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BLOG

The Growing Challenges To Drug Cos.' Preemption Defense

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In the wake of the U.S. Supreme Court's decisions in *Wyeth v. Levine*[1] and *Merck Sharp & Dohme Corp. v. Albrecht*,[2] drug manufacturers face challenges in establishing a preemption defense when they receive "newly acquired information" about a drug's side effects without clear evidence that the U.S. Food and Drug Administration would have rejected a label change adding a warning of the risk of harm.

But some courts have resisted the Supreme Court's invitation to broadly preclude preemption, by critically evaluating what constitutes "newly acquired information."

Many state common laws and statutes require drug manufacturers to warn consumers of the risks associated with prescription drugs. However, when Congress enacted the Federal Food, Drug, and Cosmetic Act,[3] it charged the FDA with ensuring drugs are "safe for use under the conditions prescribed, recommended, or suggested" in the drug's labeling.[4]

Federal regulations also set out the requirements for the content, format and order of the safety information on a drug's label.[5] Drug manufacturers have argued it is impossible to comply with both state law duties underlying failure-to-warn claims and federal law, which authorizes the FDA to approve the exact text in a drug's label. But the Supreme Court has rejected blanket application of the impossibility preemption doctrine to state law failure-to-warn claims.

The Wyeth and Merck opinions made it clear that that, while prospective drug manufacturers work with the FDA to develop an appropriate label before a new drug is approved, FDA regulations also acknowledge that drug safety information may change over time, and new information may require changes to the drug label.[6] Indeed, the drug manufacturer has a duty to conduct post-market surveillance and revise the label when there is reasonable evidence of an association of a serious hazard with a drug.[7]

The CBE Process

Drug manufacturers are generally required to seek advance permission from the FDA to make substantive labeling changes, but the agency's "changes being effected," or CBE, regulation permits manufacturers to change a label without prior approval if it is designed to "add or strengthen a … warning" where there is "newly acquired information" about the "evidence of a causal association" between the drug and a risk of harm.[8] Notably, such newly acquired information is not limited to new data, but also encompasses "new analysis of previously submitted data."[9]

A drug manufacturer can thus be held liable for failure to warn if it could have revised its label using the CBE process, but failed to do so.[10] If a plaintiff succeeds in establishing that there is newly acquired information supporting a label change, the burden then shifts to the manufacturer to show by clear evidence that the FDA would not have approved the revised label.[11]

The Supreme Court has defined "clear evidence" to mean "evidence that shows the court that the drug manufacturer fully informed FDA of the justifications for the warning required by state law and that FDA, in turn, informed the drug manufacturer that FDA would not approve a change to the drug's label to include the warning."[12]

Plaintiffs have capitalized on the phrase "newly acquired information" as a key component of the CBE process to argue that manufacturers could have unilaterally revised drug labels without FDA approval after new risks are identified. But what constitutes newly acquired information that may defeat preemption?

Courts have struggled to apply a consistent definition, in the absence of comprehensive Supreme Court guidance—and, in some instances, engaged in an expansive interpretation, resulting in the inability of the manufacturer to rely on preemption as a defense.

Expansive Interpretations of "Newly Acquired Information"

A recent California appeals court ruling in the Risperdal & Invega Cases[13] suggests some courts following Wyeth and Merck apply an expansive definition of newly acquired information.

In Risperdal, the plaintiffs argued that the manufacturer of the antipsychotic drug risperidone could have used the CBE process to warn of a direct correlation between the drug and gynecomastia, a condition characterized by the enlargement of male breast tissue, and added a recommendation for regular monitoring of prolactin levels associated with the condition.[14]

The appellate court agreed, affirming summary judgment for the plaintiffs, and finding that drug manufacturers—not the FDA—bear responsibility for the content of their labels at all times, and carry the burden to ensure warnings remain adequate while the drug is on the market.[15]

The Risperdal court discounted as newly acquired information two studies cited by the plaintiffs, because they had been submitted to the FDA as part of the drug's application.[16] But it found that the manufacturer's statistical analysis of pediatric studies, reported as table 21 in a draft manuscript that was not included in the final article submitted to the FDA, demonstrated a greater risk of side effects than the data provided.[17]

