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An impossible course: navigating the generic drug label delay

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Executive Summary

In May 2016, the FDA put off until 2017 a decision about a Final rule that would allow generic drug companies to update their labels with new safety information similar to their reference product counterparts. This marks the third time since the FDA proposed the rule that it has been shelved in the face of opposition from the pharmaceutical industry and some lawmakers. The delay, with major ramifications for consumers and industry alike, was initially discovered in an update to a timetable for the rule and officially appeared in a Federal Register Notice in mid-June. The development dismayed consumer groups and representatives for trial lawyers, who had urged the agency to close a legal loophole that prevents patients harmed by generic drugs from suing manufacturers.

Unlike brand-name drug makers, generic drug makers are not permitted to make changes to a drug's label without the FDA's approval unless the brand name drug maker makes the label change first. Instead, generic drug makers must wait for the FDA to order them to change their label. Since the passage of the Drug Price Competition and Patent Term Restoration Act (P.L. 98-417) in 1984, known as the Hatch-Waxman Act, the FDA has approved over 8,000 generic drugs. The Hatch-Waxman Act provides an expedited approval process for generic drugs that have an identical reference listed drug (RLD). As a result, while nearly 9 in 10 prescriptions filled today in the U.S. are for generic drugs, generics account for only 28 percent of drug expenditures.

Two Supreme Court decisions have helped to establish the conflicting division faced by patients and drug makers regarding drug labels. Under the federal Food, Drug, and Cosmetic Act (FDC Act) and the subsequent Hatch-Waxman Act amendments, a generic drug company "may not unilaterally change its labeling or change its design or formulation and cannot be required to exit the market or accept state tort liability." Consequently, a state law is preempted in the event a generic drug manufacturer must take actions to comply with a state law duty. Thus, patients taking a generic prescription drug are unable to recover for alleged injuries from either the brand name or generic drug maker. The brand name drug maker is not liable because it did not sell the drug directly to the patient and the generic drug maker faces the "impossibility" of providing updates to the drug label without direction from the brand name drug maker.

This White Paper provides an overview of the laws and regulations establishing the foundation of drug labels. The White Paper will also discuss the impact of the Supreme Court decisions on consumers' ability to sue a drug maker for its drug labels. Finally, this White Paper examines whether industry pressure or consumer sentiment will carry the day. As the public service announcement from the FDA shown on pg. 2 attests, it may be difficult to get generic drug approval, but as follows in this White Paper, generic drug makers are also harder to sue.

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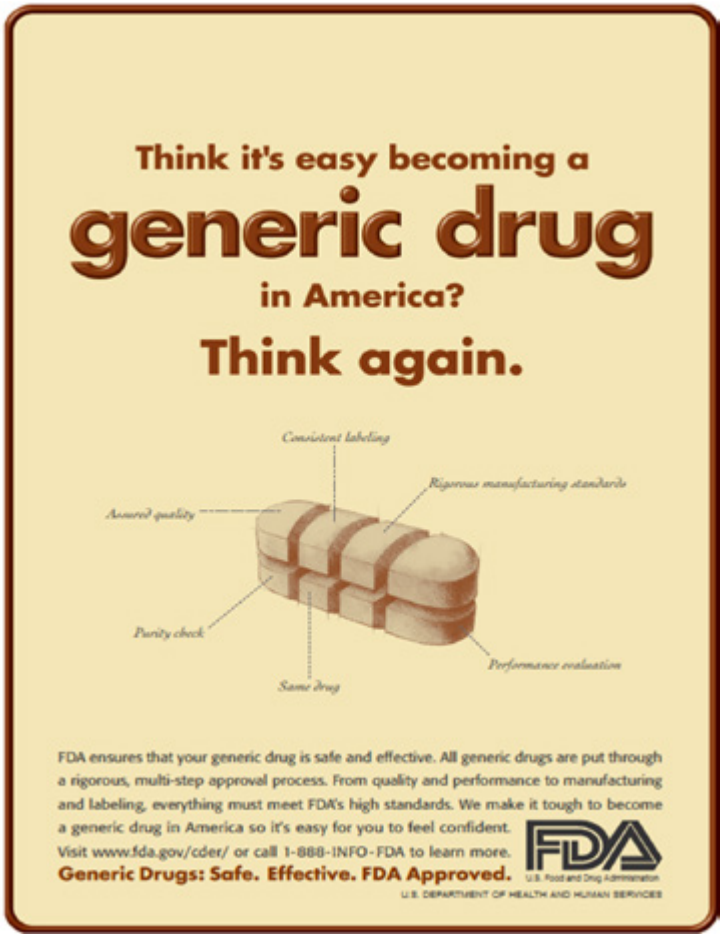
Statutory and regulatory foundation



