Forecasting the Fallout of *Wyeth v. Levine*

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ABSTRACT

The Supreme Court's recent decision in *Wyeth v. Levine* ensures that new drugs will be susceptible to lawsuits at every step of development, from inception in the first phase of clinical trials past FDA approval. The cost of increased litigation will be less innovation. By contrast, generic drug makers enjoy a greater competitive advantage over brand name drugs after *Wyeth*, since *Wyeth* did not address generic drugs or the significantly different drug regulations applicable to them. This article will focus on the effect that *Wyeth* will have on manufacturers of brand name drugs, generic drugs, and medical devices.

INTRODUCTION

On average, it takes eight years to bring a new drug to the market.[1] All new drugs must go through years of clinical trials to support a New Drug Application.[2] Even after the NDA is submitted, the FDA often requires additional testing or scientific support before approval is granted. Unlike generic drugs, there is no shortcut to the market. To the contrary, the costs associated with demonstrating a new drug's safety and effectiveness are always rising.

The Supreme Court's recent decision in *Wyeth v. Levine* ensures that new drugs will be susceptible to lawsuits at every step of development, from inception in the first phase of clinical trials past FDA approval. The cost of increased litigation will be less innovation. By contrast, generic drug makers enjoy a greater competitive advantage over brand name drugs after *Wyeth*, since *Wyeth* did not address generic drugs or the significantly different drug regulations applicable to them. This article will focus on the effect that *Wyeth* will have on manufacturers of brand name drugs, generic drugs, and medical devices.

The dust has only begun to settle from the impact of the Supreme Court's March 4, 2009 decision in *Wyeth v. Levine*. The *Wyeth* decision dismantled the preemption defense in brand name drug litigation, destroyed the FDA's credibility as the sole regulator of drugs, and gave its blessing to regulation-by-jury. And, while plaintiff's attorneys across the country rejoiced, brand name drug manufacturers braced for the fallout.

THE WYETH DECISION[3]

Wyeth involved an inadequate warning claim brought by Diana Levine against Wyeth regarding the brand name drug Phenergan, a drug designed to treat severe nausea associated with migraine headaches. Levine's medical provider made the catastrophic mistake of injecting twice the recommended dose of Phenergan into an artery in Levine's arm, ignoring her complaints of pain during the three or four minutes the drug was administered. In so doing, the medical provider ignored at least six warnings contained on the label, including multiple warnings that arterial exposure to Phenergan would result in gangrene. Levine's forearm ultimately had to be amputated, ending her career as a professional musician.

After settling with her healthcare providers, Levine sued Wyeth, who argued that Levine's claims were preempted. The trial court rejected Wyeth's preemption arguments, and a Vermont state court jury found in Levine's favor. The Supreme Court granted certiorari to consider Wyeth's argument that Levine's claims were preempted.

The majority opinion framed the issue before it as "whether the FDA's approvals provide Wyeth with a complete defense to Levine's tort claims."[4] The majority concluded that regulations applicable to branded drugs permit manufacturers to comply with differing state and federal law obligations. In rejecting the preemption argument, the majority opinion relied upon the Changes Being Effected (CBE) provision of the FDA regulations, which permits brand name drug manufacturers to unilaterally add or strengthen warnings and contraindications on a drug label without prior FDA approval. The Court reasoned that the CBE provision allowed manufacturers to comply with heightened state standards imposed by juries in product liability lawsuits.

The majority opinion put the onus for changing the label firmly on drug manufacturers, holding that the existence of the CBE provision "[made] it clear that manufacturers

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remain responsible for updating their labels." Similarly, in language sure to be repeated in front of judges and juries for years to come, the Court stated that "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times."

In addition to rejecting the "blanket" preemption argument, the Supreme Court also examined whether the FDA had ever considered, or rejected, warnings related to the claims brought by plaintiff Diana Levine. The majority opinion found against Wyeth on that issue, as well, leading the Supreme Court to hold "absent clear evidence that the FDA would not have approved a change to [the drug's] label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements."[5] *Wyeth* upheld the jury verdict for Diana Levine, and permitted a jury of laypeople to stand in the FDA's shoes in finding that Phenergan's label was inadequate.

THE REMAINS OF PREEMPTION

Wyeth left little room for branded drug makers to argue for preemption. The door was left ajar, if just a crack, for an "impossibility" preemption defense. However, the majority cautioned that "[i]mpossibility pre-emption is a demanding defense" that requires "clear evidence that the FDA would not have approved a change" to the drug's labeling.[6] In other words, FDA approval of a drug's labeling will not have a preemptive effect, but the FDA's rejection of a specific warning could preempt subsequent claims to the extent such claims would require the rejected warning to be added to the label. *Wyeth* therefore serves as an invitation to branded drug makers to submit numerous alternative iterations of warning language, in an effort to elicit an FDA rejection that can provide a preemption defense.

