CHAPTER 4

COLACICCO v. APOTEX INC.

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I. Why It Made the List

Colacicco v. Apotex Inc.[1] began as a landmark case—the latest in a series of rulings by courts increasingly willing to find state-law failure-to-warn claims against pharmaceutical companies preempted. When the United States Supreme Court granted certiorari in ***Wyeth v. Levine***, however, all eyes turned to that case. While Justice Stevens' decision in ***Levine*** painted broadly, one of the lasting legacies of ***Colacicco*** may be that it in fact represents a real-world example of a case where preemption may still apply post-***Levine***.

II. Facts of Case

Colacicco began as two consolidated cases: ***Colacicco v. Apotex*** from the Eastern District of Pennsylvania and ***McNellis v. Pfizer*** from the District of New Jersey. The plaintiffs in the two cases were, respectively, the husband and daughter of two adults who committed suicide after taking prescription antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs). ***Colacicco*** involved the generic version of Paxil®, manufactured by Apotex; ***McNellis*** involved Pfizer's Zoloft®. The plaintiff in each case claimed that labeling contained an inadequate warning on the association between the drugs and an increased risk of suicide.

Based on the facts as the Third Circuit found them, for nearly 20 years the Food and Drug Administration (FDA) actively had monitored the potential association between SSRIs and suicide. Over that time, FDA consistently rejected the scientific basis for including a suicide

[1] 521 F.3d 253 (3d Cir. 2008).

warning in the label of SSRIs. For example, in 1991, after considering the association between antidepressants and suicidal thoughts, FDA concluded that no such warning should be added to Prozac®, an SSRI similar to Paxil and Zoloft. On three separate occasions in 1991, 1992 and 1997, FDA rejected citizen petitions seeking to include a suicide warning on the Prozac labeling. Each time FDA concluded that there was insufficient evidence to include such a warning.

Moreover, FDA had approved the precise language of the Paxil and Zoloft labels on numerous occasions. FDA approved the language and placement of the suicide precaution in Zoloft's label seven separate times, both before and after the suicide in the ***McNellis*** case. Each time, FDA required the final printed labeling to be identical to the labeling approved by FDA. Additionally, just months before the suicide in the ***McNellis*** case, FDA filed an amicus brief before the Ninth Circuit reiterating its view that no scientific basis justified suicide warning for Zoloft. Similarly, FDA repeatedly approved the Paxil label in effect when the ***Colacicco*** suicide occurred, as well as Apotex's use of that labeling for its generic version of Paxil. Even when FDA began to reevaluate its position based on new evidence on a potential association between antidepressants and adolescent suicidality, FDA continued to announce in various public statements and health advisories that no evidence justified linking SSRIs with increased risk of suicide in adults.

Each case presented the question whether actions taken by FDA preempted the plaintiffs' failure-to-warn claims. The two district courts reached opposite conclusions. In ***Colacicco***, the Eastern District of Pennsylvania dismissed the plaintiff's complaint on preemption grounds. In ***McNellis***, the District of New Jersey court denied the defendant's preemption motion. The Third Circuit reviewed the cases together and issued its opinion on April 8, 2008.

III. Court Ruling

In a 2-1 decision, the Third Circuit held that plaintiffs' state-law failure-to-warn claims were preempted by FDA's actions repeatedly approving the label and publicly rejecting the scientific basis for such a warning.

IV. Rationale for Decision

The court limited its preemption analysis to whether the plaintiffs' claims were prohibited under a theory of conflict preemption. The court explained that conflict preemption occurs in two situations. First, when "compliance with both federal and state regulations is a physical impossibility," and second, when "state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." Because cases of true impossibility were rare, the court analyzed the obstacle preemption theory.

Defendants argued that in practice they could not have added a different suicide warning to the labels because FDA had clearly expressed its view that no association existed. Plaintiffs argued that because FDA's "Changes Being Effected" (CBE) regulations permit companies to strengthen the warnings unilaterally without prior FDA approval, unless FDA had expressly rejected a proposed change by a manufacturer, preemption should not apply. The defendants responded that while CBE updates do not require pre-approval, they must ultimately be approved by FDA. Thus, they argued a CBE here would have conflicted with FDA's publicly stated position on the association between suicide and SSRIs and been futile because FDA had clearly expressed its contrary views.

The court sided with defendants. It reasoned that manufacturers should not be compelled to submit CBE changes that they believed—correctly—were unnecessary. Nor was the court willing to encourage companies to submit CBE supplements in order to insulate themselves from potential liability.

