

November 2013

Practice Group:

FDA

Health Care

New FDA Rule on Drug Labeling May Mean Increased Exposure and an Uncertain Path for Generic Pharmaceutical Manufacturers

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Litigation over the labeling of pharmaceuticals dates back to the mid-1800s.¹ In only the last five years, however, two watershed decisions by the United States Supreme Court have established clear, albeit controversial, boundaries for lawsuits challenging the labeling for prescription drugs. In the 2009 case *Wyeth v. Levine*,² the Court ruled that federal drug labeling regulations did not preempt a state-law “failure to warn” claim that a brand drug’s labeling did not contain an adequate warning. Two years later, in *PLIVA, Inc. v. Mensing*,³ the Court reached the opposite conclusion with respect to state tort claims alleging inadequate labeling of generic medicines, holding in a 5-4 decision that such claims were preempted by the federal prohibition on changes to generic drug labels.⁴ *Mensing* turned on the difference between the ability of holders of a new drug application (“NDA”) – to approve a new pharmaceutical for sale and marketing in the United States – and an abbreviated new drug application (“ANDA”) – for approval of a generic drug product – to independently change product labeling. The Court has recently attributed the precarious position of ANDA holders fighting labeling claims to “Congress’ decision to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying either the drugs’ compositions or their warnings.”⁵

Responding to the line drawn by *Wyeth* and *Mensing*, the U.S. Food and Drug Administration (“FDA”) announced on November 8, 2013 that it would issue a proposed rule allowing manufacturers of generic medications to unilaterally update product labeling with newly-acquired safety information in the same way as brand companies.⁶ Such a move would do away with the legal distinction on which *Wyeth* and *Mensing* were decided and almost certainly resurrect once-dead state law failure-to-warn claims across the country, opening up generic drug makers to greater legal liability. We analyze below the legal landscape following *Wyeth* and *Mensing* and how the FDA’s rule change would shift it.

A. Drug labeling claims after *Wyeth* and *Mensing*

Wyeth involved common-law negligence and strict-liability claims under Vermont law against the manufacturer of Phenergan, a brand-name antihistamine used to treat nausea that can be administered intravenously.⁷ Phenergan’s labeling was alleged to have been defective

¹ See, e.g., *Thomas v. Winchester*, 6 N.Y. 397, 397 (1852).

² 555 U.S. 555, 581 (2009).

³ 131 S. Ct. 2567, 2581 (2011).

⁴ See *id.*

⁵ See *Mut. Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466, 2480 (2013).

⁶ “FDA takes action to speed safety information updates on generic drugs,” (Nov. 8, 2013), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm374171.htm>.

⁷ See *Wyeth*, 555 U.S. at 558-59.

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because it failed to instruct clinicians to use a lower-risk method of intravenous administration (“IV-drip”) instead of the higher risk method (“IV-push”).⁸ The Supreme Court agreed to hear *Wyeth* to resolve “[t]he question [of] . . . whether the FDA’s drug labeling judgments preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.”⁹

In a 6-3 decision, the Court’s majority found no conflict between drug labeling requirements imposed under Vermont and federal law because, here, “it was physically possible for Wyeth to comply with a state-law requirement to provide stronger warnings on Phenergan about the risks of the IV-push administration method while continuing to market Phenergan in compliance with federal law.”¹⁰ In particular, the FDA’s “changes being effected” (“CBE”) regulation,¹¹ the Court reasoned, “permitted Wyeth to unilaterally strengthen its [IV-push administration] warning, and the mere fact that the FDA approved Phenergan’s label does not establish that it would have prohibited such a change.”¹²

Mensing involved claims under Minnesota and Louisiana law that the package insert for the generic drug metoclopramide, a drug commonly used to treat digestive tract problems, failed to adequately warn that long-term use could cause tardive dyskinesia, a severe neurological disorder.¹³ The Court distinguished *Mensing* from *Wyeth* based on the different federal drug labeling duties applicable to brand-name and generic drug manufacturers.¹⁴ “A brand-name manufacturer seeking new drug approval [i.e., an NDA applicant] is responsible for the accuracy and adequacy of its label. . . . A manufacturer seeking generic drug approval, on the other hand, [i.e., an ANDA filer] is responsible for ensuring that its warning label is the same as the brand name’s.”¹⁵ *Mensing* posed the question of whether and to what extent generic manufacturers could lawfully change their labels following initial FDA approval.¹⁶

⁸ See *id.* at 560.

