

# PUBLICATION

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## Defending Other Parties in the Chain of Distribution

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On March 4, 2009, the United States Supreme Court issued its much anticipated ruling on implied conflict preemption. Although the doctrine has broader application, the decision involved a pharmaceutical failure to warn claim, and the litigation landscape for traditional pharmaceutical manufacturers now seems a bit bleak. *Wyeth v. Levine*, 555 U.S. , 129 S. Ct. 1187, L. Ed. 2d (2009). Most state product liability statutes permit a plaintiff to allege design, manufacturing, and warnings defects. Due to the nature of the product, absent a discreet manufacturing issue, a pharmaceutical product liability case is almost always a failure to warn case. In *Levine*, the Supreme Court significantly curtailed the use of implied conflict preemption as a defense to state law failure to warn claims.

But can this doctrine successfully relieve other entities in the pharmaceutical product-distribution chain from strict liability? Most, if not all, of the reported pharmaceutical cases involving implied conflict preemption have been cases in which a manufacturer that either held a New Drug Application (NDA) or an Amended New Drug Application (ANDA) asserted the defense. Under the applicable statutes and regulations in the United States, a pharmaceutical company that desires to sell an innovator drug submits an NDA to the FDA for approval. A company that desires to manufacture and sell a generic drug submits an ANDA. 21 U.S.C. §355 *et seq.*

As stated by the *Levine* Court, "[T]he purpose of Congress is the ultimate touchstone in every preemption case." *Levine*, 129 S. Ct. at 1194 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)). In other words, the assumption is that a state's police powers are not superseded by federal law absent evidence of a contrary, clear and manifest intention of Congress. *Id.* For failure to warn claims asserted against entities other than NDA or ANDA holders, it appears that Congress did intend to supersede these claims. The federal regulatory scheme for drug approval enacted generally by Congress, and in more specific detail by the FDA, does not allow entities other than NDA or ANDA holders to submit drug labeling or to make or propose drug labeling changes. Thus, it seems that state law tort failure to warn claims asserted against non-application holders in the chain of product distribution should be preempted.

### The Basis for Implied Conflict Preemption

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)). Preemption occurs in three situations: (1) when Congress explicitly states its intent to preempt state law, referred to as express preemption; (2) when Congress' intent to preempt state law in a particular area is inferred from either the comprehensive scheme of federal regulation in that area or the dominant federal interest in that area, referred to as field preemption; and (3) 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, referred to as conflict preemption. *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).

Simply put, when state and federal law conflict irreconcilably, preemption is implied. In these cases, state law must yield, and federal law prevails. The courts have delineated two instances of "conflict" that result in preemption of state law. First, state law is preempted "when compliance with both federal and state regulations is a physical impossibility." *Fidelity Fed. Sav. & Loan Ass'n v. de la Cuesta*, 458 U.S. 141, 153 (1982). Second, state law is preempted when it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Id.*; *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 522 (1992); *Geier v. Am. Honda Motor Co., Inc.*, 529 U.S. 861, 871–72 (2000) (holding that ordinary preemption principles apply to a state tort action where an actual conflict with a federal objective is at stake). By analyzing both instances in *Levine*, the Supreme Court affirmed both as appropriate bases for preemption.

## The Levine Ruling

The Supreme Court ultimately found that neither instance of conflict preemption existed in *Levine*. The Court refused to preempt the plaintiff's state law tort claim that Phenergan Injection, for which Wyeth was the NDA-holding manufacturer, contained inadequate warnings about the risk of IVpush administration of the drug. *Levine*, 129 S. Ct. at 1196–99. First, the Court reasoned that it was not impossible for Wyeth to strengthen its warning without FDA approval. *Id.* at 1199. The court relied upon the existence of the "Changes Being Effected" (CBE) regulation, which allows a NDA holder to implement a labeling change to add or strengthen a warning before the FDA has approved it, as long as subsequent approval is sought. 21 C.F.R. §314.70(c)(6) (iii). Absent clear evidence in the regulatory record that the FDA did or would reject a stronger warning for the specific risk at issue, the Supreme Court found Wyeth's claim of "impossibility" to be without merit. *Levine*, 129 S. Ct. at 1199.

