

## DRUG, DEVICE AND BIOTECHNOLOGY COMMITTEE

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### IN THIS ISSUE

*Dabney Carr and Brian Fowler of Troutman Sanders LLP examine decisions in the area of preemption in the six months since the Wyeth v. Levine decision and analyze what preemption defenses remain viable after Levine.*

### WYETH v. LEVINE, SIX MONTHS LATER – WHAT REMAINS OF PRESCRIPTION DRUG PREEMPTION?

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In the six months since the Supreme Court's March 2009 decision in *Wyeth v. Levine*<sup>1</sup>, pharmaceutical companies, their attorneys, and plaintiffs' lawyers have debated, and predictably, disagreed about the decision's impact on future prescription drug litigation.<sup>2</sup> Naturally, the plaintiffs' bar seeks to read the decision broadly, arguing that preemption of state claims involving prescription drugs is effectively dead. The *Levine* decision, however, does not support this conclusion. Indeed, in July of this year, one federal district court specifically noted that *Levine* "left open the possibility that 'some' state law claims may frustrate the achievement of congressional objectives in the federal regulation of drug labeling."<sup>3</sup> Similarly, shortly after the *Levine* decision, another federal district court noted that although *Levine* may "stand for the proposition that post-approval claims are preempted, it does not purport to hold that the same is true for pre-FDA approval claims."<sup>4</sup> Accordingly, defendants can make a strong argument that at least two categories of state law claims remain preempted in the wake of *Levine*: (1) claims alleging some form of fraud committed by the manufacturer during the drug approval process, and (2) failure to warn claims based solely on information that was known to and considered by the FDA at the

time the drug's labeling was initially approved.

### **Wyeth v. Levine**

In *Levine*, the plaintiff lost her forearm to gangrene after Phenergan<sup>®</sup>, an anti-nausea drug, was injected intra-arterially into her arm using a procedure known as "IV push."<sup>5</sup> Although intravenous administration was an approved method of administration, the Phenergan labeling stated that the preferred method of administration was intramuscular, and warned in bold, capitalized letters: "INTRA-ARTERIAL INJECTION [CAN] RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." The label did not, however, instruct clinicians to use the less dangerous "IV drip" method instead of IV push when administering the drug intravenously.<sup>6</sup>

The plaintiff argued that the labeling was defective because it did not contraindicate intravenous injection, or, at the very least, instruct clinicians to use the IV drip method when administering the drug intravenously.<sup>7</sup> Wyeth responded that FDA's labeling requirements preempted *Levine*'s claim because it was impossible for the company to comply with its state-law duty to modify the Phenergan warning label without violating federal law.<sup>8</sup> Specifically, Wyeth claimed that the FDA had previously rejected proposed labeling for Phenergan warning about the dangers of IV push, and so Wyeth contended that it could not have strengthened the label without subjecting itself to liability for misbranding. Importantly, however, the lower court reviewed the correspondence between Wyeth and the FDA regarding

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<sup>1</sup> *Wyeth v. Levine*, \_\_ U.S. \_\_, 129 S. Ct. 1187, 173 L. Ed. 2d 51 (2009).

<sup>2</sup> Although the *Levine* decision involved a branded prescription drug, since the Court's decision was handed down at least three federal district courts have applied *Levine* to claims involving generic prescription drugs as well. See *Kellogg v. Wyeth*, 612 F. Supp. 2d 437, 441 (D. Vt. 2009); *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262 (W.D. Okla. 2009); and *Stacel v. Teva Pharms.*, 620 F. Supp. 2d 899, 904-07 (N.D. Ill. 2009).

<sup>3</sup> *Forst v. SmithKline Beecham Corp.*, Case No. 07cv612, 2009 U.S. Dist. LEXIS 67471, at \*10 (E.D. Wis. July 29, 2009).

<sup>4</sup> *Long v. Wyeth*, 621 F. Supp. 2d 504, 507 (N.D. Ohio 2009).

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<sup>5</sup> *Levine*, 129 S. Ct. at 1191.

<sup>6</sup> *Id.* at 1191-92.

<sup>7</sup> *Id.*

<sup>8</sup> *Id.* at 1193.