⁹ See *id.* at 563 (internal quotations omitted).

¹⁰ See *id.* at 591-92.

¹¹ For most substantive changes to product labeling, a drug application holder is required to seek and obtain FDA approval for the change. See 21 C.F.R. § 314.70(b). The CBE regulation, however, permits certain labeling changes to be made effective upon the FDA’s receipt of a supplement containing the new information, including

(A) [t]o add or strengthen a contraindication, warning, precaution, or adverse reaction . . . (B) [t]o add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage; (C) [t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product; (D) [t]o delete false, misleading, or unsupported indications for use or claims for effectiveness; or (E) [a]ny labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

See 21 C.F.R. § 314.70(c)(6)(iii).

¹² See *Wyeth*, 555 U.S. at 573.

¹³ See *Mensing*, 131 S. Ct. at 2572-73.

¹⁴ See *id.* at 2574. The Court recognized “that the federal statutes and regulations that apply to brand-name drug manufacturers are meaningfully different than those that apply to generic drug manufacturers,” and that “the special, and different, regulation of generic drugs [has] allowed the generic drug market to expand, bringing more drugs more quickly and cheaply to the public.” See *id.* at 2582.

¹⁵ See *id.* at 2574 (citation omitted). The Federal Drug Price Competition and Patent Term Restoration Act and its implementing regulations require that abbreviated new drug applications for generic drugs contain “information . . . insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the [brand] drug referred to in the application” See 21 U.S.C. § 355(j)(4)(G); compare 21 C.F.R. § 314.94(a)(8)(iii) (requiring “[a] statement that the applicant’s proposed labeling . . . is the same as the labeling of the reference listed drug . . .”), with 21 C.F.R. § 314.127(a)(7) (“FDA will refuse to approve an abbreviated application for a new drug . . . for any of the following

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The Court held they could not and, accordingly, it decided, “[i]t was not lawful under federal law for the [generic] [m]anufacturers to do what state law required of them.”¹⁷ In other words, while

state law imposed on the [m]anufacturers a duty to attach a safer label to their generic metoclopramide[,] [f]ederal law . . . demanded that generic drug labels be the same at all times as the corresponding brand-name drug labels. Thus, it was impossible for the [m]anufacturers to comply with both their state-law duty to change the label and their federal law duty to keep the label the same.¹⁸

Addressing the broad preemptive scope of *Mensing*, a plurality of the Court stated that “different federal statutes and regulations may, as here, lead to different pre-emption results,” but that “it is not this Court’s task to decide whether the statutory scheme established by Congress is unusual or even bizarre.”¹⁹ The Court would not create similar preemption rules across the dissimilar statutory schemes applicable to brand and generic drug approval but reminded that “Congress and the FDA retain the authority to change the law and regulations if they so desire.”²⁰ Enter the FDA.

B. “Leveling the playing field”

“As a result of the decisions in *Wyeth v. Levine* and *Pliva v. Mensing*,” the FDA acknowledges, “an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and thus access to the courts is dependent on whether an individual is dispensed a brand name or generic drug.”²¹ The agency claims *Mensing* “alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date.”²²

Discussing the proposed rule last week, the head of the FDA’s Center for Drug Evaluation and Research, Janet Woodcock, told *The New York Times* that “with the generic industry having grown up, most people are taking generic drugs It’s really time to level the playing field.”²³ To accomplish this, the FDA proposes to “revise and clarify procedures for [all new drug] application holders to change the labeling of an approved drug or biological product to reflect certain types of newly acquired information in advance of FDA’s review of

reasons . . . (7) Information submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application”).

¹⁶ See *Mensing*, 131 S. Ct. at 2574.

¹⁷ See *id.* at 2577.

¹⁸ See *id.* at 2578.

¹⁹ See *id.* at 2582 (internal quotations omitted).

²⁰ See *id.*

²¹ See 78 Fed. Reg. 67985-02, 67988 (Nov. 13, 2013).

²² See *id.* at 67988-89.

²³ Katie Thomas, Label Updates May Be Allowed for Generics, N.Y. TIMES, Nov. 8, 2013, available at http://www.nytimes.com/2013/11/09/business/fda-proposes-letting-generic-drug-companies-alter-labels.html?_r=1&.