This warning-specific, "impossibility" preemption will require manufacturers to demonstrate that (1) the FDA has considered the risks alleged by the Plaintiff, (2) the manufacturer sought the FDA's approval to change the label to address the risk, and (3) the FDA refused to approve the proposed change. The main problem with this "demanding defense" is that its target is the elusive failure-to-warn claim. "Warning claims generally have that wondrous elasticity of open-endedness, a boon to creative lawyers. After all, any text, particularly labels, can be criticized by hindsight as having insufficient or unduly limited information."[7]

Wyeth gives failure to warn claims as much room to wiggle out from under preemption as one's imagination will allow. Although the regulations require that CBE submissions be based upon newly acquired information, the Supreme Court reasoned that newly acquired information is "not limited to new data, but also encompasses analyses of previously submitted data."[8] The entire body of knowledge concerning a drug and its effects are therefore fair game for plaintiff's counsel, plaintiff's experts, and the jury to second guess the decisions made by the manufacturer in crafting the language of a warning label.

The jury verdict in *Wyeth* never decided what the Phenergan label should have said, but merely concluded that the label itself was somehow inadequate.[9,10] Wyeth was given no specific guidance on what the state of Vermont, through its jury, expected to be changed to the drug's labeling, leaving Wyeth no better informed on what it allegedly did wrong after the verdict than when the lawsuit began. Further, there was no answer as to whether new or different warnings would have made a difference in Levine's case.

Similarly, the Supreme Court majority never suggested what the labeling for Phenergan should have said, but simply found that since the jury found the labeling insufficient, the Court need not revisit the jury's determination. *Wyeth* permitted liability to stand where the jury performs only half of its new function as a regional regulatory body over drug labeling. As a result, *Wyeth* may have provided the ultimate escape hatch against preemption claims, requiring only a vague allegation that the drug labeling was inadequate, without ever having to specify what would have made it sufficient or whether different labeling would have made a difference.

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EVOLUTION OF LITIGATION STRATEGY

Branded drug manufacturers generally submit language to the FDA that they expect will be approved. Under *Wyeth*, approval of a drug's labeling is insufficient to show that the FDA would not have approved a stronger or different label. Rather, *Wyeth* made clear that "[a]ffirmative, contrary FDA action is the best scenario left for preemption in litigation involving prescription drugs."[11] Branded drug manufacturers must be able to show that the FDA considered, and rejected, the changes that plaintiff's counsel and experts would require. Thus, manufacturers of branded drugs will have to become accustomed to submitting warning language that they do not expect, or even hope, the FDA will approve.

In order to lay the groundwork for any preemption defense, branded manufacturers may consider flooding the FDA with innumerable variant labels for all their products to counter likely potential claims. Also, whenever a lawsuit is filed, a manufacturer may consider making a CBE change, or a supplemental New Drug Application, that addresses the plaintiff's claims. The supplemental NDA may be the better tactic with this strategy, since it will not require the manufacturer to change the wording on the

product's label, and would permit the manufacturer to submit a variety of proposed changes. These approaches will let the FDA, and not a jury, decide whether the risk raised by plaintiff's claims warrants a heightened warning. If the labeling change is rejected, this tactic may provide the evidence needed to prevail on a preemption motion. Unless a plaintiff can be cornered into stating what he claims the warning should have said, however, the FDA's rejection may have no effect.

Naturally, this tactic may also not always work fast enough to produce results. Nonetheless, it is a low cost defense tactic that may, before the case's end, provide the "clear evidence" needed for an impossibility preemption motion. While waiting for the FDA's response, the case will continue, with discovery and document production and depositions, all at significant cost. This tactic also carries with it the risk that the FDA might actually agree with the CBE provision and adopt the wording proposed by the branded drug manufacturer, possibly causing irreparable damage to the defense.

Aside from creating these dilemmas for branded drug makers, *Wyeth* provided plaintiffs with an effective weapon to use in court, and with their clients to increase the value of their claim. No longer can manufacturers hold the threat of preemption over their opponents' heads to goad plaintiffs into a more reasonable settlement. Since *Wyeth* appears to have been crafted to conscript plaintiffs into a pharmaceutical regulatory army, plaintiffs and their counsel will have far less pressure to settle their claims. Branded drugs will therefore become the focus of a protracted pitched battle between individual consumers and branded drug manufacturers, to the detriment of the nation's collective health.