Phenergan labeling over the drug's 40-plus year history, and "found no evidence that Wyeth had 'earnestly attempted' to strengthen the intra-arterial injection warning or that the FDA had specifically disallowed stronger language."<sup>9</sup> In short, the factual record in *Levine* "lacked any evidence that the FDA set a ceiling" with regard to the labeling in question.<sup>10</sup>

The Supreme Court rejected Wyeth's appeal, stating that "absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements."<sup>11</sup> Underpinning this decision was the Court's opinion that "a central premise of federal drug regulation [is] that the manufacturer bears responsibility for the content of its label at all times."<sup>12</sup> Moreover, the FDA provided manufacturers with a means of strengthening key labeling provisions whenever necessary to insure continued safe use of a drug through its "changed being effected" (CBE) regulations. The CBE regulations permit a manufacturer to change its label 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 product."<sup>13</sup> Thus, the Court concluded, "when the risk of gangrene from IV-push injection of Phenergan became apparent, Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval."<sup>14</sup>

<sup>9</sup> *Id.* at 1192.

<sup>10</sup> *Id.*

<sup>11</sup> *Id.* at 1198 (emphasis added).

<sup>12</sup> *Id.* at 1197-98.

<sup>13</sup> *Id.* at 1196 (citing 21 CFR § 314.70(c)(6)(iii)(A), (C)).

<sup>14</sup> *Id.* at 1198.

### *The Reach of Levine*

A central tenet of the *Levine* decision is that the manufacturer, not the FDA, is ultimately responsible for the contents of its drug label. Manufacturers therefore have a duty to use the FDA's CBE process to make any post-approval label changes necessary to ensure the continued safe use of the drug. Preemption will not be found unless the manufacturer "makes a clear evidentiary showing that the FDA would not have approved a change to the label."<sup>15</sup> Although this "impossibility" standard for preemption "is a demanding defense,"<sup>16</sup> it is not insurmountable. The *Levine* decision was tied to the regulatory record that was before it, and was dependent on at least four important findings:

1. Wyeth offered no evidence that it attempted to give the kind of warning required by the Vermont jury but was prohibited from doing so by the FDA;
2. The trial court found no evidence that either the FDA or Wyeth gave more than passing attention to the issue of IV-push versus IV-drip administration;
3. The FDA had not made an affirmative decision to preserve the IV-push method and did not intend to prohibit Wyeth from strengthening its warning about IV-push administration; and
4. Wyeth did not supply the FDA with an evaluation or

<sup>15</sup> *Schrock v. Wyeth, Inc.*, 601 F. Supp. 2d 1262, 1264-65 (W.D. Okla. 2009) (citing *Levine*).

<sup>16</sup> *Levine*, 129 S. Ct. at 1199.

analysis concerning the specific dangers posed by the IV-push method.<sup>17</sup>

Thus, in theory at least, if a manufacturer proves that the FDA considered and rejected a specific label change, or if the FDA has considered a risk and specifically decided that the label is adequate in light of that risk, a state law claim of failure to warn of such a risk is preempted.

The courts will develop the exact contours of preemption in the wake of *Levine* in the years to come. It is clear, though, that a drug manufacturer must do more than simply show that it interacted closely with the FDA about a drug's safety data and that the FDA failed to require an enhanced warning despite its review of relevant data. A recent post-*Levine* decision, *Forst v. SmithKline Beecham Corp.*, illustrates this point. *Forst* involved a claim that GlaxoSmithKline's ("GSK") selective serotonin reuptake inhibitor ("SSRI"), Paxil<sup>®</sup>, required a warning about an increased risk of suicidality.<sup>18</sup> Prior to *Levine*, several courts had held failure to warn claims involving SSRIs were preempted because the FDA had publicly rejected the need for an additional warning regarding suicidality.<sup>19</sup> In *Forst*, by contrast, the court held that GSK had not provided "clear evidence" that the FDA would not have approved a change to Paxil's labeling concerning the risk of suicidality had it been proposed by GSK or initiated through the CBE process. Even though the FDA had rejected a proposed label change to add a warning about suicidality, the court held that the FDA had not prohibited all enhanced warnings, but had merely required removal of Paxil-specific language from a particular

portion of the Paxil label in favor of uniform class-wide labeling for all SSRI's.<sup>20</sup> Accordingly, "[t]he agency's action did not preclude Paxil-specific language changes to other areas of the labeling or prevent GSK from pursuing a label change through submission of a separate supplement."<sup>21</sup>

