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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
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**ADDITIONAL COMMENTS ON PROPOSED RULE:
“SUPPLEMENTAL APPLICATIONS PROPOSING LABELING CHANGES FOR
APPROVED DRUGS AND BIOLOGICAL PRODUCTS”
RIN 0910-AG94**

Public Citizen, a consumer organization with members and supporters nationwide, submits these additional comments with regard to the proposed rule on supplemental applications proposing labeling changes for approved drugs and biological products, published in the Federal Register on November 13, 2013. As stated in our comments submitted on March 13, 2014, we strongly support the proposed rule, which will enable generic drug manufacturers to revise generic drug labeling through the changes-being-effected (CBE-0) procedures, and we urge the Food and Drug Administration (FDA) to move promptly to finalize the proposal.

These additional comments review the safety problem addressed by the FDA’s proposed rule, explain why the recently proposed industry “alternative” is no alternative at all, rebut some of the industry objections to the rule, and offer some small revisions to strengthen the FDA proposal.

I. The problem

The proposed rule seeks to address a problem: A gap in FDA regulation of prescription drugs poses an unnecessary risk to patient safety.

The FDA reviews, comments on, and helps to revise labeling as part of the drug-approval process, so that the approved labeling accurately warns of known risks posed by use of the product. After the drug is on the market and prescribed to patients, however, new risks often come to light. When that happens, brand-name drug manufacturers have an obligation to revise warnings to reflect the new information. They can do so without prior FDA approval, which enables the information to reach patients and physicians without delay. The FDA did not

originally allow brand-name companies to update labeling without prior approval. The agency formally adopted that change in 1985, *at the behest of the pharmaceutical industry*, which recognized the inefficiency and delay of a system in which the FDA had to pre-approve every safety update. But as the agency has explained, “The CBE-0 supplement procedures originated from a 1965 policy based on FDA’s enforcement discretion regarding certain labeling changes that should be placed into effect ‘at the earliest possible time’.”¹ Thus, for five decades, the FDA has recognized the importance of timely dissemination of new safety information through manufacturer-initiated labeling updates.

The wording of the FDA regulations allowing preapproval safety updates seemed to apply to all prescription drug makers, not to brand-name manufacturers only. However, the FDA has stated that generic drug manufacturers cannot make labeling updates without prior FDA approval. Instead, they can make them only after being informed that the manufacturer of the brand-name equivalent has revised the labeling or if ordered to do so by the FDA.

In 2010, generics captured more than 80 percent of the market within six months of expiration of a brand-name’s patent.² In 2012, 84 percent of prescriptions were filled with generic drugs.³ A 2010 study by the Generic Pharmaceutical Association reported that, in 2009, 32 percent of 4,318 unique drug molecules were sold *solely* as generics.⁴ A 2012 study by the Generic Pharmaceutical Association notes that, for 45 percent of generics sold, no branded product is currently on the market.⁵ The FDA recently estimated the number of generic drugs with unique active ingredients for which the reference listed drug (RLD) is no longer marketed as approximately 420.⁶

Accordingly, although most patients who take prescription medication take a generic, generic drugmakers (with 84 percent of the market) are barred from making the prompt and efficient labeling changes that brand-name manufacturers (with 16 percent) can make. Furthermore, even when the medication is sold only in generic form, generic drugmakers have no duty to inform physicians and patients about newly discovered risks, unless ordered to by the FDA.

What is wrong with that situation? The FDA has been very clear that it does not have the resources to be the first-line monitor of new developments with respect to prescription drugs. For more than 30 years, the industry has not disagreed.

At the same time, new risks often come to light years after a drug first enters the market, including after the drug is sold in generic form. As described in more detail in Public Citizen’s March 2014 comments to the docket, our June 2013 study, which was restricted to a five-year

¹ FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*, Proposed Rule, 78 Fed. Reg. 67985 (Nov. 13, 2013) (quoting FDA, Supplemental New-Drug Applications, 30 Fed. Reg. 993 (Jan. 30, 1965)).

² IMS Institute for Healthcare Informatics, *Declining Medicine Use and Costs: For Better or Worse?* (May 2013); IMS Institute for Healthcare Informatics, *The Use of Medicines in the United States: Review of 2010* at 21 (April 2011) (IMS Report 2011).

³ IMS Report 2011 at 11, 15, 22.

⁴ Generic Pharm. Ass’n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010).

⁵ Generic Pharm. Ass’n, *Generic Drug Savings in the U.S.* at 8 (4th ed. 2012).