The FDC Act and the Public Health Service Act (PHS Act) "provide [the] FDA with authority over the labeling for drugs and biological products." The FDA is authorized to enact regulations to facilitate the review and approval of applications regarding the labeling for drugs and biologics. FDC Act Sec. 502(f) states that "a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage, methods, duration of administration, or application." FDC Act Sec. 502(j) mandates that "a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling."

Hatch-Waxman. In 1984, the Hatch-Waxman Act created an abbreviated pathway for generic drug approvals. The generic drug maker must show that the generic drug is the same and bioequivalent to the reference brand name drug. Under the "sameness" requirement, the generic drug must provide the same safety and efficacy. Specifically, the generic drug must demonstrate that it has the identical active ingredient, strength, dosage and administration, and has the same safety label. In the 22 years preceding Hatch-Waxman, only 15 generic drugs had been approved by the FDA. One year after Hatch-Waxman, more than 1,000 abbreviated new drug applications (ANDA) for generic drug approvals were submitted to the FDA.

In the past, the FDA requested that holders of applications for approved products make labeling changes related to safety to address serious risks. The FDA learns of the potential for such serious risks from a variety of sources, including FDA Adverse Event Reporting System (FAERS). In most cases, application holders responded to these requests for labeling changes by negotiating appropriate language with FDA staff to address the concerns and then submitting a supplement or amended supplement to obtain approval of the changes. Negotiations were often protracted, and FDA had few tools at its disposal to end negotiations and require the changes.

Once a drug is approved, its labeling can be updated in four different ways, as explained in 21 C.F.R. Sec. 314.70. If a drug label change is sought to reflect a new indication for use, the drug maker needs to submit a new drug application (NDA) referencing clinical trials data. The drug maker may be required to submit a prior approval supplement (PAS) if FDA requests or requires that a drug label be updated in light of new safety developments, or if the manufacturer (including ANDA holders) proposes other substantial changes to the label. In the third category of drug label updates, if the label change is minor, such as an extension of an expiration dating period for a product, the FDA permits drug makers to report the change in an annual report. In the fourth category of drug label updates known as a "changes being effected" (CBE) supplement, the changes must be submitted to the FDA either (1) immediately or (2) within 30 days prior to a change going into effect in order for the FDA to review. The CBE allows for "moderate changes" to the label.

Currently, for substantive changes to a drug label, a brand name drug maker must submit a PAS and obtain FDA approval for the change to the label. FDA regulations require manufacturers of pharmaceutical and biological products to submit reports of adverse drug experiences that occur after approval. In promotion of

public health, the FDC Act permits immediate labeling changes based on newly acquired safety information about the drug when the manufacturer submits one of the CBE supplements. Thus, under 21 C.F.R. Sec. 314.70(c), a CBE supplement must be submitted for any change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug.

The High Court's road to impossibility

The FDC Act does not create a private cause of action; instead, claims are brought under state law (state statute or common law). Accordingly, if a jury finds that a generic drug's warnings were insufficient and the manufacturer therefore is liable for the injuries, that finding is tantamount to a determination that state law prohibits what federal law already dictates.

In two separate decisions with major implications for prescription drug users, the Supreme Court found that generic drug makers were not liable for failure-to-warn or design defect injuries arising from the use of a generic drug because the current regulatory scheme made it impossible for a generic drug maker to unilaterally change its drug label before the brand name drug maker did so. Under the current regulatory scheme, brand name drug makers have a responsibility to change a label whenever they discover important new information about a drug, and generic manufacturers are required to follow suit.