Regardless, the *Levine* Court could have eliminated the preemption defense altogether, but it did not. Instead, the Court emphasized that congressional intent remained "the touchstone in every pre-emption case,"<sup>22</sup> and noted "that some state-law claims might well frustrate the achievement of congressional objectives."<sup>23</sup> Thus, in those instances in which the frustration of congressional objectives is clear, preemption may remain as a viable defense.

**Claims Based On Pre-Approval Conduct, Including "Fraud-On-The Agency" Claims.**

Prior to *Levine*, it was well settled that federal law preempted state-law claims alleging that a drug manufacturer defrauded or misled the FDA in conjunction with an NDA.<sup>24</sup> This type of preemption, often referred to as "*Buckman*" preemption, is rooted in *Buckman Co. v. Plaintiffs' Legal Committee*.<sup>25</sup> In *Buckman*, the plaintiffs claimed that a manufacturer of bone screws had secured FDA approval for the screws by fraudulently representing their purpose to the FDA. If the

<sup>17</sup> *Id.* at 1198-99.

<sup>18</sup> *Forst*, 2009 U.S. Dist. LEXIS 67471.

<sup>19</sup> See, e.g., *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008).

<sup>20</sup> *Forst*, 2009 U.S. Dist. LEXIS 67471, at \*12.

<sup>21</sup> *Id.*

<sup>22</sup> *Levine*, 129 S. Ct. at 1194.

<sup>23</sup> *Id.* at 1204.

<sup>24</sup> A July 2009 outlier opinion from the District of Utah deserves note. In *Lake-Allen v. Johnson & Johnson, L.P.*, the court held that "the federal preemption articulated in *Buckman* extends only to medical devices and not to prescription drugs." 2:08cv930, 2009 U.S. Dist. LEXIS 64860, at \*10 (D. Utah July 27, 2009).

<sup>25</sup> *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 121 S. Ct. 1010, 148 L. Ed. 2d 854 (2001).

misrepresentations had not been made, the plaintiffs argued, the FDA would not have cleared the screws for marketing, and plaintiff would not have been injured.<sup>26</sup> In concluding that the claims were preempted, the Supreme Court noted that “policing fraud against federal agencies is hardly ‘a field which the States have traditionally occupied’” such as to warrant any presumption against preemption.<sup>27</sup> The relationship between a federal agency and the entity it regulates, the Court held, “is inherently federal in character because the relationship originates from, is governed by, and terminates according to federal law.”<sup>28</sup> Emphasizing the flexibility inherent in the statutory and regulatory framework, the Court held that the plaintiffs’ fraud-on-the-FDA claims conflicted with federal law:

The conflict stems from the fact that the federal statutory scheme amply empowers the FDA to punish and deter fraud against the Agency, and that this authority is used by the Agency to achieve a somewhat delicate balance of statutory objectives. The balance sought by the Agency can be skewed by allowing fraud-on-the-FDA claims under state law.<sup>29</sup>

Courts have emphasized that “*Buckman* teaches that state tort remedies requiring proof of fraud committed against the FDA are foreclosed since federal law preempts such claims.”<sup>30</sup> Further, lower courts have applied

*Buckman* not only to claims alleging fraud on the FDA, but also to “any claim based on a contention that [the defendant] provided inaccurate or incomplete information to the FDA,”<sup>31</sup> as well as claims alleging failure to report adverse events to the FDA.<sup>32</sup>

The *Levine* decision should have no impact on “*Buckman*” preemption. Importantly, in *Levine* “the Court emphasized that it was Congress’ intent to have state law complement federal drug regulation because ‘manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.’”<sup>33</sup> The Court further noted:

State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA’s premise that manufacturers, not the FDA, bear the primary

<sup>26</sup> *Id.* at 343.

<sup>27</sup> *Id.* at 347.