⁶ FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, Preliminary Regulatory Impact Analysis* at 9 (2013) (FDA Regulatory Impact Analysis).

period, identified 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added *after* generic market entry. The undisputed fact is that new safety issues commonly arise after generics have entered the market, and that fact underscores the public health imperative of maintaining an incentive for manufacturer surveillance of safety concerns throughout the life of the product. In fact, the FDA’s regulatory impact analysis found that 48 percent of safety-related CBE-0 changes are made for drugs with generic equivalents.⁷

The problem, then, is that shortly after generic drugs enter the market, the brand-name company’s incentive to do the monitoring necessary to identify safety risks and to spend money making labeling changes to disclose those risks drops precipitously. At the same time, because the FDA currently does not allow generic drugmakers to initiate labeling changes and because of the 2011 *PLIVA v. Mensing* decision,⁸ generic manufacturers—despite their dominant market share—have little to no incentive to engage in robust safety surveillance for their products. As a result, new risks may not be brought to the FDA’s attention, and patients and physicians may not be warned until the problem becomes so acute that the FDA eventually identifies it on its own and orders a labeling change.

II. The FDA’s Proposal

To address this problem, the FDA has proposed to allow generic drug manufacturers to revise labeling to add warnings or other newly acquired safety information through a process similar to the one in use for 30 years for brand-name manufacturers, known as the “changes being effected” or CBE-0 process. The proposal would fill the regulatory safety gap by creating a mechanism for generic drugmakers to update drug labeling to provide warnings based on new information. It would give generic drugmakers flexibility, responsibility, and accountability commensurate with their role in today’s prescription drug marketplace. Like their brand-name counterparts, generic drug manufacturers would have the ability to provide prompt safety updates to patients and physicians, subject to FDA oversight and with a procedure in place to ensure that updates are made in a timely manner across the board for all manufacturers of the same drug product. As the FDA concluded in proposing the rule, the rule would increase patient safety, is fully consistent with the sorts of variations between brand-name and generic labeling already built into the regulations, and would not impose burdensome costs on manufacturers.

As one study found, drug manufacturers initiate 58 percent of safety-related label changes and 78 percent of changes to the adverse reaction section.⁹ “Both the FDA and drug sponsors play an important role in the identification of safety issues, which inform FDA’s regulatory actions to protect the public’s health. In addition, the gamut of safety-related drug label changes may continue to take place several years after postmarket approval, emphasizing the importance of continued drug safety surveillance throughout a product’s lifecycle.”¹⁰ The FDA proposal builds on the foundation of joint manufacturer-agency responsibility, extending to generic companies the ability to revise that brand-name companies have had and frequently used—to the benefit of patients—since 1985.

⁷ FDA Regulatory Impact Analysis at 7 (analyzing labeling changes made in 2009 and 2010).

⁸ 131 S. Ct. 2567 (2011).

⁹ Jean Lester, et al., *Evaluation of FDA safety-related drug label changes in 2010*, 22 *Pharmacoepidemiology and Drug Safety* 302, 303, 305 (2013).

¹⁰ *Id.* at 305.

In addition to creating a mechanism for more and prompt safety updates to generic drug labeling, which would have the beneficial effect of reducing patient injury, the proposal would have the benefit of restoring to patients injured by generic drugs the ability to hold the manufacturer accountable to the patient for failure to warn of a known risk. In 2009, relying in part on brand-name manufacturers' authority to make changes through the CBE-0 process, the U.S. Supreme Court held that brand-name manufacturers can be held liable to patients for injuries caused by failure to warn. In 2011, the Court held that generic drug manufacturers cannot be held liable because they have no responsibility for the content of the warnings. By giving generic drugmakers such responsibility, the FDA proposal would restore patients' right to sue, thus creating an incentive for drugmakers to craft and maintain adequate labeling and providing an avenue for a patient to seek compensation when she is injured because a manufacturer failed to update the labeling.

III. The Industry Proposal

In November 2014, the Generic Pharmaceutical Association and the Pharmaceutical Research and Manufacturers of America jointly proposed to the FDA an "alternative" to the agency's proposed rule. The industry alternative, however, would exacerbate, rather than solve, the safety problem that the FDA proposal seeks to address.

