Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 51, Room 6304
Silver Spring, MD 20993-0002

Dear Dr. Ostroff,

The American Association for Justice (AAJ), formerly the Association of Trial Lawyers of America (ATLA), hereby submits additional comments in strong support of the Food and Drug Administration's (FDA) proposed rule entitled: *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*.[1] On February 18th, the FDA announced a public meeting in order to listen to comments on and alternatives to their Proposed Rule, in addition to reopening the docket to collect additional information. As a result, AAJ submits these comments to supplement previous comments[2] filed in support of the Proposed Rule.

AAJ, with members in the United States, Canada and abroad, is the world's largest trial bar. It was established in 1946 to safeguard victims' rights, strengthen the civil justice system, promote injury prevention and foster public health and safety. AAJ is an advocate for numerous individuals who have been harmed by generic drugs. In this capacity, AAJ continues to advocate for the FDA to finalize this rule, as originally drafted. The Proposed Rule would require generic drug manufacturers to promptly update labeling to include new safety information using the "Changes Being Effected" (CBE) process. This change will promote timely communication of safety information to patients and physicians. Current rules that preclude generic drug manufacturers from updating their safety information through the CBE process have a detrimental impact on all consumers. Since generic drug labels may not reflect current knowledge about safety risks a drug poses to consumers, AAJ supports the Proposed Rule and ensuring both brand name and generic drug manufacturers have access to the CBE process.

A. The CBE Process Is Critical to Consumer Safety

The CBE process provides 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. It is in the best interests of patients to ensure that the CBE process can be used by brand name and generic drug manufacturers alike. Empowering drug manufacturers to update certain safety information while FDA reviews

[1] *See* 78 Fed. Reg. 67985.
[2] *See* Comment of the American Association for Justice (March 13, 2014) located at: http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0500-0048.

the change, instead of requiring prior FDA approval, allows drug manufacturers to communicate safety information in a timely fashion while promoting consumer safety.

a. The CBE Was Created to Further Patient Safety

As the November 2013 notice of proposed rulemaking properly acknowledged, all drug manufacturers, whether of branded or generic products, "have an ongoing obligation to ensure their labeling is accurate and up-to-date."[3] A drug is misbranded in violation of the Food Drug & Cosmetic Act (FDCA) when its labeling is false or misleading, or does not provide adequate directions for use and adequate warnings.[4] "When new information becomes available that causes information in labeling to be inaccurate, the application holder must take steps to change the content of its labeling."[5]

Moreover, when such new information raises or increases concerns about the risks posed by a particular drug, it is critically important that such new safety information be communicated quickly to the medical community and to users of the drug. Indeed, it was precisely for this reason that the FDA first developed the concept of a changes being effected labeling change half century ago. The agency recognized that the public interest in "drug safety" and the "public health" would be best served through the adoption of a regulatory policy permitting the dissemination of new safety information through labeling changes "at the earliest possible time."[6] To implement that policy, the FDA announced that, in the exercise of its enforcement discretion, the agency would "take no action against a drug or applicant solely because" it had added a new warning to its approved labeling "prior to" FDA approval for that action, provided that the applicant simultaneously submitted a supplemental application seeking approval for the change.[7] This policy of non-enforcement eventually became the CBE-0 supplement process, now codified in 21 C.F.R. 314.70. Nothing has changed in the last fifty years that would alter the conclusion that the dissemination of new safety information "at the earliest possible time" will promote "drug safety" and the "public health."[8]

b. The Phenomenal Success of Generic Drugs Necessitates Expansion of the CBE Process

In recent years access to the CBE process for both brand name and generic drug manufacturers has become even more critical. Risks associated with a drug often do not become known until after a drug has been on the market for a number of years, even after generic drugs have entered the market.[9] With over 80 percent of all prescriptions now being filled by generic drugs, they can and should have a vested interest in ensuring that their products are adequately

[3] 78 Fed. Reg. at 67987.
[4] *See* 21 U.S.C. 331(a), (b); 21 U.S.C 352(a), (f), (j).
[5] 78 Fed. Reg. at 67986-87.
[6] 30 Fed. Reg. 993-94 (Jan. 30, 1965).
[7] *Id*.
[8] *Id.*
[9] 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).

labeled. This necessitates allowing generic drug manufacturers to update their labeling information using the CBE process, and to continue to allow brand name manufacturers to use the CBE process in the same manner they have done for many decades.

B. The GPhA/PhRMA Regulatory Alternative Is Seriously Misguided

In response to the FDA's proposed changes, trade associations for the generic drug industry (GPhA) and for name-brand pharmaceutical companies (PhRMA) have jointly proposed an alternative regulatory approach.[10] While they euphemistically dub this misguided regulatory proposal "Expedited Agency Review," what they are really proposing is elimination of the CBE process that has served us well for the past fifty years. In their proposal, GPhA and PhRMA suggest that when a drug company, or FDA on its own initiative, requests a labeling change based on new safety information concerning a drug, the agency would have to initiate a review to determine whether a labeling change was called for. The FDA would be required to conclude the review within a fixed period of time, and all holders of approved NDAs or ANDAs for the drug would be required to quickly implement the change.

