDA REMS requirements can render the company's drug misbranded and result in substantial penalties. Penalties for noncompliance start at $250,000 per violation.

With REMS, drug companies, especially generic drug manufacturers, face increased regulatory hurdles and costs. For one, the additional burden of producing and distributing medication guides and direct-mail to educate pharmacists and prescribers about drug safety issues will entail additional costs. Substantial investments also have to be made in establishing Web-based support resources and call centers necessary to implement risk mitigation strategies. Since REMS may be required at any stage of the product lifecycle, drug manufacturers also have to set in place a continuous monitoring program to ensure compliance. This requires ongoing program administration and additional manpower.

REMS-related costs can be overwhelming, particularly for small generic drug manufacturers with little room under their revenue base to support higher fixed costs. The FDA has always required that generic drug makers have the ability to monitor drug effects on their consumers, but REMS adds another layer of complexity resulting in additional costly steps. Industry players see far-reaching cost implications that will ultimately impact consumers. Dr. John Parente states that "the biggest impact of REMS is exposure. In the past, generic drug makers would use the branded drug makers as a shield, but now they are in the spotlight as well."

To meet REMS requirements, generic drug manufacturers must go beyond ensuring that the necessary controls are in place to evaluate effectively known or potential drug risks, as specific guidelines must be followed when REMS is required by the FDA. Insurance underwriters also will need to review risk evaluation and mitigation strategies to assess whether a drug manufacturer is more or less likely to incur liability losses. The result of these reviews will have a significant bearing on insurance premiums and the

ability to obtain adequate insurance coverage. Drug companies must adjust existing risk management policies to account for REMS.

Managing Risks in Light of Preemption and REMS

The latest decisions on preemption, particularly *Wyeth v. Levine*, as well as the emergence of REMS, have significantly changed the U.S. pharmaceutical landscape, making it imperative for generic manufacturers to ensure that risk evaluation, mitigation, and management practices are in place. The following are recommended precautions and procedures that pharmaceutical makers should consider.

- **Take internal steps to cover all bases.** Generic drug companies should establish procedures that will enable them to track effectively and follow various state and federal rules. They should ensure that adequate internal controls are in place to ensure full compliance through their operations. This includes not only hiring legal experts, but placing the responsibility for REMS in the hands of a capable multidisciplinary team. Dr. John Parente adds that, "following the guidelines that branded drug makers always needed to follow is a good rule of thumb".
- **Vigilantly monitor pending legislation.** Manufacturers of generic drugs should vigilantly monitor pending legislation that seeks to alter current regulations that address the applicability of the CBE regulation to generic manufacturers.
- **Keep a complete record of all communications with the FDA.** One key lesson learned from *Wyeth v. Levine* is the importance of proving that FDA has either considered or denied a change to a drug's label. Therefore, it is important for generic drug companies to keep a complete record of all correspondence with the FDA, particularly on changes to a drug's label.
- **Proactively communicate with the FDA.** In light of the *Levine* Supreme Court decision, and the possibility that it will hear the *Mensing* and *Demahy* cases, generic drug manufacturers should be prepared for the possibility that they might have to abandon the federal preemption defense in failure-to-warn cases. In doing so, they will take on certain label-change obligations after the ANDA is granted. As explained by James Clair, "Generic drug companies must gear up their vigilance when adverse effects arise, and proactively communicate with the FDA regarding proposals of major label changes and Dear Doctor letters."
- **Ensure adequate insurance limits.** Since generic manufacturers anticipate increased exposure to product liability litigation, they should ensure that their insurance policies have adequate limits. Manufacturers should watch for limit accumulations across products, as policies can hit their limits quickly when considering multiple suits.

Conclusion

The trend against preemption as a shield against product liability claims based on state law and the emergence of REMS have dealt a big blow to the pharmaceutical industry, particularly to manufacturers of genetic drugs. To survive in the evolving pharmaceutical landscape, drug makers should set in place a number of risk management precautions and procedures. Apart from monitoring pending legislation seeking to alter current regulations that address the applicability of CBE regulation to generic manufacturers, they should also set up effective internal controls that will ensure full compliance throughout their operations.

About Lexington Insurance Company

For nearly 40 years, Lexington has been underwriting wide-ranging healthcare risks, providing cutting-edge risk management and exceptional claims service to help insureds protect their bottom line. Our knowledge and expertise in the healthcare industry provide distinct advantages to our policyholders who range from hospitals to remote ambulatory facilities, from physicians to group practices and long term facilities. Our coverages run the gamut from medical professional liability to property insurance. Not only does Lexington provide a broad, flexible policy form to address the myriad of risks of the healthcare industry, we are also at the forefront in helping healthcare organizations meet one of the greatest challenges of the day - enhancing patient safety.

About Advisen

Advisen helps insurance professionals to gain and retain their clients. Advisen does this by managing business information on over 15 million entities in every industry, while integrating market data - policy transactions, wordings and severity losses to enable professional's insight into their client work. Advisen furthers that insight with timely news, critical risk analytics and time-saving workflow tools for over 500 industry leading insurance firms. Advisen delivers actionable information and risk models at a fraction of the cost to have them built internally. Designed by risk and insurance experts, and used daily by more than 100,000 professionals, Advisen combines the deepest data sets with proprietary analytics and provides insight into risk and insurance that is not available from any other firm.

Advisen is headquartered in New York. For more information, visit http://www.advisen.com or call +1.212.897.4800 in New York or +44(0)20.7929.5929 in London.