***Mensing* and failure-to-warn.** In 2011, the Supreme Court ruled in *Pliva v. Mensing* that generic drug makers could not be held liable for failing to warn patients about the risks of their products because the companies had no control over what the warning labels said (see *Supreme Court favors pharmaceuticals in twin decisions*, July 7, 2011). Because it was impossible for the generic drug makers in *Mensing* to "independently do under federal law what state law requires of [them]" – to change the drug label – the Supreme Court concluded that the state law failure-to-warn claims against the manufacturers were preempted.

The issue on appeal in *Mensing* was whether the failure-to-warn claims of two individuals who allegedly suffered neurological disorders as a result of taking generic Reglan (a digestive tract drug) were not preempted. In a 5-4 decision, the Court rationalized that if the generic drug manufacturers had independently changed their labels to strengthen the warnings, they would have violated the federal requirement that generic drug labels be the same as the corresponding brand name drug labels.

The court reasoned that it was impossible to comply with both state and federal law. Additionally, the Court rejected the argument that the manufacturers' preemption defense failed because they failed to request that the FDA change the corresponding label on the brand name drugs. At the time of its ruling, the Supreme Court recognized that its decision made "little sense" to injured consumers who sued generic drug companies. However, Justice Clarence Thomas wrote for the Court, "Congress and the [FDA] retain the authority to change the law and regulations if they so desire."

Mensing struck a blow to litigation recourse for injured consumers by curtailing products liability lawsuits for those who took generic versions of prescription drugs. It appeared doubtful that many state-law-based failure-to-warn claims against generic drug makers would remain viable and this was borne out as numerous circuit courts rejected dozens of lawsuits against generic drug makers, placing patients in a legal limbo about who bore responsibility for their injuries - the brand or generic drug maker (see *Doctor's orders, 'uninfluenced' decision stops off-label suit*, April 10, 2015; *Catch-22 for patients injured by generic drugs*, July 14, 2014; *Court notes unfairness of decision barring consumers' recovery in failure-to-warn suit*, December 3, 2013; *Consumer's lawsuit against generic drug manufacturer preempted by federal law*, June 26, 2013; *Injured patient's claims against generic drug makers were preempted by FDA approval*, June 24, 2013; *Court must evaluate consumer's non-warning design defect and breach of implied warranty claims against generic drug manufacturer for viability*, June 17, 2013; *Warning label claims against generic metoclopramide drug preempted*, April 18, 2013). People who had been harmed by a

> *The Supreme Court recognized that its decision made "little sense" to injured consumers who sued generic drug companies*

generic drug would be unable to sue even as those who had taken the brand-name version of the same product won million-dollar judgments.

The ruling did not affect similar lawsuits against brand name drug makers because they have the ability under federal law to change their warning labels if necessary and, thus, do not face the same impossibility as the generic drug makers. As appellate courts were striking down failure-to-warn based lawsuits against generic drug makers, injured generic drug users attempted with varying success to find ways around the Supreme Court's prohibitions. Not surprisingly, the Court turned its attention towards various design defect based lawsuits.

***Bartlett* and design defect.** In *Mutual Pharmaceutical Co. v. Bartlett*, the Supreme Court considered whether design defect claims under New Hampshire law were preempted and determined that manufacturers do not have the option of redesigning a generic drug because, under the FDC Act's requirements, "were [a manufacturer] to change the composition of its [generic drug], the altered chemical would be a new drug that would require its own NDA [new drug application] to be marketed in interstate commerce" (see *Design-defect lawsuits against generic drug manufacturers preempted by federal law*, June 24, 2013.)

Rejecting the First Circuit's decision that design defect claims against generic drug makers were not preempted by *Mensing* because the drug maker could simultaneously comply with both state and federal law by choosing not to sell the medication altogether, the Supreme Court noted that "New Hampshire law ultimately required [the defendant manufacturer] to change [the drug's] labeling." The Court further explained that the First Circuit's "stop selling" argument "as incompatible with our pre-emption jurisprudence." As Justice Alito explained for the majority, the Court's "pre-emption cases presume that an actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability," for "if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be 'all but meaningless.'"