Second, the Court ruled that state law claims for failure to warn, such as those pursued by *Levine*, did not stand as an obstacle to Congress's competing goals in enacting the Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. §301 *et seq.*, of protecting and promoting the public health by entrusting prescription-drug label decisions to an expert agency, namely the FDA. *Levine*, 129 S. Ct. at 1199. The Court held that Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness and noted the following somewhat overlapping evidence: (1) no provision by Congress of a federal remedy in the FDCA for people injured by unsafe drugs; (2) no express preemption by Congress in the FDCA of such state law claims, as enacted by Congress for medical devices; and (3) congressional silence on preemption in the face of its of the prevalence of state law tort claims. *Id.* at 1200. The Court gave no weight to the FDA's conclusions that such state law claims are an obstacle and should be preempted. The Court noted that the FDA's statements endorsing preemption (1) were a change from the FDA's earlier position; (2) were not made in a regulation having the force of law, but rather in a preamble to a regulation, 71 Fed. Reg. 3922, 3934–35 (2006); and (3) were made without offering any interested party notice or opportunity to comment. *Id.* at 1201–03.

*Levine*, however, did not analyze the conflict presented when a state's strict product liability law attempts to hold entities in the product chain other than NDA and ANDA holders (hereafter collectively referred to as application holders) liable for failure to warn claims. In that instance, the conflict between state and federal law is different and seemingly suited, under the *Levine* analysis, to justify preemption. To understand why, it is necessary to examine the congressional objective behind the FDCA and the resulting federal regulatory regime for drug approval and labeling.

## Congress' Objective for the FDCA

Congress passed the FDCA and its various amendments to both protect and promote the public health by ensuring that drugs are made available to the public, while also ensuring that those drugs are safe and effective for their intended uses. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 134 (2000). As part

of this act, Congress created the FDA and invested the agency with responsibility for reviewing the safety and efficacy of new drugs before allowing them to be sold in interstate commerce. 21 U.S.C. §393. Congress created a general regulatory framework requiring FDA drug approval, and the FDA fleshed out the more specific details of the regulatory approval scheme by issuing corresponding regulations. 21 U.S.C. §§355(a), 393; 21 C.F.R. §300, *et seq.*

## Federal Regulation of Drug Approval

Under the FDCA, no entity may sell a new drug in interstate commerce before applying to the FDA and obtaining the FDA's approval of that drug. 21 U.S.C. §355(a). For an innovator drug, the applicant seeking approval must submit an NDA, which shows that the drug is safe and effective. 21 U.S.C. §355(b)(1)(A). For a generic drug, the applicant must submit an ANDA showing that the generic drug is bioequivalent to a drug that has already been found safe and effective (a.k.a., a "listed" drug). 21 U.S.C. §355(j)(2)(A)(iv). Thus, the entire regulatory approval scheme for drugs applies to the interaction between the FDA and the "applicant" or "holder of the approved application," which the FDA refers to as the "owner" of the drug. 21 C.F.R. §314.72. In the FDCA, "*Applicant* means any person who submits an application or abbreviated application or an amendment or supplement to them under this part to obtain FDA approval of a new drug... and any person who owns an approved application or abbreviated application." 21 C.F.R. §314.3(b).

To gain approval, an applicant must submit as part of its application its proposed labeling for the drug. 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). After approval, the applicant is subject to continuing "pharmacovigilance" duties—to monitor, analyze and report on the adverse effects associated with the drug, including those events reported in the published literature. 21 U.S.C. §355(k); 21 C.F.R. §§314.80 and 314.98. Only the applicant may withdraw or submit an amendment to an unapproved NDA or ANDA. 21 C.F.R. §§314.60, 314.65, 314.96. Only the applicant may submit a supplement proposing a change to an approved NDA or ANDA, including a change to the labeling. 21 C.F.R. §§314.70, 314.71(a), 314.97. Only the applicant may transfer ownership of its NDA or ANDA. 21 C. F. R. §314.72.

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In sum, only an applicant has the right— and duty—to interact with the FDA about the drug's approval and all issues that subsequently arise while the drug is on the market. This necessarily includes all issues pertaining to the drug's labeling.

## Federal Regulation of Drug Labeling

"Drug labeling serves as the standard under which the FDA determines whether a product is safe and effective." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). The FDA approves a drug application only if it finds that "the drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof." 21 U.S.C. §355(d)(1). FDA regulation of drug labeling is "[t]he centerpiece of risk management... which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care

practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). Thus, the labeling must contain "a summary of the scientific information needed for the safe and effective use of the drug." 21 C.F.R. §201.56(a)(1).

