FDA Proposes Significant Changes to Generic Drug Labeling Requirements, Which If Adopted, Will Likely Eliminate the Preemption of State Failure-To-Warn Claims For Generic Drug Companies

William H. Kitchens

On November 13, 2013, the U.S. Food and Drug Administration (FDA) published a proposed rule that will require generic drug firms to update the labeling of their drugs in light of new safety risks even though the labeling of the reference listed drug (RLD) for those products has different warnings, precautions, adverse reactions, contraindications and other information.[1] If adopted, the rule change would likely negate a recent U.S. Supreme Court opinion finding that state failure-to-warn claims with respect to generic drugs are preempted by federal law.

Background

Currently, FDA regulations do not permit the holder of an approved abbreviated new drug application (ANDA) to change its labeling to add new safety information until the brand name company that holds the new drug application (NDA) for the RLD modifies its labeling.

The rationale for the requirement is to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. Similarly, this restriction prevents generic drug manufacturers from minimizing safety risks associated with a drug. But, this practice has also meant that generic drug manufacturers, who are aware of safety risks not currently reflected in the labeling of the RLD, have been unable to update their own labeling independently.

Whether ANDA holders should be allowed to use revised labeling that differs from the RLD has been the subject of much debate., especially as a result of recent U.S. Supreme Court opinions establishing different duties to warn for brand and generic manufacturers. In the 2009 case of *Wyeth v. Levine*,[2] the Supreme Court held that the Federal Food, Drug, and Cosmetic Act (FDCA) does not generally preempt state-law failure to warn claims against manufacturers of brand name drugs. Two years later in *Pliva v. Mensing*[3], the Court reached the opposite result by noting that the FDCA generally prohibits generic manufacturers from unilaterally changing their drug labels to strengthen warnings or to add risk information and instead requires the labeling of generic drugs to conform strictly to that of the brand name RLD. But, importantly, the Court acknowledged that "Congress and the FDA retain the authority to change the law and regulations if they so desire."[4]

As a result of these two decisions, an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and in turn, access to the courts seemed to turn on whether an individual was dispensed a brand name or a generic drug. In the wake of these decisions and the capture of an increasing share of market by generic drugs, consumer advocates and some members of Congress argued that consumers could not be adequately protected if generic manufacturers were under no obligation to warn them. Moreover, critics of this judicial dichotomy argue that it robs generic drug manufacturers of any incentive to conduct robust postmarketing surveillance, evaluation, and reporting, and negates the motivation to ensure that the labeling for their drugs is accurate and up-to-date—a requirement that is fundamental to the statutory mandates of the FDCA and FDA regulations.

1 78 Fed. Reg. 67,985-67,999 (Nov. 13, 2013).
2 555 U.S. 555 (2009).
3 131 S.Ct. 2567 (2011).
4 Id. at 2582.

Key Elements of the Proposed Rule

The proposed rule provides that when an ANDA holder has "newly acquired information" that presents "sufficient evidence of a causal association" between an unlabeled warning and the approved generic drug, the generic manufacturer must submit a Changes Being Effected (CBE-0) supplement to its ANDA and immediately implement the changed labeling. FDA explained its rationale by noting:

> We are proposing to change our regulations to expressly provide that ANDA holders may distribute revised labeling that differs from the RLD upon submission of a CBE-0 supplement to FDA. FDA's proposed revisions to its regulations 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. This proposal is also intended to ensure that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements.[5]

Moreover, the agency noted 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."[6]

FDA's intent is to permit differences to exist between the labeling of the NDA holder and the ANDA holder on a temporary basis. Under the proposed rule, the official approval of the change initiated by the generic drug would be deferred until the corresponding brand name drug has submitted and secured approval of the labeling change originally initiated by the generic.

While the proposed rule does allow generic drug labeling to differ, at least temporarily, from the branded drug, ANDA holders would be required to send the NDA holder both the labeling change and a copy of the information supporting the change (with any personally identifiable information redacted). This requirement would be waived if the original NDA has been withdrawn. Any changes ultimately approved by FDA would affect both the generic and the RLD holders' labeling. The agency stated it would create a FDA Web page dedicated to posting information about pending CBE-0 labeling supplements for safety-related labeling changes and noted that other changes could be submitted using a prior approval supplement (PAS). This is intended to enhance transparency and facilitate access by healthcare providers and the public to newly acquired information about important drug safety issues so that this information may be used to inform treatment decisions.

Open Issues

FDA acknowledges that there may be potential confusion if multiple generic manufacturers submit CBE-0's at the same time for different reasons. In such situations is there significant potential that healthcare providers may opt to ignore multiple notifications about pending changes, and if so, how should this problem be addressed?

The proposed rule does not explain what will happen if a generic drug manufacturer is made aware of a safety-related issue, petitions FDA to change the label, but FDA refuses. Will this make the generic manufacturer subject to failure-to-warn claims, or would the federal preemption standard under *Pliva* stand?

Although evidence certainly shows that new information on a drug's safety does arise years after FDA approval, it remains to be seen how often relevant "new" safety information will first be detected by generic manufacturers.

The proposed rule, if adopted, will likely eliminate the preemption of failure-to-warn claims with respect to generic drugs. This is because the reasoning in *Pliva* will no longer be valid as generic drug companies, like brand name companies, will be required to change their drug labels to strengthen warnings independently when they become aware of safety risks not currently reflected in the labeling of the brand name drug. Whether the negation of the *Pliva* holding will also reduce preemption with respect to design defect claims, as addressed by the Supreme Court earlier this year in *Mutual Pharmaceutical*, will likely remain an open question until further examination by lower federal courts and perhaps,

5 78 Fed. Reg. 67989 (Nov. 13, 2013).
6 Id. It should be noted that this reference appears to be limited to failure-to-warn warning claims and may not reduce preemption with respect to design defect claims as seen in the Supreme Court's recent decision in *Mutual Pharmaceutical Co. v. Bartlett*,133 S.Ct. 2466 (2013).

ultimately by the Supreme Court again. It is important to recognize that the Court's decision in *Mutual Pharmaceutical* was not based merely on the inadequacy of the generic drug's labeling. As the majority opinion states "the FDCA requires a generic drug to have the same active ingredients, route of administration, dosage form, strength, and labeling as the brand-name drug on which it is based." Consequently, whether generic drug manufacturers may continue to argue that their legal duty not to change a drug's design triggers preemption in state law design defect cases remains unanswered by the proposed rule.

Finally, will the proposed rule generate more questions concerning potential differences between the generic and the RLD? FDA has had to address such situations recently, resulting in several generics being withdrawn from the market for not being bioequivalent.

Comments on the Proposed Rule

Interested persons may submit comments on the proposed rule by January 13, 2014.

Authors and Contributors

William H. Kitchens
Partner, Atlanta Office
404.873.8644
william.kitchens@agg.com

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