The court also rejected the plaintiffs' claims that the drug manufacturers had failed to provide FDA with sufficient information to make a valid determination regarding the warning at issue. The court stated that if such a claim was supported by sufficient evidence, it should have been brought before FDA, and plaintiffs had not done so. The court also found that FDA had access to research studies conducted by various SSRI manufacturers that had looked for a link between SSRIs and suicide, and that FDA had conducted its own review of aggregated data from all SSRI manufacturers. Despite having access to all this information, FDA still concluded that there was insufficient evidence linking SSRIs to an increased risk of suicide in adults and that the suicide warnings desired by the plaintiffs would therefore be false and misleading.

The Court also addressed how much deference to give to FDA's public position that some state-law failure-to-warn claims were preempted by the Federal Food, Drug, and Cosmetic Act (FDCA). FDA had stated this view both in the preamble to the 2006 amendments revising drug labeling regulations and in various amicus briefs, including the amicus brief filed in the *Colacicco* case. The Third Circuit determined that an agency's position regarding preemption was entitled to deference of approximately the level set forth in ***Skidmore v. Swift & Company***.[2] Despite the plaintiffs' claims to the contrary, the court did not find any inconsistency between FDA's position in the 2006 preamble and its historical position on preemption. The court also noted that it was important to consider the agency's rationale for its position as to the impact of state-law requirements in the instant case and its potential to interfere with FDA's accomplishment of regulatory objectives.

Obviously important to the court's decision was FDA's clear and publicly stated position that no evidence supported an association between SSRIs and a heightened risk of suicide.

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[2] 323 U.S. 134 (1944).

FDA had expressed this view in its numerous approvals of the labels for the drugs at issue, rejection of multiple citizen petitions related to SSRIs, and public health advisories and statements. The court explicitly stated that its holding was limited to circumstances where FDA had publicly rejected the warning that plaintiffs claimed state law required. The court did not decide whether preemption would be appropriate in other situations, such as if FDA had not rejected the substance of the warning at issue or if FDA had only stated its position after a lawsuit had been brought. The court also stated that it was not deciding if mere approval of labeling by FDA is sufficient for preemption purposes.

Judge Ambro filed a lengthy dissent. The dissent relied heavily on the presumption against preemption and opined that the majority decision had under-emphasized the importance of congressional intent in preemption analysis, which he found lacking in the case. Although Judge Ambro agreed with the majority on the appropriate level of deference to give FDA, he concluded that FDA had taken an inconsistent position on preemption over the years and thus its current position regarding preemption deserved little deference.

In examining the interaction between FDA regulation of the drugs at issue and state tort law, rather than finding a conflict, Judge Ambro concluded that the two are complementary. He stated that the majority's decision "threatens the institutional framework that we have for balancing safety and efficacy in the pharmaceutical industry while compensating victims of wrongful injuries." Important to this conclusion was the fact that drug manufacturers have the best information about the safety of their products and that it is highly unlikely a manufacturer would be punished by FDA for over-warning. Judge Ambro also denounced what he referred to as "backdoor federalization"—a trend among federal courts of finding preemption. Based on the lack of express preemption, the text of the FDA regulations and the recent nature of FDA's position on preemption, he concluded that state tort law had not been displaced in this case and therefore the plaintiffs' failure-to-warn claims were not preempted.

V. Impact of Decision

In March 2009, while the plaintiffs' petition for writ of certiorari to the U.S. Supreme Court was pending, the Supreme Court issued its long-awaited decision on preemption of failure-to-warn claims in *Wyeth v. Levine*.[3] In *Wyeth* v. *Levine*, the Court held that the FDCA did not preempt failure-to-warn claims involving a prescription drug. The Justices decided the case 6-3; lopsided enough to reflect an authoritative decision, yet close enough to reveal ideological divisions. Justice John Paul Stevens, the most senior member of the court (appointed by President Ford in 1975) and a longtime proponent of a limiting view of preemption, wrote the decision.

[3] 555 U.S. — (2009).

The plaintiff in the case, Diana Levine, was a professional musician and songwriter who went to a clinic for treatment of her nausea. The clinic gave her Wyeth's injectable anti-nausea medication Phenergan®, which can be administered intravenously or through intramuscular injection. The labeling warned that with intravenous (IV) injection "extreme care" should be used to avoid intra-arterial injection. After receiving an intravenous injection of the drug through an IV-push (in which the drug is injected into an intravenous line already in place), the drug entered Ms. Levine's artery and she developed gangrene, resulting in amputation of her arm.