The defendant argued that the table could not be newly acquired information, because it did not reveal risks of a different type or greater severity, and in fact, table 21 did not change the overall rate of gynecomastia that was reported on the label.[18]

While the court agreed that table 21 did not change the rate of gynecomastia reported on the label, it did provide additional information about elevated prolactin levels during different time periods, and those elevated levels were more likely to lead to side effects, including gynecomastia.[19] The court held that "[i]mpossibility preemption requires the drug manufacturer to show that it fully informed FDA," notwithstanding the fact that table 21 was not newly acquired by the defendant.[20]

The Connecticut superior court in *Roberto v. Boehringer Ingelheim Pharmaceuticals*[21] likewise found that the manufacturer of Pradaxa, an anticoagulation drug designed to prevent strokes in patients with irregular heart

rhythms, failed to fully inform the FDA of the risk of major gastrointestinal bleeding.[22] The court first discounted several articles and internal draft documents and communications that did not evidence "a different type or greater severity or frequency than previously included in submissions to FDA."[23]

But in what it referred to as a "close call," the court found that Pradaxa's European label constituted newly acquired information, because it disclosed for the first time an elevated risk of major gastrointestinal bleeding.[24] "[D]espite the differing labeling standards," the court found it "possible that a foreign label may contain information that qualifies as newly acquired information under our country's CBE regulation and that would be permissible to include in the U.S. label."[25]

While the European label did not present new data, it reflected new risk analyses related to a previously submitted clinical trial.[26] The court also found that, although the defendants had transmitted the European label to the FDA as part of their periodic update report, the record did not establish this transmission occurred before the plaintiff's injury.[27] Accordingly, the court concluded that the plaintiff's failure-to-warn claim was not preempted.[28]

Critical Interpretations of "Newly Acquired Information"

Recent decisions by other courts, however, suggest a more critical analysis of what constitutes newly acquired information.

In *Ridings v. Maurice et al.*,[29] the plaintiffs brought claims against the manufacturers of Pradaxa in a Missouri district court similar to those asserted in the Roberto case.[30] But after a preemption hearing, the Ridings court found the plaintiffs fell short of establishing that any materials constituted newly acquired information, concluding that nearly all of the "new" materials relied on data provided to FDA before the drug's approval.[31]

In contrast to the Roberto court, the Ridings court found that information in the drug's European label and a related clinical overview statement was substantially similar to data provided to the FDA before approval, noting that foreign drug labeling is the product of "different and distinct regulatory standards."[32] It concluded that "the actual warnings approved for a foreign label are not in and of themselves newly acquired evidence when they are based on consideration of substantially similar information."[33]

The court also discounted the defendant's internal computer modeling exercises, exploring whether exposure measurement might further improve Pradaxa's "positive benefit-risk balance," concluding that the simulation testing "was a bad idea that simply did not pan out."[34]

Finally, the court found that "arguably relevant information" in early drafts of a paper or internal communication do not meet the threshold for newly acquired information.[35] The court reasoned that "preliminary discussions do not provide reliable evidence of new risks," equating them to "uncorroborated trial balloons."[36]

While "it is fully appropriate for a scientific dialogue to take place, and disagreement to occur, during the drafting of a major paper," the court concluded that "ultimately, a preliminary opinion or dissenting voice is just that—it is not a final opinion."[37]

And based on similar evidence, the superior court in *Adkins v. Boehringer Ingelheim Pharmaceuticals Inc.* came to the same conclusion,[38] granting summary judgment to defendants on the basis of preemption.[39] In contrast to the Risperdal decision, which turned on the defendant's failure to submit to the FDA a draft data table in a manuscript, the Adkins court "expressed reluctance to rely on a draft of an article … especially when the final version differs."[40]

Even at the pleadings stage, drug manufacturers have occasionally prevailed on motions to dismiss complaints that fail to sufficiently allege they had newly acquired information revealing risks of a different type or severity than warned of in drug labels or that were not already submitted to the FDA.