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the change through a CBE-0 supplement.”²⁴ In particular, the agency’s proposed revisions to the regulations implementing the rules for post-approval labeling changes under the Federal Food, Drug, and Cosmetic Act, if adopted, would

- (1) enable an ANDA holder to submit a CBE-0 supplement for generic drug labeling that differs from the labeling of the reference listed drug (“RLD”), e.g., the approved brand equivalent; and
- (2) establish that the labeling criteria in § 314.70(c)(6)(iii) apply equally to NDA and ANDA holders.²⁵

In the event of a labeling update, the rule would require an ANDA holder to provide notice of the proposed change to the NDA holder for the RLD at the same time that the supplement to the ANDA is submitted to the FDA.²⁶ “This proposal would ensure that the NDA holder for the RLD is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.”²⁷ The rule would not alter the obligation of all NDA and ANDA holders to conduct surveillance, evaluation, and reporting of postmarketing adverse drug experiences and to propose revisions to product labeling where appropriate. The above changes, the FDA says, “would create parity between NDA holders and ANDA holders with respect to submission of CBE-0 supplements for safety-related labeling changes based on newly acquired information” and improve “communication of important drug safety information to prescribing health care providers and the public”²⁸

C. Concluding thoughts: look behind the curtain

The FDA’s proposed rule change seeks to put brand and generic drug manufacturers on equal footing in order to promote up-to-date drug product labeling with important, newly acquired safety information. But there clearly is more to the rule than its stated public health goals.

The rule, first, will have the intended effect of eliminating the shield to liability established by *Mensing* for failure to make safety label changes. The FDA advises that “[i]f this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs.”²⁹ Reviving these claims inevitably will subject generic drugs previously “out of bounds” to new labeling suits, begging the question of whether, as a practical matter, generic labeling would in the future be influenced in some measure by the looming threat of legal challenges.

Also problematic – for manufacturers, prescribers, and consumers alike – would be disagreements among multiple drug application holders, be they NDAs or ANDAs, over the interpretation of postmarketing safety data and whether and when they warrant a label change. As the FDA points out, “decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree,

²⁴ See 78 Fed. Reg. at 67985; see also footnote 11, *supra*. A “CBE-0 supplement” is a CBE submission that is effective upon receipt by the FDA, as opposed to a “CBE-30” submission, which becomes effective 30 days after the FDA’s receipt of the submission. Compare 21 C.F.R. § 314.70(c)(6), with (c)(1).

²⁵ See 78 Fed. Reg. at 67989; see also footnote 11, *supra*.

²⁶ See 78 Fed. Reg. at 67986.

²⁷ See *id.*

²⁸ See *id.* at 67989; 67996.

²⁹ See *id.* at 67989.

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and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information.”³⁰ Unmooring a generic drug’s labeling from that of the bioequivalent RLD, the FDA concedes, may lead to differences in safety-related labeling.³¹ This is especially true in a situation where multiple ANDA holders submit CBE-0 supplements with labeling changes that differ from each other and from the RLD.³²

Needless to say, confusing or inconsistent labeling for therapeutically equivalent medicines could pose serious health risks for consumers and sow confusion among drug firms, pharmacy providers, and health care practitioners. Those risks would be exacerbated if, as the FDA predicts, “health care practitioners are unlikely to review product labeling for each of the generic drugs that may be substituted for the prescribed product when making treatment decisions with their patients based on the balance of potential benefits and risks of the drug product for that patient.”³³ To require or expect otherwise, meanwhile, may frustrate the longstanding public policy of reducing health care costs by promoting generic substitution by health care providers. Allowing the labeling for a generic drug and its brand equivalent to diverge, even temporarily, thus presents potentially serious health and economic consequences.

A rule permitting ANDA holders to update product labeling irrespective of whether the revised labeling differs from that of the RLD seems to be at cross-purposes with the “federal duty of ‘sameness’” recognized in *Mensing* and by the FDA.³⁴ Perhaps more fundamentally, it calls into question the judgment by Congress decades ago that proof of bioequivalence was sufficient for the FDA to approve the manufacture (including labeling) and sale of new generic drugs. The safety and business concerns raised by the November 13 proposed rule undoubtedly will generate robust public discussion, making the rule’s final provisions a mystery well worth monitoring. The public comment period for the proposed rule closes January 13, 2014.

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³⁰ See *id.* at 67991.

³¹ See *id.* at 67989.

³² See *id.*

³³ See *id.*

³⁴ See *Mensing*, 131 S. Ct. at 2574-75 (“The FDA . . . tells us that it interprets its regulations to require that the warning labels of a brand-name drug and its generic copy must always be the same – thus, generic drug manufacturers have an ongoing federal duty of ‘sameness.’”).

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