Brand and Generics Companies Unite to Pressure FDA
They Want the Agency to Drop Its Safety-Label Plan and Adopt Their Alternative

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one wouldn’t think that the idea of drug companies red-flagging safety concerns about a product would be that controversial in this day and age. Yet the Food and Drug Administration (FDA) has encountered stiff opposition in its effort to allow generic drug companies to change their labels quickly, without prior agency approval, when they discover adverse effects in patients once their generic reaches the market. Brand-name drug manufacturers can do that via submission of a “changes being effected” (CBE) supplement, but generics manufacturers cannot. However, once the FDA reviews and approves the CBE supplement, all drug manufacturers selling that product must change their labels. That FDA review can take nine to 12 months, according to David Gaugh, Senior Vice President for Sciences and Regulatory Affairs of the Generic Pharmaceutical Association (GPhA).

A 2013 FDA proposal to put generics companies on the same “automatic” footing as brand-name companies1 has raised all sorts of objections, from patent-holders and generics companies alike, on both ostensibly substantive and legal grounds. Gaugh says the proposed changes exceed the FDA’s authority and are contrary to provisions of the Federal Food, Drug, and Cosmetic Act. “The proposed rule would contradict Hatch-Waxman’s goal of encouraging competition, by driving competitors out of the market,” he adds. Generics companies are most worried about product liability lawsuits against them if they suddenly get the responsibility of unilaterally changing safety labels once adverse information about a drug they sell comes into their possession. Brand-name companies can be sued, and frequently are, for not adding new safety warnings to labels quickly enough.

Product liability suits are costly to defend, even when the company wins. In June 2015, for example, a state court in Philadelphia sided with Pfizer in a trial in which its labeling of Zoloft (sertraline) was at issue. Plaintiffs argued that Pfizer had failed to disclose that pregnant women taking Zoloft could deliver children with birth defects. The Zoloft label warns physicians to weigh the benefits of using the medication against its risks to pregnant women before prescribing it. Pfizer lost patent protection in 2006, and sertraline is now available in generic form.

Possible customer confusion also worries generics companies. Theoretically, numerous generics companies could update their labels with different safety warnings simultaneously if the FDA proposal becomes final. “We believe the methodology FDA is proposing with multiple manufacturers submitting different label changes will ultimately do more harm than good by creating confusion for all stakeholders,” says John Ducker, President and Chief Executive Officer of Fresenius Kabi U.S.A., which specializes in medicines and technologies for infusion, transfu-

Emotions Run High at Public Hearing
The political complexities bedeviling the FDA’s proposal were on full display at the public meeting the agency held on March 27, 2015.2 Six people told heart-breaking stories of children or themselves being hurt by generic drugs.

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Emily Mitchell, a 29-year-old woman from Chattanooga, Tennessee, told of taking fluoxetine, the generic form of Prozac, after being diagnosed with obsessive-compulsive disorder. She continued to take it while pregnant. Her son was born with a congenital heart defect and died in her arms days later. She told the FDA hearing that she had watched a TV commercial while she was pregnant asking viewers whether they had a child with a heart defect, and if so, it might be because the mother had been taking Prozac or fluoxetine during pregnancy. “My heart sank,” she recalled. “I grabbed my medication bottle, and there wasn’t any type of warning on it about taking while pregnant. I want justice, and I want the FDA and all drug companies to put safety first.” Mitchell’s expenses to visit Washington were paid by the American Association for Justice, the professional lobby for trial lawyers.

Two representatives of different groups of African-Americans made conflicting statements. Derrick Humphries represented groups such as the National Association for the Advancement of Colored People and the National Urban League. Maryland State Senator Catherine Pugh is President of the National Black Caucus of State Legislators (NBCSL). Humphries said the FDA’s proposal jeopardizes patient safety, safe access for patients, physicians, pharmacists, and payer accessibility to generic medicines. He favored the PhRMA/GPha alternative. Pugh said Humphries may be correct about the proposed rule limiting minority communities’ access to medications because it may add costs to generic drugs. But Pugh added, “We at NBCSL believe that safety of these drugs trumps costs, and unsafe generic brand-name drugs pose a threat to our communities, as it would others. We at NBCSL support the concept of making safety information for generic drugs available as soon as possible.”