In her subsequent suit against Wyeth, Ms. Levine argued that Wyeth's labeling was flawed because it should not have allowed, or should have more strongly warned against, administration of the drug through an IV-push. Wyeth responded by arguing preemption; it said that it could not comply with both the requirements of FDA and a state court jury. Because FDA had directed it to use the warning, had approved it and had rejected a different warning on intra-arterial injection, Wyeth argued that it should not be held liable for failing to do what FDA required it to do.

In rejecting the preemption defense, the Supreme Court relied primarily on the CBE regulation, which was so important in *Colacicco*. The Court held that "newly acquired information" can mean new analysis of previously existing data. Wyeth also argued that CBEs were often risky and impractical; the Court rejected this argument as being, in its view, unsupported by the record. Finally, the Court gave no deference to FDA's 2006 statements on preemption.

The reasoning in *Levine* provides fuel for both sides of the debate in *Colacicco*. Favoring the view that *Colacicco* is essentially overruled are the following points: First, the *Levine* court took a broad view of the presumption against preemption. Second, it gave FDA's recent statements supporting preemption no deference. Third, it gave great weight to the feasibility of the CBE process.

On the other hand, *Levine* can be seen as standing for a "clear evidence" standard under which preemption will still apply if there is "clear evidence that the FDA would not have approved" the label changes urged by plaintiff. Under this view, the facts of *Colacicco* provide a solid basis for preemption even when the company did not submit a CBE.

As the Third Circuit recognized, FDA had repeatedly and publicly rejected the need for the very warning that the plaintiffs argued state law required. On numerous occasions, FDA publicly stated that insufficient scientific evidence existed of an association between SSRIs and suicide. Over the course of many years, FDA specifically rejected a number of citizen petitions calling for suicide warnings in SSRI labels, concluding in each instance that there was a lack of scientific basis for such a warning. FDA had also issued multiple public

statements and health advisories over the years reflecting its conclusion. Thus, although the defendants in *Colacicco* never attempted to implement the suicide risk warning through the CBE process, there was persuasive evidence, as determined by the court, that a proposed CBE supplement was unnecessary and that FDA would not have approved the warning if the defendants had proposed it. These facts may constitute the type of "clear evidence" referred to by the *Levine* court. In contrast, in *Levine* the court found no evidence that FDA had given more than "passing attention" to the risk at issue, noting only "sparse" and "intermittent" correspondence between the manufacturer and FDA.

The Supreme Court, however, did not clarify what constitutes "clear evidence," thus leaving lower courts to determine on a case-by-case basis what meets this standard. In early 2010, in another case against the manufacturer of Paxil, the Seventh Circuit examined the very same facts considered by the Third Circuit in *Colacicco* and found that they did not constitute clear evidence that FDA would have rejected the suicide warning sought by the plaintiffs. Unlike the Third Circuit, the Seventh Circuit did not find persuasive FDA's previous rejections of the citizen petitions concerning Prozac—a different SSRI manufactured by a different company—and gave little weight to the regulatory history of that drug. The court also found it unlikely that FDA would have refused to allow Paxil's manufacturer to warn about a possible risk of suicide for young adults when it had already warned the public about the suicide risk for pediatric patients. Finally, the court noted that FDA's subsequent decision in 2007 requiring an adult suicide warning on all SSRIs makes it less likely that FDA would have rejected the plaintiffs' proposed warning in 2003.

Just days after issuing its opinion in *Levine*, the Supreme Court vacated the Third Circuit's judgment in *Colacicco* and remanded the case for further consideration in light of *Levine*. Upon receiving the case on remand, the Third Circuit ordered the parties to brief the effect of *Levine* on the court's prior decision. FDA notified the court that it was withdrawing its previously filed amicus brief because it had not had time to conduct a further assessment of the preemption issues following the Supreme Court's decision. After receiving the parties' briefing on *Levine*'s impact, the court decided not to re-examine its prior holding and instead vacated its judgment and remanded the cases to their respective district courts for further proceedings consistent with the Supreme Court's decision. The court stated that the parties could reassert their preemption arguments in light of *Levine* before the district courts. The *Colacicco* case was remanded to the Eastern District of Pennsylvania where it is still pending. In November 2009, Apotex filed a new motion for summary judgment on preemption grounds, which has not yet been ruled on. The *McNellis* case was remanded to the District of New Jersey and the parties settled in January 2010.

VI. Conclusion

Whether the Third Circuit's preemption finding will survive in light of the Supreme Court's holding in ***Levine*** is therefore yet to be determined. A broad reading of ***Levine*** would require a company to have submitted a CBE with ***all*** evidence it had about the risk at issue. A more constrained, real-world view of ***Levine*** would consider whether the evidence that exists—irrespective of the process from which it derived—demonstrates "clear evidence" that FDA would not have accepted a stronger warning.