For example, in *Drescher v. Bracco Diagnostics Inc.*,[41] an Arizona federal district court granted a motion to dismiss the complaint alleging the defendant's gadolinium-based MRI contrast agent failed to warn patients with normal renal

function of an increased risk of nephrogenic systemic fibrosis.[42] The court reviewed and considered the cited studies referenced in the complaint, and found they only supported a causal association between retained gadolinium and risk to patients with renal impairment.[43]

And in *Vardouniotis v. Pfizer Inc.*,[44] the plaintiff alleged that the defendant failed to warn of certain side effects for its smoking cessation medication, despite newspaper articles and scientific journal publications identifying those effects after the drug's approval.[45] The New York state court rejected these conclusory allegations when the plaintiff failed to append the cited studies to the complaint or her motion to dismiss, also noting that the plaintiff failed to allege any new material was based on data that had not been submitted to the FDA.[46]

In the wake of Wyeth and Merck, some courts have broadly interpreted the basis for a potential label change via CBE regulation as the grounds for denying the application of a preemption defense. But other courts have been willing to critically evaluate whether purported newly acquired information is sufficiently reliable to justify a plaintiff's desired label change.

These cases show that the preemption defense remains available for post-market failure-to-warn claims. But they also highlight the burden on a drug manufacturer to ensure label warnings remain adequate while the drug is on the market, and to revise the label through the CBE process if it identifies any new information not previously submitted to the FDA that may constitute reasonable evidence of an association with a serious risk.

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[1] Wyeth v. Levine, 129 S. Ct. 1187 (2009).

[2] Merck Sharp & Dohme Corp. v. Albrecht, 139 S. Ct. 1668 (2019).

[3] 21 U.S.C. §§ 301-392.

[4] Id. at § 355(d).

[5] See 21 C.F.R. § 201.57(c) (2019).

[6] Wyeth, 129 S. Ct. at 1197; Merck, 139 S. Ct. at 1673.

[7] See 21 C.F.R. §§ 201.80(e), 314.80(b).

[8] See 21 C.F.R. § 314.70(c)(6)(iii)(A); see also Wyeth, 129 S. Ct. at 1196.

[9] Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,604 (Aug. 22, 2008); Wyeth, 129 S. Ct. at 1197.

[10] Merck, 139 S. Ct. at 1677-78.

[11] Wyeth, 129 S. Ct. at 1198; Merck, 139 S. Ct. at 1678.

[12] Merck, 139 S. Ct. at 1672.

[13] Risperdal & Invega Cases, 49 Cal. App. 5th 942 (2020).

[14] Id. at 947, 957.

[15] Id. at 954.

[16] Id. at 957.

[17] Id. at 958.

[18] Id.

[19] Id.

[20] Id. at 959.

[21] Roberto v. Boehringer Ingelheim Pharmaceuticals, No. HHD-CV-16-6068484-S, 2019 WL 5068452 (Conn. Super. Ct. Sept. 11, 2019).

[22] Id. at *1, 22-24.

[23] Id. at *16-17, 19-20.

[24] Id. at *21-22.

[25] Id. at *21.

[26] Id. at *22.

[27] Id. at *23.

[28] Id. at *24.

[29] Ridings v. Maurice et al., No. 4:15-CV-00020, 2020 WL 1264178 (W.D. Mo. March 16, 2020).

[30] Id. at *1.

[31] Id. at *15.

[32] Id. at *16-18.

[33] Id. at *17.

[34] Id. at *18.

[35] Id. at *20.

[36] Id.

[37] Id. (internal citation omitted).

[38] Adkins v. Boehringer Ingelheim Pharm. Inc., No. HHD-CV-16-6065131-S, 2020 WL 1890681 (Conn. Super. Ct. Mar. 13, 2020).

[39] Id. at *8-13.

[40] Id. at *9.

[41] Drescher v. Bracco Diagnostics Inc., No. 4:19-CV-00096, 2020 WL 699878 (D. Ariz. Jan. 31, 2020).

[42] Id. at *1.

[43] Id. at *4-5.

[44] Vardouniotis v. Pfizer Inc., No. 152029/2019, 2020 WL 3890928 (N.Y. Sup. Ct. July 7, 2020).

[45] Id. at *7.

[46] Id. at *8.

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