# Congress of the United States

Washington, DC 20510

April 24, 2015

Dr. Stephen Ostroff, M.D.
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

**Re: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, Docket No. FDA-2013-N-0500**

Dear Dr. Ostroff,

For the past two years, we have urged the FDA to revise its rules to ensure that generic drug manufacturers can promptly update their labeling to include new safety information. We see this ability as a critical safeguard for consumers, because generic drugs often comprise a large majority of the market. Generic drug manufacturers have access to up-to-date reports of consumers' adverse safety events and the ability to identify needed safety revisions.

We welcomed the FDA's Proposed Rule in November 2013[1] that adopted this approach by allowing generic drug manufacturers to use the "Changes Being Effected" (CBE-0) process,[2] which permits manufacturers to update their labeling subject to simultaneous (instead of prior) review by the FDA. This mechanism has long been available to brand name manufacturers. The FDA's Proposed Rule will help ensure that *all* drug manufacturers—whether brand name or generic—have the same responsibility to ensure that labeling information on their products is accurate and up-to-date.

Last month, the FDA announced a public meeting to receive comments on the Proposed Rule and potential alternatives to the FDA's approach.[3] One such alternative would not only eliminate the FDA's proposal to bring generics into the CBE regime; it would significantly undercut the current CBE-0 process by preventing even brand name manufacturers, once a generic has entered the market, from promptly updating their safety information upon learning of an adverse event.[4] Under this industry proposal, neither generic nor brand name manufacturers could initiate a CBE-0 labeling change to convey important safety information; prior FDA approval would be required in all instances. This proposal represents a significant step backward, undoing an important patient safety rule that has been in place for brand name drug manufacturers for over 30 years.

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[1] 78 Fed. Reg. 67985 (Nov. 13, 2013).
[2] *See* 21 C.F.R. § 314.70(c)(6).
[3] 32 Fed. Reg. 8577 (February 18, 2015).
[4] Joint letter from GPhA and PhRMA to Dr. Hamburg Re: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, November 14, 2014, available at http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0500-0082.

As you know, the CBE-0 process serves an essential public safety function. It ensures that patients, caregivers, and doctors are made aware of new information regarding the safety of prescription drugs at the earliest possible time. When the FDA implemented the CBE-0 regime 30 years ago, drug manufacturers actively advocated for such a rule to avoid unnecessary delays before a change is made.[5] Criticizing then-existing rules that required FDA approval before manufacturers could update their labeling information or make certain other changes, manufacturers said: "this requirement is unnecessary, takes FDA reviewers away from more important work, and causes costly delays for applicants who must defer making changes in approved products until the supplement is approved."[6] This rationale for the CBE-0 process remains even more relevant today, as more drugs enter the market and FDA faces ever-tighter resource constraints.

The FDA's Proposed Rule sets forth a reasonable and responsible solution for ensuring rapid communication of safety information.

First, extending the CBE-0 process to generic manufacturers reflects current realities about the market for generic drugs. Some 86 percent of all prescriptions are now filled by the generic version of a drug.[7] In some cases, the branded drug exits the market altogether after generic entry, leaving only generic products on the market.[8] Often, risks associated with a drug do not become known until after a drug has been on the market for an extended period of time, including after generic drugs have entered the market. Given these realities, generic manufacturers will often have the most recent, relevant knowledge of adverse events; indeed, they may be the only manufacturers left in the market to monitor a product and ensure its labeling is up-to-date.[9] We agree with the FDA's conclusion that this factor warrants giving generic drug manufacturers the means to update their labeling information using the CBE-0 process, in the same manner that brand name manufacturers have done for over 30 years.