FDA Responds to Supreme Court Decision

The FDA decided to propose the rule after a 2011 Supreme Court decision. The court ruled in \textit{PLIVA v. Mensing}, by a 5–4 vote, that Gladys Mensing could not recover damages for debilitating injuries she received from a drug with an inadequate warning label because her prescription was filled with a generic version of the drug rather than with the brand-name version.4 The court had previously held in \textit{Wyeth v. Levine} that federal law does not pre-empt failure-to-warn claims against brand-name drug manufacturers. The \textit{Mensing} decision created an arbitrary distinction, whereby a court’s ruling on whether or not a consumer can obtain relief turned solely on the happenstance of whether his or her prescription was filled with a brand-name drug or a generic drug.

Brand-name companies have been allowed to make safety changes to their labels since 1985 via the CBE process. In 2013, the FDA proposed to give generics manufacturers the same opportunity by allowing them to file with the agency a CBE-0 supplement. The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the “Highlights of Prescribing Information.”

The proposed rule requires a company with an approved abbreviated new drug application (ANDA)—that is, a generics company—to submit a CBE-0 supplement if the company obtains or receives new information that should be reflected in product labeling to accomplish any of the following objectives:

1. To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under §201.57(c), the requirements for full prescribing information in FDA regulations.
2. To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose.
3. To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product.
4. To delete false, misleading, or unsupported indications for use or claims for effectiveness.

The ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the holder of the new drug application (NDA) for the reference listed drug—that is, the brand-name company—at the same time that the supplement to the ANDA is submitted to the FDA (unless approval of the NDA has been withdrawn). To make the safety-related changes to drug labeling described in a CBE-0 supplement readily available to prescribing health care providers and the public while the FDA is reviewing the supplement, the FDA proposed to establish a dedicated Web page where the FDA would promptly post information about labeling changes proposed in a CBE-0 supplement.

Critics Make Multi-Pronged Attack on Proposal

Criticism of the proposed rule has centered on the possibility of consumer confusion when a generic label differs from the brand-name label. Concerns have also been voiced about higher generic costs, with a consultant to the GPha publishing a controversial study forecasting a $4 billion-a-year hit to consumers. Those increased costs would arise as generics companies passed their expected and actual legal costs to consumers. Product liability suits could result from several scenarios, according to the GPha:

- If the first ANDA applicant’s proposal is accepted, every other ANDA applicant that did not submit its own CBE-0 or that submitted a CBE-0 with different language will be subject to state-law tort suits (including the NDA holder).
- If a proposal submitted by an ANDA applicant following the first ANDA applicant’s submission is accepted, the first ANDA applicant and every other ANDA applicant that did not submit its own CBE-0 or that submitted a CBE-0 with different language will be subject to state-law tort suits (including the NDA holder).
- If the FDA rejects the proposals submitted by all applicants and instead adopts its own language, all applicants will be subject to state-law tort suits (including the NDA holder).
- If each instance, all manufacturers will be subject to state-law tort suits for not making a change earlier.

Candis Edwards, Senior Vice President of Clinical Regulatory Affairs at Amneal Pharmaceuticals, says she is not convinced that the FDA’s proposed rule as it now stands would change some of the outcomes that some consumers have been experiencing. “And so Amneal is taking the position that we actually oppose the proposed labeling rule,” she states. She reiterates a common theme sounded by representatives of generics companies: An active ingredient can be sold in generic form...
by many companies, sometimes as many as 20. Amlodipine has 29 different ANDA approvals listed in the FDA's Orange Book.

Douglas Boothe, Executive Vice President and General Manager for Pharmaceutical Products at Perrigo Corporation, says, “Currently, there are over 300 companies with 15 or more approved ANDAs, some of those ANDAs held by companies marketing over-the-counter [OTC] products.” He wants OTC products removed from the scope of the proposed rule.