<sup>28</sup> *Id.*

<sup>29</sup> *Id.* at 348.

<sup>30</sup> *Garcia v. Wyeth-Ayerst Labs.*, 385 F.3d 961, 966 (6th Cir. 2004); see also *Mason v. SmithKline Beecham Corp.*, 546 F. Supp. 2d 618, 627 n.5 (C.D. Ill. 2008); *In*

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*re Aredia and Zometa Prods. Liab. Litig.*, No. 3:06-MD-1760, 2008 U.S. Dist. LEXIS 26859, at \*4 (M.D. Tenn. April 2, 2008); *Webster v. Pacesetter, Inc.*, 259 F. Supp. 2d 27, 36 (D.D.C. 2003); *Bouchard v. American Home Prods. Corp.*, 213 F. Supp. 2d 802, 813 (N.D. Ohio 2002); *Flynn v. American Home Prods. Corp.*, 627 N.W.2d 342, 346-49 (Minn. Ct. App. 2001); *Dawson ex rel. Thompson v. Ciba-Geigy Corp.*, 145 F. Supp. 2d 565 (D. N.J. 2001); *Globetti v. Sandoz Pharms. Corp.*, No. CV98-TMP-2649-S, 2001 WL 419160 (N.D. Ala. Mar. 5, 2001).

<sup>31</sup> *Miller v. DePuy Spine, Inc.*, 2:07cv1639, 2009 U.S. Dist. LEXIS 49602, at \*11 (D. Nev. May 1, 2009).

<sup>32</sup> *Webster*, 259 F. Supp. 2d at 36.

<sup>33</sup> *Longs*, 621 F. Supp. 2d at 509 (emphasis in original) (quoting *Levine*).

responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.<sup>34</sup>

Relying on this language, three post-*Levine* cases have held that “*Buckman*” preemption remains available.<sup>35</sup> Thus, claims alleging that the manufacturer committed fraud on the FDA, that a manufacturer concealed or misrepresented information to the FDA, or that a manufacturer provided inaccurate or incomplete information to the FDA remain preempted because such claims directly conflict “with the FDA’s authority to determine which drugs are sufficiently safe and effective to be marketed.”<sup>36</sup>

#### **Claims Based on Information Known to the FDA at the Time of Initial Approval.**

In addition to *Buckman* preemption, one federal district court decision since *Levine* has held that claims based on information or risks known to the FDA at the time a drug is approved remain preempted after *Levine*. “While *Wyeth* [*v. Levine*] may stand for the proposition that post-FDA approval claims are preempted, it does not purport to hold that the same is true for pre-FDA approval claims.”<sup>37</sup> As a result, preemption should still apply, for example, to claims that the FDA did not fully appreciate the dangers revealed in studies submitted as part of a New Drug

Application (NDA) or claims that a manufacturer failed to provide full information about a drug as part of an NDA. Such claims necessarily require a jury to speculate as to what the FDA would have done if it had different information before it, and so inevitably meddle in the FDA’s decision to approve a drug. As Justice Stevens recognized in his concurring opinion in *Buckman*, claims based on what FDA would have done if provided different information prior to approval are inherently speculative.<sup>38</sup> Such a claim cannot proceed because it depends on “speculation as to the FDA’s behavior in a counterfactual situation” that is not “grounded in the agency’s explicit actions” and so requires “second-guessing the FDA’s decision-making or overburdening its personnel . . . .”<sup>39</sup>

Allowing claims based on information available to the FDA prior to approval would directly undermine and conflict “with the FDA’s authority to determine which drugs are sufficiently safe and effective to be marketed,”<sup>40</sup> and “would raise the same inter-branch meddling concerns that animated *Buckman*.”<sup>41</sup> As a result, “the circumstances surrounding the FDA’s approval of a drug cannot be litigated in the course of [a] private products liability suit.”<sup>42</sup> Thus, a claim that the FDA should have either rejected a manufacturer’s application for approval of a drug or that the FDA should have insisted on additional warnings before approving a drug should remain preempted.<sup>43</sup>

<sup>34</sup> *Levine*, 129 S. Ct. at 1202.