Second, the FDA's Proposed Rule reasonably accommodates concerns that generics' participation in the CBE-0 process would result in inconsistent labels among equivalent products. The FDA's Proposed Rule requires any generic manufacturer that makes a labeling change to distribute its revised labeling "on a temporary basis" while the FDA reviews it; the

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[5] Food and Drug Administration, New Drug and Antibiotic Regulations, 47 Fed. Reg. 46622, 46634-35 (Oct. 19, 1982).
[6] *Id.* at 46634.
[7] Generic Pharmaceutical Ass'n, GENERIC DRUG SAVINGS IN THE U.S. at 3 (2014), *available at* http://www.gphaonline.org/gpha-media/gpha-resources/2014-generic-drug-savings-in-the-u-s-report/.
[8] Public Citizen, GENERIC DRUG LABELING: A REPORT ON SERIOUS WARNINGS ADDED TO APPROVED DRUGS AND ON GENERIC DRUGS MARKETED WITHOUT A BRAND NAME EQUIVALENT (2013), available at http://www.citizen.org/hrg2138 (identifying 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added after generic market entry, from Jan. 2008-March 2013).
[9] *Id.* at 11 ("Whether because of price competition or other reasons, it is not uncommon for the brand name manufacturer to exit the market entirely after generic entry, leaving generic products as the only marketed versions of the drug. In that situation, the limitation on generics' ability to update labeling to provide the most current warning information takes on added significance, particularly when the drug is known to pose serious risks.").

generic manufacturer must also share the revised labeling with the brand name manufacturer (if one still exists) so it may participate in the review.[10] The new labeling information must be posted to an FDA web page so that it is available to prescribing health care providers and the public. Following FDA's approval of the labeling change, all other generic manufacturers of that drug must submit conforming labeling changes within a period of 30 days (unless FDA orders otherwise), to ensure consistency of labeling.[11]

While some temporary differences in labeling may occur during the period in which the generic manufacturer's CBE-0 Supplement is reviewed, the provisions described above minimize those differences.[12] Notably, similar temporary differences in labeling information *already* occur when a brand name manufacturer submits a CBE-0 Supplement, since generic drug manufacturers need not implement the change until the labeling change is approved by the FDA.[13] The FDA's Proposed Rule effectively minimizes labeling differences while ensuring that brand name and generic manufacturers both have the ability to keep their labeling information up-to-date.

We understand that some have raised objections about the economic impact of the FDA's Proposed Rule on generic manufacturers. We are some of Congress's leading supporters of accessible, affordable generic drugs, and would not advocate action that unduly penalizes this important industry. However, generic manufacturers *already* have a legal obligation to monitor for adverse events and report such events to the FDA.[14] And to the extent generic manufacturers object that the Proposed Rule could make them liable to injured customers if they fail to adequately update their safety information, such concerns ring hollow. The costs of patient injuries caused by a drug company's failure to meet its warning obligations would otherwise be borne unfairly by insurance companies, the government, and injured patients themselves. Importantly, the Proposed Rule is designed to improve warning information, which should reduce, not increase, the number of patients needing compensation for injury.

The inconsistent legal regime that governs liability for brand name and generic drug manufacturers is yet another important reason for implementing the Proposed Rule. In the 2011 case *PLIVA v. Mensing*, the United States Supreme Court held that generic manufacturers' current exclusion from the CBE-0 process means they cannot be held accountable if a patient is

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[10] 78 Fed. Reg. at 67985, 67989-94.

[11] Id. The FDA Amendments Act of 2007 also ensured that FDA may act so that product labeling is promptly amended to accommodate new safety information. Pub. Law 110-85, 121 Stat. 925 (2007).

[12] Although the Hatch-Waxman Act generally requires generic drug labels to have the same labeling as the Registered Listed Drug at the time of approval, the statute permits differences in certain circumstances, including because the drug is produced or distributed by different manufacturers. 21 U.S.C. §355(j)(2)(A)(v) (2013). For example, FDA regulations already permit discrepancies caused by "labeling revisions made to comply with current FDA labeling guidelines or other guidance." 21 C.F.R. §314.94(a)(8)(iv) (2014).

[13] See FDA, GUIDANCE FOR INDUSTRY: REVISING ANDA LABELING FOLLOWING REVISION OF THE RLD LABELING, at 5 (May 2000), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072891.pdf.