In light of its previous *Mensing* decision, the Court noted that federal law prevents generic drug manufacturers from changing their labels. As such, the Court concluded that because federal law prohibited the generic drug manufacturer from taking the remedial action required to avoid liability under New Hampshire law, the rule of impossibility preemption applied and design defect claims against generic drug makers generally were preempted. Appellate courts followed suit (see *Generic drug manufacturers may not unilaterally change ingredients, thus preemption of design defect claims affirmed*, May 1, 2014). At the close of the majority opinion, the Court stated that it "would welcome Congress' 'explicit' resolution of the difficult pre-emption questions that arise in the prescription drug context."

Blanket preemption rejected. Not surprisingly, *Mensing* and *Bartlett* did not settle the contentious issue of drug product labeling. In early 2015, the Supreme Court declined to review *Teva Pharmaceuticals USA, Inc. v. The Superior Court of Orange County*, a case that highlighted the extent to which generic drug makers are able to independently and quickly act to provide consumers with risk information. The petition before the Court was whether a generic drug maker should be held responsible for failing to immediately update its product labeling to match the equivalent brand-name medicine.

In a lawsuit involving a California woman who was prescribed a generic version of Fosamax, a brand name drug made by Merck used to treat osteoporosis, the consumer argued that Merck had made a change to Fosamax's drug label; thus, the generic drug makers—Teva Pharmaceuticals and Caraco Pharmaceuticals in this case—were obligated to do the same. Merck had updated the label in 2010 and again in 2011 to warn about the risk of femur fracture with use of Fosamax. Court documents substantiated claims that comparable changes were made to other generic drug labels roughly six weeks after each of the brand name drug label updates.

The generic drug makers maintained they should not be held accountable for a failure-to-warn against any risks because the Supreme Court effectively ruled in both *Mensing* and *Bartlett* that generic drug makers could only make changes after a brand name drug maker did. The generic drug makers contended that federal law preempted state laws governing a failure to warn about risks, and the lawsuit should not have been allowed to proceed. Alleging impossibility, the generic drug makers argued they could not comply with state law because any updates to product labeling would have amounted to a violation of federal regulations that require generic labels to be the same as brand name labels. The California appellate court rejected this idea because the injured consumer's claims relied upon the generic drug makers' failure to update their labels, not that state law required different or stronger drug labels.

Several federal courts have found that *Mensing* does not prohibit these failure-to-update claims. In *Fisher v. Pelstring M.D.*, 817 F. Supp. 2d 791 (D.S.C. 2012), a consumer asserted that the FDA had approved strengthened warnings for the branded drug, but the generic manufacturer failed to incorporate those new warnings into its labeling and that had it done so, the

prescribing physician would have acted differently. *Mensing* did not bar this type of labeling discrepancy because in those circumstances, the generic manufacturer could – and indeed, is required by federal law – to change its labeling too.

Current state of drug labeling

In 2013, the FDA proposed changing the rules to "create parity" between generic and brand name drug makers for how they update their labels, exposing generic companies to legal liability if they failed to properly warn of a drug's risks (*Proposed rule*, 78 FR 67985, November 13, 2013; see *FDA proposal would speed release of safety information on generic drugs*, November 13, 2013). Whether the FDA's response was partly attributable to the public outcry after the Supreme Court's twin decisions shielding generic drug makers in *Mensing* and *Bartlett* or other to less publicly known factors is unknown. What is known is that under the proposal, generic drug makers would for the first time be able to independently update their product labeling with newly-acquired safety information before the FDA's review of the change in the same way brand drug manufacturers do.

Generic drug makers also would be required to inform the new drug application (NDA) holder of the RLD about the change. The brand name drug maker, in turn, would be expected to consider the information provided by the generic drug maker as part of its review and evaluation of adverse drug experience information for its RLD drug. The FDA would then evaluate whether the proposed change is justified and make an approval decision on the generic drug labeling change and the corresponding brand drug labeling change at the same time, so that brand and generic drug products would ultimately have the same FDA-approved prescribing information.