The applicant seeking approval of an innovator drug must include in the NDA a copy of the proposed drug labeling, along with references to the scientific information and data in the technical sections of the NDA that support the inclusion of each statement in the labeling. 21 U.S.C. §355(b)(1)(F); 21 C.F.R. §314.50(e)(2)(ii). The applicant seeking approval of a generic drug must include the same material in the ANDA and must also show, in a side by side comparison, that the proposed labeling for the generic drug is the same as the approved labeling for the listed drug. 21 U.S.C. §355(j) (2)(A)(v); 21 C.F.R. §314.94(a)(8)(i)–(iv).

Because drug labeling is critical to the FDA's determination that a drug is safe and effective, the process for changing, or even proposing a change to, the product labeling after approval is highly regulated. As mentioned, the right to propose a labeling change is bestowed only upon the applicant or the application holder and the labeling change mechanism is spelled out specifically in the applicable federal regulations. 21 C.F.R. §314.70. A labeling change—even a change made before approval is sought— can only be proposed to the FDA by the applicant using a supplemental application. *Id.*

### **Conflict Preemption Is Warranted**

The federal regulatory scheme for drug approval and labeling is precisely what creates the conflict justifying preemption of state tort law inadequate warnings claims asserted against non-application holders. Indeed, how is it possible for any entity that is not applying for, or does not hold, the NDA or ANDA for a drug to comply with state law tort duties requiring it to change a drug's warning, or else risk significant liability? Consider, for illustration, the plight of a contract, or "outsource" manufacturer, or that of a distributor. Assume that the application holder has decided, perhaps for economic reasons, to hire a contract manufacturer to make and package the drug and a distributor to distribute the drug to customers. Most state court product liability statutes simply hold all "manufacturers" and "distributors" liable for all "defects," without qualification. This includes inadequate warnings defects. Per the plain language of most state product liability statutes, the contract manufacturer and the distributor find themselves potentially liable for claims that the drug's warnings were inadequate.

These parties could perhaps have some sort of contractual obligation to report information to the application holder if they learn information about the drug that might pertain to its safety and efficacy. This is a big "if" in some instances. But neither the contract manufacturer nor the distributor has any right or mechanism under either the FDCA or the corresponding regulations to force or require the application holder to make, or to even to propose, a labeling change to the FDA.

To avoid state law liability, then, the contract manufacturer or distributor has two avenues to consider to "fix" the labels itself: (1) ask the FDA to change the product labeling; or (2) change the product labeling, disregarding the approval process mandated by Congress and the FDA. In *Levine*, the Court held that Wyeth, as the NDA holder, could simply have changed the label under the CBE regulation. In contrast, a contract manufacturer or a distributor cannot change the label or even ask the FDA to do so. There simply is no mechanism in the current federal regulatory scheme for a non-applicant or non-application holder either inside or outside of the chain of product distribution to seek FDA permission for approval of a change to a drug's labeling. 21 C.F.R. §314.70. A contract manufacturer and a distributor are in essentially the same position as every other entity or person in the product distribution chain, including sales representatives, retail pharmacists, doctors, and even patients. None are permitted by Congress or the FDA to submit a

supplemental drug application to the FDA for a labeling change. Presumably, the FDA would disregard any "supplemental application" submitted by any entity other than the applicant or application holder.

Further, for an unauthorized party, such as a non-application holder, to make a labeling change without seeking FDA approval would violate the FDCA. Even an applicant or application holder does not have such unregulated power over the content of drug labeling. 21 C.F.R. §314.70. All labeling changes made even by the authorized parties—the application holders— must, at some point, be approved by the FDA. 21 C.F.R. §314.70. Because federal law does not permit non-application holders to make or propose changes to a drug's labeling, state laws holding these entities liable for failure to do so are in direct conflict with federal law, and simultaneous compliance with both state and federal law is impossible. Thus, state law claims should be preempted as to non-application holders in the chain of product distribution. *Colacicco*, 521 F.3d at 261.