The industry proposal would eliminate the CBE-0 option for any drug for which generic equivalents are on the market. After generic entry, not only the generic drugmaker but also the brand-name drugmaker would be barred from initiating labeling changes to warn of new safety information. Instead, a drug manufacturer aware of information that shows a safety update is warranted would be permitted only to inform the FDA, which would then review the information and make a decision whether to order a change within a set period of time. By extending to brand-name manufacturers the existing bar on generic manufacturers' initiating labeling updates, the industry alternative would also presumably (and surely intentionally) have the effect of eliminating failure-to-warn lawsuits against brand-name companies, once a generic equivalent reaches the market.

The industry proposal includes no incentives to push drugmakers to request labeling changes and would eliminate the existing incentive for brand-name manufacturers to engage in robust safety surveillance for their products. With no ability to make changes and no accountability to patients for failing to do so, brand-name companies would have no reason to be vigilant or to encourage the FDA to add new warnings—as we see from the situation with generic manufacturers today. As a result, drug labeling would inevitably have fewer safety updates, thereby leaving physicians and patients in the dark.

The proposal also includes no enforcement mechanism for forcing the FDA to act on a request within a short time period. It is generally very difficult to enforce time limits on the agency, and drugmakers would have no incentive to expend resources pushing the FDA to act on a request. In short, the industry proposal would result in fewer safety updates, more slowly made.

At the same time, it would extend to brand-name manufacturers the generic manufacturers' immunity from liability to patients for failing to update warnings.¹¹

The industry "alternative" is a transparent attempt to minimize manufacturer responsibility for post-marketing vigilance and to enjoy and extend immunity from suit. It does not pretend to address the safety gap—the problem that, after generic entry, the brand-name manufacturer has reduced or no incentive to monitor safety and update labeling, and the generic manufacturer has no responsibility at all for initiating labeling changes to add or revise safety warnings.

IV. Feasibility

The generic drug industry has complained that, because generic drug companies do not perform the clinical trials that support a new drug application and because often one company does not control the entire market for a given product, generic drug companies lack the information needed to update safety warnings. This contention is incorrect.

First, all drugmakers, brand-name and generic alike, are required to do the same pharmacovigilance with regard to their products. Both "have an ongoing obligation to ensure their labeling is accurate and up-to-date," and their products are misbranded when they fail to fulfill this obligation.¹² "[A]ll holders of NDAs, ANDAs, and BLAs are required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA."¹³

Second, the experience of our organization demonstrates the fallacy of the claim that a generic drugmaker lacks sufficient information to initiate safety updates. Public Citizen, of course, does not manufacture or sell any drugs. Yet we have over our 40 years used publicly available information, including adverse event reports available through the FDA and published studies, as the basis for 33 citizen petitions seeking labeling changes. Some petitions sought labeling changes for multiple drugs, including in some cases all drugs within one or more classes. Labeling changes to address the issues we flagged were eventually made for more than 50 drugs addressed in our petitions. In that same time period, we have been unable to find a single instance of a generic drug company petitioning the agency for permission to make a labeling change. Because current regulations give the generic drugmakers no responsibility for labeling, and thus for product safety, those companies therefore appear not even to use available tools to monitor for new safety information.

Given that the FDA proposal is feasible, lawful, and would not cause confusion, the industry's real objection to the FDA's proposal to close the safety gap in drug labeling is plainly that adoption of the proposal would eliminate the broad immunity from failure-to-warn lawsuits bestowed by the U.S. Supreme Court on generic drug manufacturers in June 2011. Indeed, the industry is currently going so far as to argue that a generic drugmaker cannot be held accountable

¹¹ The industry idea apparently addresses two purported concerns that the generic drug industry has pushed to justify its opposition to the FDA proposal: the notion that the proposed rule would result in inconsistent labeling that will confuse physicians, and the argument that the proposed rule would violate a "sameness" requirement imposed by the Hatch-Waxman Amendments. Our March 2014 comments discuss in some detail why neither concern is valid.

¹² FDA, Proposed Rule, 78 Fed. Reg. at 67987.

¹³ *Id.* at 67986 (citing 21 C.F.R. §§ 314.80(b), 314.98(a), 600.80(b)).

for failure to warn of risks even when the drugmaker failed to update its labeling or send a Dear Doctor letter *after* the brand-name manufacturer updated the product labeling, as generic drugmakers are required to do. See *Teva Pharms. USA, Inc., v. Superior Court*, 217 Cal. App. 4th 96 (2013), *cert. denied*, 135 S. Ct. 1152 (U.S. 2015); *Huck v. Wyeth, Inc.*, 850 N.W.2d 353 (Iowa 2014), *cert. denied*, 2015 WL 1400937 (U.S. 2015); *Teva Pharms. USA, Inc. v. Hassett*, 74 A.3d 202 (Pa. Super. Ct. 2013), *pet. for cert. pending*, No. 14-705.