Active versus passive surveillance. Generic drug makers have objected, saying that such a change would create confusion because drugs that were equivalent could carry different warning labels. Additionally, generic drug makers argued that adoption of the proposed rule could allow consumers to file failure-to-warn claims against generic drug makers and negatively impact the viability of the generic drug industry. Cooperating with their brand name counterparts, generic drug makers proposed an alternative, referred to as the Expedited Agency Review (EAR), which would make the FDA the final arbiter of label changes. The EAR would be a four step process that would result in NDA and ANDA holders updating their labels within 30 days of an FDA determination via electronic labeling.

The drug makers argued that only the FDA had the full picture of a drug's safety risks, specifically access to all significant clinical trial data and any associated adverse events; individual companies did not have the same resources and were limited to a certain subset of patients. Under the industry proposal, coincident with implementation of the EAR process, the FDA would issue a guidance document on the identification and submission of "new safety information" to define NDA and ANDA holders' responsibilities in the process. In its request to the FDA, the drug makers noted that the FDA's active surveillance system, known as the Sentinel Initiative, would allow the agency to identify adverse events that may be related to medical products. The drug makers stated that public health could be protected more effectively with the FDA's active involvement as opposed to current passive reporting requirements.

Generic drug makers would for the first time be able to independently update their product labeling with newly-acquired safety information

As noted earlier in this White Paper, the FDA never set a specific introduction date. The delay of the rule until at least April 2017 was accomplished by an FDA update in a regulations timetable and officially published in a follow-up notice in the *Federal Register* in early June (*Notice*, 81 FR 37294, June 9, 2016; *Regulatory agenda sees CMS eye innovation, FDA blink on drug label rule*, June 9, 2016). Not surprising, as this marks the third time that the generic drug label rule has been delayed amid opposition from the pharmaceutical industry and some lawmakers.

Guidance in lieu of rulemaking

On July 8, 2016, the FDA issued draft guidance describing a new process permitting generic drug companies that wish to change or update their drug labels could submit proposed changes for FDA approval, limited to instances in which the innovator of the original brand name drug has withdrawn product from the market for reasons other than safety or effectiveness (see *Approval-withdrawn NDAs complicate label updates*, July