More fundamentally, in addition to being impossible under the regulatory framework, both of the supposed "options" are based on the faulty presumption that a nonapplication holder would or should have scientifically valid information regarding potential inadequacies in a drug's labeling. Under the regulatory scheme enacted by Congress and implemented by the FDA, no entity other than an applicant or an application holder has the obligation to conduct and report on the investigation of the drug before approval, or to conduct post-marketing pharmacovigilance after the drug's approval, to educate itself about the side-effect profile of the drug and assess the adequacy of the labeling. 21 U.S.C. §355; 21 C.F.R. §314.80. And in the real world, generally speaking, that is not the role that either a contract manufacturer or a distributor plays in the product chain. In some instances, a distributor could possibly pick up anecdotal information about a drug from customers and report it to the application holder. A contract manufacturer with no customer interaction likely would not even gain anecdotal information. But anecdotal information, in any event, may or may not be appropriate to report to the FDA, and may or may not support a labeling change. In light of the regulatory requirements, the application holder is the only entity in a position to make that call.

This lack of appropriate knowledge by non-application holders supports the second basis justifying preemption of failure to warn claims asserted against them. Allowing failure to warn claims against nonapplication holders would seem to obstruct Congress' competing objectives of ensuring that drugs are readily available to the public, but are also safe and effective. *Levine* allowed a state product liability law to require a "different" labeling decision by the application holder. The Supreme Court held that such state laws, rather than obstructing Congress' objectives, added additional "oversight," of the achievement of those objectives. The Supreme Court found no obstruction because ultimately, the manufacturer, not the FDA, is the "master" of the drug's label. *Levine*, 129 S. Ct. at 1202.

It is a different matter altogether, however, to allow a state product liability statute to require other entities that are not part of the federal regulatory scheme for drug labeling to ensure a label's adequacy or else risk significant liability. The FDCA and the corresponding regulations expressly state that the wording of drug labeling must be approved before dissemination, and Congress and the FDA expressly required the applicant or application holder alone to ultimately bear responsibility for the content of a drug's labeling. Congress or the FDA could have implemented a different regulatory scheme that allowed drug labeling changes to be made by any party in the chain of product distribution without FDA approval. They could also have permitted, or even required, entities other than the applicant or the application holder to gather scientific information about a drug and provide it to the FDA. They did not, even presumably in the face of knowledge that many other entities would be involved in the process of placing a drug in interstate commerce. And rightly so.

As noted earlier, drug labeling "serves as the standard under which the FDA determines whether a [drug] is safe and effective" for specific uses under specific conditions. 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985); see also 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). The FDA must ensure that scientifically valid warnings are disseminated because "[d]issemination of unsupported warnings risks diluting those that are scientifically

supported and/or discouraging safe and effective use of a particular drug." *Colacicco*, 432 F. Supp. 2d at 537 (citing the FDA's *Colacicco* Amicus at 13.) Thus, the process of gathering, receiving, and assessing warning information about a drug must necessarily be methodical, controlled, and supported by well-documented scientific evidence, and the ultimate content of the labeling must undergo a central approval process, or Congress's competing objectives cannot be achieved.

### **Other Parties,**

The application holder charged with the duty to investigate the safety and effectiveness of a drug before approval and to monitor that safety and effectiveness after approval is in the best position to submit scientifically based warning information or label changes to the FDA for consideration. Drug labeling should not, and cannot, be proposed or changed by even a well-intentioned party—such as a contract manufacturer or a distributor—whose role in the product chain may or may not provide it with adequate scientific information to support its suggested changes. Allowing, or even requiring, such potentially unreliable input from other entities would only serve to make the FDA's job of determining if a drug is safe and effective as labeled that much more difficult.

Faced with the prospect of significant state law liability for inadequate warnings and the inability to "fix" those warnings, parties such as contract manufacturers and distributors may see no real option but to refrain from making or selling drugs that might potentially expose them to this liability. This potential stifling of both the manufacture and distribution of drugs would contravene Congress's objective of making safe and effective drugs readily available to the public.

### **Conclusion**

A defendant in the product distribution chain other than the application holder may find greater success than the application holder in asserting federal preemption of state law failure to warn claims made against it, regardless of the state of the FDA regulatory record regarding the warning at issue. This entity has no right to participate in the federally regulated labeling approval process, and thus, should not be held liable in state tort law for inadequate warnings. To be sure, some non-application holders sometimes may have other viable defenses available to attempt to escape liability, but those other defenses often involve fact intensive, and thus expensive, inquiries. However, preemption is a legal doctrine that potentially can be raised earlier in the life of a case without extensive discovery, making it an attractive option to explore to attain an early dismissal.