Moreover, the industry’s economic analysis of the proposal is focused entirely on costs related to liability for failure to warn—a telling indication of its motive for opposing the FDA proposed rule. Although the industry has criticized the FDA for not taking potential liability costs into consideration, the FDA has not, to our knowledge, ever considered such costs. For example, when the FDA in 2008 issued a final rule revising numerous aspects of its drug labeling regulations, it stated in a lengthy preamble discussion that it believed the final rule broadly preempted failure-to-warn claims against prescription drugmakers.¹⁴ Such preemption would have constituted a significant change, as litigation by injured patients against drugmakers was common and had been for many decades. Yet the FDA’s economic analysis did not mention costs (incurred or saved) related to potential liability.¹⁵ Similarly, the FDA’s January 15, 2008, proposed rule on Supplemental Applications Proposing Labeling Changes for Drugs, Biologics, and Medical Devices (Docket No. 2008N-0021) stated that the change would have no significant economic impact.¹⁶ Yet the FDA explicitly intended it to bolster an industry argument—then pending before the U.S. Supreme Court and later rejected—that FDA regulation preempted failure-to-warn claims against brand-name drug manufacturers.¹⁷

The FDA was right not to take liability costs into account in the proposed rule for other reasons as well. First, when a patient is injured because a drug did not have adequate warnings, costs are incurred—medical costs, lost earnings, and other costs. If these costs shift from a patient to a drugmaker, or from Medicare (that is, taxpayers) to a drugmaker’s insurance company, the costs do not increase, they only transfer. For this reason, liability costs are not a cost created by the proposal, even if the proposal would result in a transfer of some costs. Second, the purpose of the rule change is to make products safer so that patients are injured less often. If the rule is successful in decreasing injury, costs attributable to injury will decrease not increase.

V. Suggested Revisions

Although Public Citizen strongly supports the FDA proposal, we propose some small adjustments.

First, the proposal is not clear whether manufacturers “may” use the CBE-0 process or whether they “must” use it.¹⁸ The text of § 314.70(c)(6) and proposed (c)(8) also use “may.” We

¹⁴ See 71 Fed. Reg. 3922, 3934-36 (Jan. 24, 2006).

¹⁵ *Id.* 3969-84.

¹⁶ See 73 Fed. Reg. 2858 (Jan. 16, 2008) (proposed rule); 73 Fed. Reg. 49603 (Aug. 22, 2008) (final rule).

¹⁷ See Letter from U.S. Solicitor General to S. Ct., in *Wyeth v. Levine*, No. 06-1249, filed Jan. 16, 2008 (informing Court of proposed rule and stating that it is relevant to issues in *Wyeth v. Levine* and other preemption cases).

note that a different regulation, 21 C.F.R. § 201.57(c)(6), requires application holders to update labeling promptly to include a warning about a clinically significant hazard *as soon as* there is reasonable evidence of a causal association with a drug. The agency’s use of the mandatory “must” in the proposed rule and accompanying commentary reflects that CBE-0 is a way to implement changes that § 201.57(c)(6) requires. In finalizing the rule, however, the FDA should clarify this point.

Second, at the FDA’s public hearing on March 27, 2015, David Ceryak, speaking on behalf of Eli Lilly and Company, suggested some specific changes to the wording of the proposed rule. Mr. Ceryak stated: “According to new section 314.97(b) of the rule, unless a reference listed drug (RLD) has been withdrawn, a generic CBE will be approved only upon the approval of the same labeling change for the RLD. We are concerned that making approval of a generic CBE contingent on approval of the same change for the RLD essentially places the responsibility for these generic-initiated changes with the RLD sponsor.” He suggested: “[T]he new section 314.97(b) should make it clear that FDA will act on the application or application(s) it receives—which may or may not include one from the RLD—and that the approval(s) or complete response(s) will be made based on those applications. The rule should not assume in every case a decision will be made first on an RLD’s application or that the RLD will put an application on file.” Public Citizen supports revising the rule to clarify that a CBE-0 supplement for an ANDA holder may be approved even absent a corresponding CBE-0 supplement from the NDA holder.

VI. Conclusion

For the reasons stated above, in Public Citizen’s March 2014 comments, and in Public Citizen’s August 2011 citizen petition, we urge the FDA to finalize the proposed rule, and thereby to better protect patients from preventable injury.

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