In defending their product, branded drug manufacturers will need to consider and develop the following themes for trial:

The Label Story. The jury will need to understand the exhaustive process that went into crafting the language of the label, and the FDA's role in approving it. Defense counsel will need to show the jury that the same evidence and data presented to them was presented to the FDA, and that the FDA concluded that the language on the label was appropriate. The jury should also be reminded about the dangers of overwarning, which dissuades doctors and patients from taking vital medicines. Even if this argument was not sufficient for the Supreme Court, it should impress upon a jury of ordinary common sense that it may not be qualified to second guess the FDA's judgment.

The Causation Story. Plaintiff's counsel will likely seek to avoid committing to any particular warning language, relying on the fact that *Wyeth* upheld a verdict where the jury did not reach a conclusion as to what the label wording should have been. Yet, plaintiff's counsel must prove that plaintiff's injuries were caused by the inadequate warning. Accordingly, the ambiguity of plaintiff's criticism of the label supports the argument that plaintiff lacks scientific evidence that some hypothetical warning would have made a difference in the outcome of the particular case.

The Human Story. Plaintiff will focus the jury's attention on the risks—and, likely, the risks as applied to one consumer—but not the benefits of the drug for all consumers. Not only will the manufacturer need to demonstrate the benefits of the drug, but it may consider seeking out testimony from individuals for whom the drug has been a life-saver.

The Corporate Story. Plaintiff's counsel will point to the profits earned from drug sales to argue that the manufacturer places profit over people. The manufacturer will need to show that it is peopled by dedicated professionals whose bottom line is measured not in dollars, but in the development of safe and effective medicines to improve the health and quality of life of their families and everyone else. In our current economy, jurors may also be more sympathetic than ever to the fact that corporations are not funded by a bottomless well of money, and that a punishing verdict will punish the corporation's employees and its consumers.

GENERICS—NO NEWS IS GOOD NEWS?

While preemption for branded drugs and their manufacturers may have received a knockout blow in *Wyeth*, generic drugs and their manufacturers should retain a strong preemption defense. Only 16% of the dollars spent by consumers are for generic drugs, though generics account for 69% of the total prescriptions filled in the United States.[12] This significant exposure to potential inadequate warning suits likely led the Generic Pharmaceutical Association (GPhA) to submit an amicus brief in *Wyeth*.[13] While the GPhA's amicus brief supported Wyeth's argument, it correctly advised the Court that generic drugs are subject to a significantly different regulatory regime and oversight as compared to branded drugs, and asked the Court to avoid painting with too broad a brush if it rejected Wyeth's preemption argument. While the Supreme Court never addressed these differences, *Wyeth* does not appear to stand as an obstacle to preemption in the context of generic drugs.

The laws and regulations applicable to generic drugs provide for an expedited path to the market, but permit generic drug to adhere to rigid requirements regarding the design and labeling of such drugs. With regard to preemption analysis, there are several key differences between the regulation of branded and generic drugs:

- Generic drugs are approved pursuant to an Abbreviated New Drug Application, whereas new drugs must be approved pursuant to the more onerous New Drug Application;
- A generic drug maker need not conduct clinical trials, but rather need only show that the generic drug is bioequivalent to the branded drug for which it is the generic equivalent. The bioequivalent branded drug is also called the reference listed drug (RLD).[14] By regulation, the generic drug maker cannot deviate from the FDA-approved labeling for the branded drug, but must demonstrate that the generic drug's labeling is the same as the RLD's labeling.[15]

- After receiving approval, the generic drug's label must remain consistent with the FDA-approved label for the RLD.[16] While branded drug manufacturers can make changes without FDA approval pursuant to the CBE provision, the FDA has issued its own guidance on this regulation to make it clear that it will not permit generic drug makers to make CBE changes.[17]

Thus, both the regulations and the FDA's own interpretation of those regulations demonstrate that generic manufacturers cannot utilize the CBE provision. Notably, the FDA's interpretation of the regulations applicable to generic drugs is entirely different from its interpretation of the legal effect that its approval should have on the preemption defense in personal injury actions, and which the Supreme Court roundly rejected as unpersuasive.

The *Wyeth* decision did not mention generic drugs, and did not address the regulations applicable specifically to generic drugs. Notably, the preemption arguments available to generic manufacturers are based upon the plain language of applicable laws and regulations, as well as the FDA's own explanation as to how it enforces those regulations. While *Wyeth* certainly could have offered more substantive guidance for generic drug cases, it certainly did not undermine any of the arguments previously available to generic drug makers.