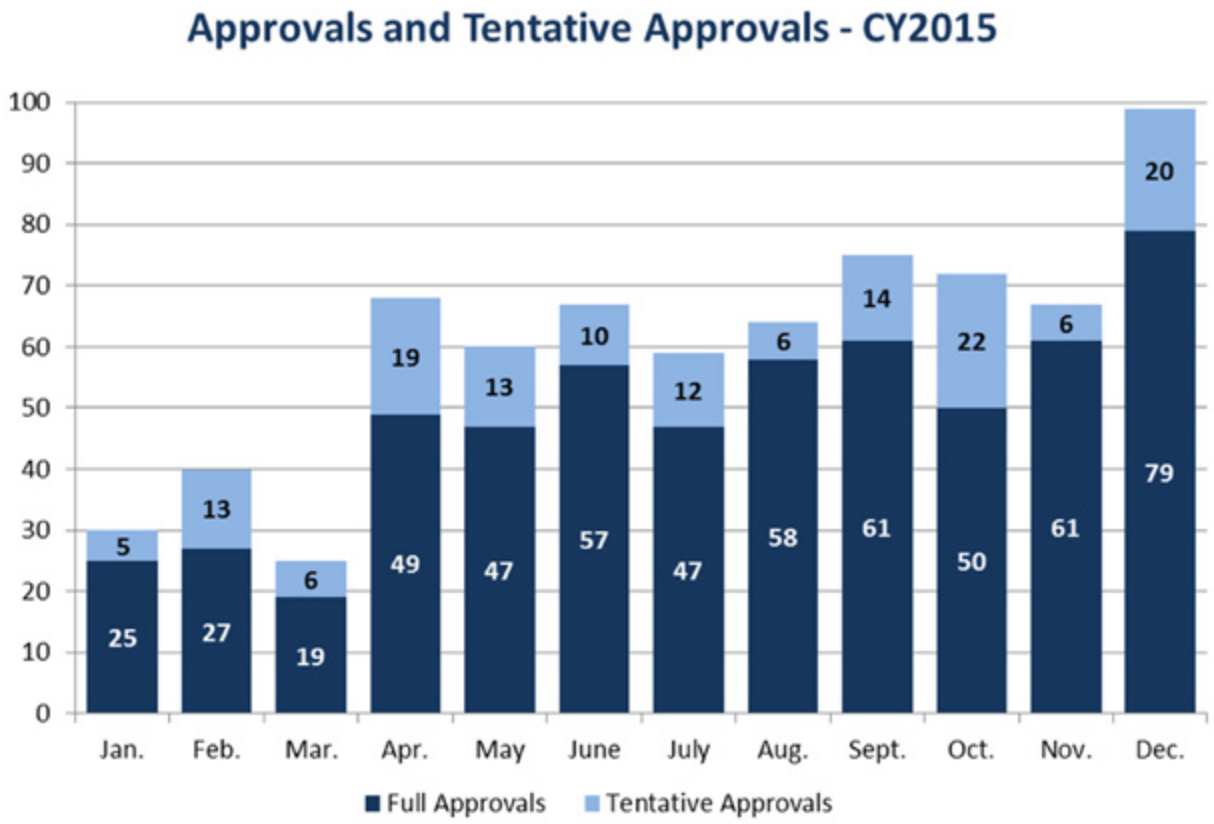
11, 2016). The draft guidance seemed to recognize that when the brand name drug has been withdrawn under these circumstances, "the labeling of those pending or marketed [generic] products may need to be updated to reflect changes that would have been necessary had the [brand name drug] not been withdrawn." Most notably, the draft guidance did not address the status of the overall proposed generic labeling rule originally proposed in November 2013.

Consumers vs. industry

Consumer advocate groups such as Public Citizen were dismayed with the FDA's delay. The group previously petitioned the FDA to revise its generic labeling rules stressing that until the rule was issued the legal loophole preventing patients harmed by generic drugs from suing drug makers would continue. The consumer advocates are upset by the delay and see a growing danger to public safety as generics take over the market, noting that several hundred drugs are now sold only by generic drug makers, who are only offered nonbinding recommendations to change or update their drug labels as described in the FDA's draft guidance. According to the FDA's Office of Generic Drugs (OGD) Annual Report for 2015, generic drug prescriptions comprised 88 percent of the pharmaceutical market; in effect, 88 percent of people prescribed generic versions of prescription drugs are unable to rely on tort-based remedies for injuries caused by the generic drug use. The OGD awarded 580 approvals and 146 tentative approvals in 2015. This total includes 99 approvals and tentative approvals in December 2015, which is the most approvals and tentative approvals granted in a single month since the start of the generic drug program.

These advocacy groups argue that even if generic drug makers discover dangerous aspects to their drugs that there is no obligation to report or warn users of the dangers. Taking it a step further, some groups have warned that when there is no liability, there is no incentive to protect the public's health. For their part, generic drug makers have been battling the FDA over concerns that they will face an untold number of lawsuits filed by consumers who claim they were harmed by the medicines if consumer groups are successful.

The Generic Pharmaceutical Association (GPhA), an industry trade group, argues that the added regulatory requirements and litigation costs could eventually add $4



billion to the nation's health care bill. According to the industry group, the rule would create confusion if only some generic drug makers adopt language about a side effect, leading to vastly different labels. Lobbying by industry groups has not gone unnoticed by Congress. A month before the FDA issued its delay, the House Appropriations Committee proposed a spending bill that would prevent the FDA from using funding to enact the rule this year.

As such, attorneys representing consumers injured by generic drug use are relying upon alternate cause of action arguments — some of which are making headway in the courts. For example, in the multidistrict testosterone replacement therapy litigation, the federal court reconsidered a previous ruling to allow the litigation to resume based on fraudulent off-label marketing rather than design defects and failure to warn (see *Preemption does not prohibit state off-label promotion claims*, March 9, 2016). Albeit found in a limited number of cases, some consumers have been successful in using the "innovator liability theory" to proceed with lawsuits.