<sup>35</sup> *In re Aredia and Zometia Prods. Liab. Litig.*, No. 3:06-0659, 2009 U.S. Dist. LEXIS 72095, at \*4-5 (M.D. Tenn. Aug. 13, 2009); *Miller*, 2009 U.S. Dist. LEXIS 49602 at \*11; *Longs*, 621 F. Supp. 2d at 507-08.

<sup>36</sup> *Longs*, 621 F. Supp. 2d at 507-08; see also *Miller*, 2009 U.S. Dist. LEXIS 49602, at \*11.

<sup>37</sup> *Longs*, 621 F. Supp. 2d at 509.

<sup>38</sup> *Buckman*, 531 U.S. at 354 (Stevens, J., concurring).

<sup>39</sup> *Id.*

<sup>40</sup> *Longs*, 621 F. Supp. 2d at 507-08.

<sup>41</sup> *Garcia*, 385 F. 3d at 966.

<sup>42</sup> *In re: Aredia*, 2008 U.S. Dist. LEXIS 26859, at \*5 (citing *Zammit v. Shire US, Inc.*, 415 F. Supp. 2d 760, 767 (E.D. Mich. 2006)).

<sup>43</sup> *Zammit*, 415 F. Supp. 2d at 768-69.

Moreover, the CBE regulations which formed the foundation for the decision in *Levine* are inapplicable to information or risks known to the FDA at the time of approval. If manufacturers were free to make unilateral changes to labeling the day after the FDA's approval based on information previously available and known to the FDA, the approval process would be undermined, and the FDA's careful balancing of risks and benefits as reflected in the labeling would be thwarted. Even commentators who are critical of preemption of claims involving pharmaceuticals acknowledge that "[a]t the time of approval, the FDA's knowledge-base may be close to perfect," and that as of the day of a new drug approval, "the FDA's determination about labeling ought not be subject to re-examination by courts or juries in failure-to-warn cases."<sup>44</sup> Thus, *Levine* should not alter the conclusion that claims based on dangers, adverse reactions or data known to the FDA at the time of approval are preempted.

Preemption may not extend, however, to claims based on post-approval analyses of data submitted to the FDA prior to approval. An April 2009 decision from the Texas Court of Appeals involving Wyeth's branded prescription drug Prempro<sup>®</sup> illustrates this point.<sup>45</sup> Prempro was approved by the FDA in 1995 specifically on the condition that Wyeth include in its label specific language concerning the risk of breast cancer. The plaintiff used Prempro from 1997 to 2001, at which time she was diagnosed with breast cancer. In 2002, an independent organization, the Women's Health Initiative (WHI), released findings from a large clinical study

involving Prempro which had been stopped early because of growing evidence of the risk of breast cancer. Based on this study, Wyeth changed the Prempro label and strengthened the warnings about the risk of breast cancer. The plaintiff alleged that had Wyeth conducted its own study like the one conducted by WHI, it would have strengthened the label much earlier, plaintiff would not have taken the drug, and thus would not have developed cancer.<sup>46</sup> The lower court held that plaintiff's failure to warn claims were preempted. On appeal, and following the *Levine* decision, however, the Texas Court of Appeals reversed, holding that Wyeth had not shown that the FDA would have rejected a stronger warning concerning breast cancer prior to plaintiff's use of the drug.<sup>47</sup>

### **Conclusion**

There is no doubt that *Levine* significantly narrowed the availability of a preemption defense in a pharmaceutical product liability case. It did not, however, eliminate the defense. As district court decisions in the last six months have shown, preemption remains an available defense to claims that a defendant defrauded, misled or otherwise failed to provide information to the FDA during the NDA process and claims based on information or data known to the FDA at the time a drug was approved.

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<sup>44</sup> David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-To-Warn Claims*, 96 Geo. L.J. 461, 465 (2008).

<sup>45</sup> *Brockert v. Wyeth Pharms., Inc.*, 287 S.W.3d 760, 2009 Tex. App. LEXIS 2546, at \*20-21 (Tex. App. April 14, 2009).

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<sup>46</sup> *Id.*, 2009 U.S. Tex. App. LEXIS 2546, at \*5-6.

<sup>47</sup> *Id.* at \*20-21.



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