Since the CBE process is not available to generic drug makers, the holding in *Wyeth* should be inapplicable to cases involving generic drugs. In fact, the reasoning in *Wyeth* should support preemption in these cases, since it is impossible under current regulations for generic drug manufacturers to make any changes to the label, and therefore generic drug manufacturers cannot simultaneously comply with differing state and federal labeling standards.

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The generic drug industry should gain a short-term competitive advantage over the branded drug industry because of increased litigation costs that *Wyeth* will impose on branded drug manufacturers. Over the long term, however, the chilling effect on drug innovation could cause the generic drug industry to suffer along with its branded counterpart.

MEDICAL DEVICES IN THE CROSSHAIRS

Just a year before the *Wyeth* opinion, an 8-1 majority held in *Riegel v. Medtronic* that FDA approval of a pre-market approved device preempted subsequent state law tort claims alleging defective design or inadequate warnings.[18] A movement to overturn *Riegel* has followed.[19] The *Wyeth* decision has further invigorated this movement by making an "unfortunate distinction" between drugs and medical devices.[20] If successful, the legislation would cause the Supreme Court's ruling in *Riegel* to be moot.[21]

While *Riegel*'s detractors decry the "unfortunate distinction" the Supreme Court has made between devices and drugs, the distinction was supported by at least three significant differences between the applicable laws and regulation.

- The decision in *Riegel* was based on the Court's interpretation of an express preemption provision, which prohibits states from imposing different requirements with regard to a device's safety and effectiveness. There is no analogous express preemption provision for pharmaceuticals. Rather, *Wyeth* analyzed whether implied preemption applied to Levine's claims.
- There is no equivalent CBE provision for medical devices. Medical device manufacturers must have the FDA's approval before it makes any change to a device that would affect its safety and effectiveness.
- Prior to *Riegel*, nearly every circuit had already reached the same conclusion reached by the Supreme Court in *Riegel*. Prior to *Wyeth*, nearly every circuit had already concluded that FDA approval of a branded drug did not create a blanket preemption of subsequent state law tort claims.

Importantly, *Riegel* affected only a small percentage of the devices on the market. Specifically, it applied only to devices that had received Pre-Market Approval—devices that the FDA reviewed for safety and effectiveness. Most devices are subject to a different review, and may be approved if shown to be "substantially equivalent" to a predicate device that had been on the market prior to the enactment of the Medical Device Amendments.

Despite these significant differences, medical devices find themselves in Congress' crosshairs, as the movement to "level the playing field" builds.[22] The device industry faces a more complicated challenge by this legislation, however. While pharmaceutical cases focus on the label, a medical device case typically involves claims against both the warnings and the design. While litigation is expensive, it is relatively simple to change a label or a warning if a jury determines that it is inadequate. Changing a device's design, however, is a much more complicated task.

Any change in the design of a medical device will require extensive development and engineering. Further, any design change affecting the device's safety and effectiveness must first be approved by the FDA before it can actually enter the market. Additional phases of clinical trials and scientific study will therefore be necessary in order to support the request to change the design. Thus, regulation-by-jury not only means exponentially higher litigation costs for device makers, but it also threatens to impose an endless development and testing process, perhaps resulting in the development of fewer medical devices.

WHY HAVE THE FDA AT ALL?

Wyeth requires branded drug manufacturers to adopt an entirely new litigation strategy, and likely adjust their approach to developing new drugs and monitoring the drugs it has on the market. Medical device manufacturers may have to follow suit if Congress legislatively overrules *Riegel*. No longer can manufacturers rely on the FDA as the final word on whether drugs (and possibly devices) are safe and effective. Rather, that question will always be ripe for adjudication, and subject to endless second-guessing and inconsistent determinations.

Ironically, Congress long ago created the FDA to put an end to the inconsistent patchwork of state laws and regulations applicable to drugs and devices. *Wyeth* dilutes that authority under the reasoning that the FDA is too overworked to handle so much responsibility in the first place. This reasoning will become a self-fulfilling prophecy, as the FDA may be called upon to reject scores of proposed warnings submitted to fend off inadequate warnings claims. Judicial deference will be afforded the FDA not for what it has *approved*, but only for what it has *rejected.* If the FDA's initial evaluation of safety and effectiveness cannot be trusted, then why have an FDA at all?