[14] See 21 U.S.C. § 331 (a)-(b),(k) (2006); 21 C.F.R § 314.98; 21 U.S.C. §355(k).

injured due to inadequate labeling information.[15] As a result, consumers who are injured because of inadequate labeling have no remedy if they took the *generic* version of a drug, while those who took the brand name version of the drug may seek recourse for their injury.[16] This inconsistency between consumers who take generic and brand name drugs is directly counter to the intent of the Hatch-Waxman Act and to generic substitution laws that have been implemented across the country.[17] As we noted in our previous Congressional Comments submitted to the FDA, physicians have cautioned that such inconsistent liability rules for a patient injured by a generic instead of brand name drug create "an ethical dilemma" for prescribing doctors.[18] As academics have observed, "for generics to succeed, they must have equal value to branded drugs. In economic terms, they must be perfect substitutes, and, in safety terms, this requires a duty to disclose risks equal to that of its branded drug. A critical component of the value equation for any product is a consumer's recourse in the event the product is defective."[19]

The FDA and safety experts have long held that state law offers an important layer of consumer protection that complements FDA regulation.[20] In its November 2013 notice of proposed rulemaking, the FDA correctly recognized that the inability of a generic drug manufacturer to improve its labeling information—and to be held accountable to injured patients if it fails to do so—"alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust post-marketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date."[21] By correcting these misaligned incentives, the Proposed Rule again strengthens and improves the quality of the labeling information for generic drugs.

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[15] Pliva v. Mensing, 131 S. Ct. 2567 (2011).

[16] For representative patient stories, see Alliance for Justice, Unequal Justice: Pliva v. Mensing, available at http://www.afj.org/multimedia/first-monday-films/unequal-justice-pliva-v-mensing.

[17] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 5585; *see* Hearing on S. 2748 Before the S. Comm. on Labor & Human Res., 98th Cong. (1984).

[18] Brief of the Am. Med. Ass'n et al. as Amici Curiae in Support of Respondents at 15-16, *PLIVA v. Mensing,* 131 S. Ct. 2567 (2011), 2011 WL 794118 at *29 ("Divergent liability rules for brand name and generic drugs pose an ethical dilemma for physicians.")

[19] Stacey B. Lee, PLIVA v. Mensing: Generic Consumers' Unfortunate Hand, 12 YALE J. HEALTH POLICY, LAW & ETHICS 209, 241 (2012) (further noting, "Th[e] absence of generic manufacturer oversight may reasonably diminish consumer confidence in the safety and effectiveness of generic drugs.")

[20] *See* Wyeth v. Levine, 555 U.S. 555 at 579 (2009), noting that the FDA has "long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation", and observing "state tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly." *See also* Brief of the Am. Med. Ass'n et al. as Amici Curiae in Support of Respondents, *Pliva v. Mensing*, supra note 18, at 25 ("The longstanding coexistence of state and federal law and FDA's traditional recognition of state law remedies buttress the conclusion that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.") (internal citations omitted); Lee, 12 YALE J. HEALTH POLICY, LAW & ETHICS at 243 ("The potential damage awards from state failure-to-warn litigation provides drug manufacturers with incentives to quickly provide full and clear information to physicians and FDA that otherwise may not come to light. Without such a mechanism, generic manufacturers may be motivated to act merely in their immediate financial interest, and, subsequently, become less forthcoming in providing safety-related data.")

[21] 78 Fed. Reg. at 67988-89.

We share a common goal of ensuring that safe, affordable generic drugs are available to American consumers. At the same time, we believe strongly that all drug makers, including generic manufacturers, should be able to take appropriate steps to enhance warning information given to doctors and consumers. The FDA's Proposed Rule takes significant and overdue steps to achieve this goal. We urge you to reject weakening alternatives and act swiftly to finalize the Proposed Rule.

Sincerely,

Senator Patrick J. Leahy
Ranking Member
Senate Judiciary Committee

Representative Frank Pallone
Ranking Member
House Energy & Commerce Committee

Senator Patty Murray
Ranking Member
Senate Health, Education, Labor & Pensions Committee

Representative John Conyers, Jr.
Ranking Member
House Judiciary Committee

Senator Richard Blumenthal
Ranking Member
Senate Committee on Veterans' Affairs

Representative Chris Van Hollen
Ranking Member
House Budget Committee

Senator Al Franken

Representative Gwen Moore

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Elizabeth Wagner

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