There are myriad problems with this proposal. First, it presumes that the FDA is in the best position—and in a better position than the pharmaceutical companies who manufacture the drug—to determine whether new safety information exists that justifies a labeling change. This is not the case. It is the sponsor of a drug that is likely to have the greatest access to medical and scientific research about the drug. Moreover, as this agency is well aware, and numerous studies have documented, the FDA simply lacks the staff and resources to effectively monitor the safety of the thousands of drugs that it regulates.[11] The Supreme Court identified three recent studies that had come to the conclusion that "the budget and staff of the Food and Drug Administration are inadequate to permit the discharge of its existing responsibilities for the protection of the American public."[12] For this reason, our federal regulatory system has quite properly placed the primary responsibility for drug safety on a drug's manufacturer.

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[10] *See*, Letter to Dr. Margaret Hamburg, Commissioner, FDA, from GPhA and PhRMA (Nov. 14, 2014) located at: http://www.regulations.gov/#!documentDetail;D=FDA-2013-N-0500-0082.

[11] *See Wyeth v. Levine*, 555 U.S. 555, 572 (2009) ("The FDA has limited resources to monitor the 555 U.S. 555drugs on the market and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.").

[12] *Id*., (citing FDA Science Board, Report of the Subcommittee on Science and Technology: FDA Science and Mission at Risk 2, 6 (2007), online at http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf ("[T]he Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities"); National Academies, Institute of Medicine, The Future of Drug Safety: Promoting and Protecting the Health of the Public 193–194 (2007) ("The [FDA] lacks the resources needed to accomplish its large and complex mission . . . . There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the agency's ability to improve and expand this essential component of its mission"); GAO, Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process 5 (GAO–06–402, 2006), http://www.gao.gov/new.items/d06402.pdf ("FDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket safety issues"); *see* also House Committee on Oversight and Government Reform, Majority Staff Report, FDA Career Staff Objected to Agency Preemption Policies 4 (2008) ("[T]he Office of Chief Counsel ignored the warnings from FDA scientists and career officials that the preemption language [of the 2006 preamble] was based on erroneous assertions about the ability of the drug approval process to ensure accurate and up-to-date drug labels")).

Through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. Manufacturers are charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market.[13] The joint proposal from GPhA and PhRMA seeks to absolve their member companies of this federal responsibility to ensure drug safety while leaving patients and consumers to suffer the negative consequences of their omissions.

The joint proposal purports to both "maximize patient safety and minimize the chance for any confusion about safety warnings."[14] In fact, it would sacrifice patient safety. The proposal would drastically limit the situations in which a manufacturer is permitted to make a change to a drug's safety labeling and would inevitably result in significant delay before consumers are made aware of important information about the safety of their medications. It would also eliminate all accountability for both brand name and generic drug manufacturers for their products. This would be catastrophic to patient safety and would increase patient risk.

a. Sentinel and E-Labeling Are Not Substitutes for the CBE Process

The GPhA and PhRMA alternative seems to suggest that because the FDA is adopting new technology meant to increase drug safety, the CBE process is no longer necessary and that the FDA can and should approve all labeling changes. This contention is inaccurate. Both the Sentinel System and e-labeling do provide important safety improvements that ensure that patients, consumers and health professionals have better and faster safety information related to prescription medications. But neither are intended to, nor would they be adequate to replace the CBE process. The Sentinel System merely monitors medical product safety by tracking reports of adverse events linked to the use of prescription medications and the e-labeling proposed rule would require drug manufacturers to distribute prescribing information electronically ensuring that the most up-to-date version of the prescribing information is available to health care professionals and the public. Even when both of these advances are fully realized, the FDA still would not have the resources to be fully responsible for a drug's safety. If, in the vast majority of cases, as is suggested by the alternative proposal, the FDA was responsible for labeling changes, consumers and health professionals will remain unwarned about potential adverse events for significantly longer than under the FDA's proposal.

b. Both Brand Name and Generic Drug Manufacturers Should Be Accountable for the Products They Sell

The not-so-secret agenda behind this joint proposal is not simply to absolve drug companies of their responsibilities under federal law, but under state law as well. In addition to ensuring timely warnings to consumers, the Proposed Rule serves another equally important purpose: reinstating consumers of generic drugs the ability to seek recourse for their injuries through the justice system. In 2011, the United States Supreme Court in *Pliva vs. Mensing* held that generic drug manufacturers could no longer be held accountable for failure to warn

[13] *Id.* at 567.
[14] Letter to Dr. Hamburg at 1.

consumers of injuries associated with their products. This holding created a troubling disparity between consumers who used generic drugs who cannot hold manufacturers accountable and consumers who take brand drugs who can hold the manufacturer accountable. The ability of consumers to bring state law based tort claims provides an essential layer of consumer protection that supplements FDA regulation. The ability to hold manufacturers accountable in court if they fail to adequately warn patients of a known hazard has long been thought to provide a powerful incentive to drug manufacturers to ensure that their labeling always reflects the most current safety information.