ENDNOTES

1. Healthcare Economist, *Cost to bring drug to market: $802m*, April 29, 2006. Available at http://healthcare-economist.com/2006/04/29/802m/. *See* DiMasi, Hansen, Grabowski, Journal of Health Economics, *The price of innovation: new estimates of drug development costs*, vol. 22, pp. 151-185 (2003). See *also* Lynne Taylor, *Despite fast reviews, new drugs still take eight years*, October 1, 2008 (available at http://www.eatg.org).
2. *Id. See generally* 21 U.S.C. § 355(d).
3. *Wyeth* was a historic decision, and its majority, concurring and dissenting opinions have been subject to exhaustive analysis. For a more detailed analysis and critique of *Wyeth, see* James M. Beck and Mark Heremann, Drug and Device Law Blog, *Wyeth v. Levine and the End of Deregulation*, March 5, 2009 (available at http://druganddevicelaw.blogspot.com/2009/03/wyeth-v-levine-and-end-of-deregulation.html.). *See also* Jim Copland and Paul Howard, Washington Times, *A 'Cure' Worse than Gangrene: Supreme Court's gift to trial lawyers hurts us all*, March 9, 2009.
4. *Wyeth v. Levine*, 555 U.S. ____, No. 06-1249, slip op. at 1 (March 4, 2009) (available at http://www.supremecourtus.gov/opinions/08pdf/06-1249.pdf
5. *Wyeth v. Levine*, 555 U.S. ____, No. 06-1249, slip op. at 1 (March 4, 2009) (available at http://www.supremecourtus.gov/opinions/08pdf/06-1249.pdf
6. *Id.* at 15.
7. *Id.* at 15, 16.
8. Hoenig, Michael, New York Law Journal, *Drug Warning Claims Not Preempted*, v. 241, March 9, 2009
9. *Wyeth*, No. 06-1249, slip op. at 12.
10. This is likely because Levine argued at trial that IV push should have been contraindicated altogether, thereby eliminating one method of administration that the FDA explicitly permitted in approving the drug and its labeling. The Court avoided discussion of this aspect of the trial court's proceedings, and thereby avoided having to distinguish the analysis in *Wyeth* from *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000). In *Geier*, the Supreme Court held that a plaintiff was preempted from bringing a state tort claim that would effectively eliminate one of the options from the menu of choices for window glazing design available under the Federal regulations. This argument should preempt a similar claim in a pharmaceutical case where a plaintiff alleges that an FDA-approved method of administration should be forbidden.
11. *Wyeth*, No. 06-1249, slip op. at 8.
12. James M. Beck and Mark Heremann, Drug and Device Law Blog, *Wyeth v. Levine and the End of Deregulation*, March 5, 2009 (available at http://druganddevicelaw.blogspot.com/2009/03/wyeth-v-levine-and-end-of-deregulation.html.)
13. GPhA Statement Regarding Hearing on "Protecting Consumer Access to Generic Drugs Act of 2009," March 31, 2009. Available at http://www.gphaonline.org/media/press-releases/2009/gpha-statement-regarding-hearing-%E2%80%9Cprotecting-consumer-access-generic-drugs.
14. Available at http://www.abanet.org/publiced/preview/briefs/pdfs/07-08/06-1249_ PetitionerAmCuGenPharmAssoc.pdf.
15. *See* 21 U.S.C. § 355(j)(2)(A)(iv). *See also* 21 C.F.R. § 314.92(a)(1).
16. *See* 21 U.S.C. § 355(j)(2)(A)(v).
17. 21 C.F.R. § 314.150(b)(10).
18. The FDA's position on *See Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices—Proposed Rule*, 73 Fed. Reg. 2848, 2849, n. 1, (Jan. 16, 2008).
19. *Riegel v. Medtronic*, 128 S. Ct. 999 (2008).
20. *See* Paul Halpern, *Supreme Court Decision May Not Shield Medtronic Sprint Fidelis from Legal Action*, (February 24, 2008), http://www.lawyersandsettlements.com/articles/10038/medtronic-decision.html; Jacqueline Bell, *High Court Aims to Alter Product Liability Landscape*, (February 26, 2008), http://productliability.law360.com/Secure/printview.aspx?id=48015
21. *See* Young, Donna, BioWord Today, *Washington Actions Loaded with Implications for Biotech*, vol. 20, issue 44 (March 9, 2009).
22. *Id. See also* H.R. REP. NO. 111-1346 (2009)
23. Medical Device Safety Act of 2009, H.R. 1346, 111th Cong., 1st Sess. (2009).

SUMMARY

Branded drug makers may have no choice but to rely upon this overtaxed resource to provide support for prospective preemption arguments. Unless the FDA develops a process