Generics companies have procedures for monitoring adverse effects, of course, Marcie McClintic Coates, Vice President and Head of Global Regulatory Affairs for Mylan, Inc., says interpreting post-marketing safety data is complex. It involves analysis of post-approval clinical data, detailed review of adverse drug experience reports, the context of relevant clinical studies, estimates of drug usage, adverse drug experience reporting dates, estimates of background, and rates of the adverse event, among other relevant information. According to Coates:

Generic companies lack access to all of the required data to make a scientifically substantiated label change; although, the rule as written would require generics to unilaterally make label changes and distribute the label before FDA’s review of this comprehensive data. As a result, patient safety would be compromised when generic drug manufacturers distribute revised labeling that also includes risk information that FDA may later determine, based on the full dataset, is not scientifically accurate.

The GPhA–PhRMA alternative would establish defined time parameters for the FDA to act on label changes that are made following the FDA’s receipt and review of new safety information from either an NDA or ANDA holder, or following receipt of data through the sentinel system or any other database that appears to suggest a need for a label change. If the FDA decides a labeling change is warranted, it would notify all NDA and ANDA holders within 15 days, and they would have 30 days in which to issue revised electronic labeling.

Countering Industry Arguments

An economist working for the American Association for Justice disputed the $4 billion estimate of added costs to consumers made by Alex Brill, CEO of Matrix Global Advisors. The FDA contends that although the proposed rule would eliminate the pre-emption of certain failure-to-warn claims with respect to generic drugs, it would nonetheless not result in higher costs to generic manufacturers. “I find these two assertions to be patently inconsistent,” Brill states.

But Frank Ackerman, Senior Economist of Synapse Energy Economics, said the Brill estimate was fundamentally mistaken on three separate grounds: in terms of the understanding of what the cost–benefit analysis should include, in terms of the specifics of the calculation, and in terms of the significance of the calculation were it found to be correct. His major criticism is that Brill based his calculation on what American industry in general spent on product liability insurance in general between 1980 and 1984. “So this is a fresh up-to-the-minute picture of what product liability insurance cost when President Reagan first thought it was morning in America,” Ackerman chides.

Public Citizen’s Health Research Group disputes the contention that generics companies do not have enough information to change safety labels unilaterally, without the FDA’s approval. “You don’t need access to the totality of the data to make important safety updates,” says Michael Carome, MD, Director of the Health Research Group. His group has successfully petitioned the agency to add new safety warnings, including boxed warnings, to the labels of multiple drugs, based on its review of FDA reports and the scientific literature. Its petition to add boxed warnings about the risk of tendon rupture to the labels of all fluoroquinolones, many of which were generic, was based on reports in the FDA Adverse Event Reporting System. “Generic companies have access to that same data,” Dr. Carome states.

The PhRMA–GPhA alternative doesn’t sit well with some groups, either. The Alliance for Justice argues that the alternative would shelter brand-name companies from product liability lawsuits once the first generic competitor enters the marketplace. At that point, changes to either the brand-name or generic label would require prior approval by the FDA. No longer would manufacturers be permitted promptly to update a safety warning in advance of the FDA’s review of the change, irrespective of the critical safety information that the change may provide. So a drug company could defend itself by saying: “The FDA approved our change.”

Even the AARP, which submitted a brief in the 2011 Supreme Court case supporting Gladys Mensing and which believes generics companies should be liable for labeling under state tort law, has problems with the FDA’s proposed rule. David Certner, Legislative Counsel and Legislative Policy Director for Government Affairs, explains the AARP’s concerns:

It is essential for generic drug manufacturers to be able to make appropriate updates to their labeling without having to wait for changes to be initiated by a brand-name drug manufacturer. While the AARP wholeheartedly supports the goal of ensuring new drug safety information is available to consumers as quickly as possible, we do have some concerns that the proposed rule could lead to inconsistent labeling on multiple versions of equivalent drugs for a substantial period of time. The resulting confusion could affect confidence in generic drugs and complicate decision-making conversations between providers and consumers about appropriate drug therapies based on their safety, efficacy and quality.

The AARP’s alliance with the drug manufacturers on this issue probably spells withdrawal of the FDA’s original proposal and issuance of a new proposal that hews closer to what the PhRMA and GPhA have proposed.

REFERENCES