The FDA has long "regarded state law as a complementary form of drug regulation."[15] State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA's premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times. Thus, the FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.[16]

Under the reasoning of the Supreme Court decision in *Pliva, Inc. v. Mensing*, however, adoption of the joint proposal's recommendation would immunize all drug manufacturers, brand-name as well as generic, from failure-to-warn liability under state law. *Mensing* explains that the ruling against preemption in *Wyeth v. Levine* was based on Wyeth's ability to strengthen the warnings on its drug Phenergan without prior FDA approval through the CBE process. Under the joint proposal, however, drug companies would be unable to strengthen its warnings without the FDA's prior approval, thereby preempting state-law warning claims on grounds of impossibility.

C. Industry Business Practices Have Caused Extreme Generic Drug Prices and Increased Industry Profits

The generic drug industry has put forth the argument that the Proposed Rule is going to cause increased drug prices and drive drug companies from the market. However, generic drug prices are already on the rise and it is a direct result of generic drug manufacturer business practices. Since the *Mensing* decision, half of all generics sold have become more expensive. In some cases, this price increase was both rapid and dramatic. One 2014 study found that more than a dozen generics prices increased 10-fold over 12 months.[17] As noted in a recent congressional hearing on the matter, more than 1,200 generic medications increased an average of 448 percent in the same time.[18]

While several theories have been advanced as to the cause of these staggering prices,

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[15] 555 U.S. at 572.
[16] *Id.*
[17] Katz, Alan. "Surprise! Generic-Drug Prices Spike." *Bloomberg Businessweek*, December 12, 2013. Available at http://www.businessweek.com/articles/2013-12-12/generic-drug-prices-spike-in-pharmaceutical-market-surprise.
[18] United States Senate Committee on Health, Education, Labor and Pensions (HELP), Subcommittee on Primary Health and Aging, Why Are Some Generic Drugs Skyrocketing In Price?, November 20, 2014; Available at http://www.help.senate.gov/hearings/hearing/?id=a7beb0ef-5056-a032-521e-c63f76dda7f3.

evidence seems to point to decreased market competition. One leading theory for reduced market competition among generic manufacturers is the consolidation of market power through mergers and acquisitions.[19] Another is due to changes in the industry or manufacturing challenges, which lead to market exits.[20]

Regardless of the reason, the result is the same: only one, two or three companies continue to manufacture medicines and prices rise. For example, when one of the three manufacturers of the drug Digoxin exited the market, it allowed for the other two to increase its price by more than 1,000%.[21] As a result of these price spikes, companies are enjoying record sales and earnings, with one digoxin manufacturer reporting an increase in earnings from $4.5 to $16.9 million.[22]

D. Conclusion

Americans count on the FDA to protect their health and safety and the Proposed Rule as originally drafted goes a long way to promote consumer safety by ensuring that generic drug companies can improve the warning information for their products in the same way that brand manufacturers can under existing law. The alternative proposed by GPhA and PhRMA would be a major setback in consumer safety regulation and would pose an unacceptable risk to the public's health and wellbeing. As a result, we urge the FDA to finalize the Proposed Rule, without significant change, as quickly as possible.

Sincerely,

Lisa Blue

Lisa Blue
President
American Association for Justice

[19] Lazarus, David. "What's behind the huge price jump for some generic drugs?" *Los Angeles Times*, October 21, 2014. Available at http://www.latimes.com/business/la-fi-lazarus-20141021-column.html.

[20] Testimony of Aaron Kesselheim, United States Senate Committee on Health, Education, Labor and Pensions (HELP), Subcommittee on Primary Health and Aging, Why Are Some Generic Drugs Skyrocketing In Price?, November 20, 2014; Available at http://www.help.senate.gov/imo/media/doc/Kesselheim.pdf.

[21] Testimony of Rep Elijah E. Cummings, United States Senate Committee on Health, Education, Labor and Pensions (HELP), Subcommittee on Primary Health and Aging, Why Are Some Generic Drugs Skyrocketing In Price? November 20, 2014, Available at http://www.help.senate.gov/imo/media/doc/Cummings.pdf.

[22] Rosenthal, Elisabeth. "Rapid Price Increases from Some Generic Drugs Catch Users by Surprise." *New York Times*, July 9, 2014. Available at http://www.nytimes.com/2014/07/09/health/some-generic-drug-prices-are-soaring.html?_r=0.