Caveat innovator and liability

Innovator liability holds brand name drug makers responsible for injuries caused by a generic drug's warnings on the classic tort principle of foreseeability of harm. In other words, the brand name drug makers know that generic versions will have identical warnings and know that many consumers will ultimately use the generic version, thus it is foreseeable to the branded manufacturers that consumers of generic products will be injured by any failure to warn on its part.

Foreseeable reliance. Prior to *Mensing*, a California appellate court had found in *Conte v. Wyeth, Inc.*, that brand name drug makers could be held responsible for injuries to a generic drug user. The court found that because generic and brand name drugs were required to be identical, a physician's reliance on the brand name drug's warnings when prescribing the generic version was foreseeable. It was also foreseeable that a pharmacist would substitute a generic for a brand name drug as allowed or required by state law or insurance plan. Thus, the court concluded a brand name drug maker could be held responsible for injuries caused by a generic drug.

Similarly, the Alabama Supreme Court decided in *Wyeth, Inc. v. Weeks*, that Wyeth, the brand-name manufacturer of Reglan®, could be held liable for its failure to warn a patient about risks related to the long term use of Reglan's generic equivalent (see *'Innovator liability' may leave brand manufacturer liable for injuries caused by generics*, August 18, 2014). The Alabama high court, in a self-proclaimed narrow holding, decided that the highly regulated prescription drug industry gave rise to unique circumstances where a brand-name drug manufacturer retained a duty to warn consumers of risks in its competitor's product, contrary to that of manufacturers in other industries.

In its first attempt at answering the question, the Alabama Supreme Court reasoned that Wyeth could be held liable by a patient who used a generic version of the drug because brand name drug makers retained a duty to warn physicians about risks related to the brand-name version of the drug, which carried over to generic labels, (see *Liability of brand name drug maker for failure to warn physicians may extend to consumers of generics*, January 16, 2013). On application for rehearing, the Alabama high court was asked to answer the question again. On its second look at the issue, with a narrower focus, the Alabama court reached the same conclusion.

Added regulatory requirements and litigation costs could eventually add $4 billion to the nation's health care bill

Weeks represented the only instance in which a state high court determined that the brand name drug maker could be liable for injuries caused by a generic version of the drug that the innovator did not manufacture because of its primary labeling responsibilities. Alabama set itself apart from the vast majority of jurisdictions, which have rejected the theory of innovator liability.

The following year, a federal court dismissed state tort claims against the generic drug manufacturers based on federal law preemption (see *Claims against generic Reglan® manufacturers preempted by federal law*, August 4, 2015). The complaint had alleged that the brand name drug makers failed to communicate any updated information to the prescribing physician and, therefore, the court joined with other courts around the country in finding that the state tort claims were preempted by federal law. As noted earlier, under Hatch-Waxman, generic drug makers are not required to demonstrate that their labeling is accurate or adequate; they are only required to ensure that their warning labels are identical to the corresponding brand name drug labels.

In Alabama, business interests vigorously lobbied the state legislature to reverse the state supreme court's position, and in 2015 a majority of the state's lawmakers agreed, passing legislation to close lawsuits based on innovator liability.

Conclusion

At this point in time with a projected issuance date of spring 2017, both consumers and industry alike are left in limbo as to the FDA's eventual decision on the generic drug label rule. It is evident that the loophole created by Supreme Court jurisprudence will only be addressed by passage of either the FDA generic drug label rule or congressional legislative action, neither of which appears to be imminent.

Mensing foreclosed state failure to warn cases against generic drug manufacturers. Since that decision, both the federal government and consumers injured by generic drug use have attempted to counter the ruling. While generic drug makers have been largely successful in pushing back efforts to bypass *Mensing*, the FDA's generic drug label rule was widely viewed as a return to pre-Mensing. In essence, brand and generic drug makers would be equally at risk for failure to warn claims. Not surprisingly, more litigation can be expected if the FDA rule is promulgated. In the interim, consumer and industry groups will watch developments closely.