Congress of the United States
Washington, DC 20515

January 22, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
White Oak 32
Silver Spring, MD 20993

Dear Commissioner Hamburg:

We write to express grave concerns regarding a regulation proposed[1] by the Food and Drug Administration (FDA) that would change longstanding policy regarding the 1984 Hatch-Waxman Act (P.L. 98-417). The proposed regulation would allow generic manufacturers to alter an abbreviated new drug application (ANDA) label without the FDA's prior approval. We strongly believe that such a rule would conflict directly with the statute, thwart the law's purposes and objectives, and impose significant costs on the drug industry and healthcare consumers. We respectfully request the Agency explain and reconsider this departure from decades of settled practice.

The Hatch-Waxman Act opened the drug market to competition for the first time and effectively created the modern generic drug industry. Over the course of the past 30 years, the generic drug industry has generated trillions of dollars in healthcare savings. The key to the success of the Hatch-Waxman Act is the requirement for "sameness" with the brand name drug counterpart in all respects—including labeling.[2] By requiring generic drug products to be materially identical to their brand-name counterparts, generic drugs can forego the years of costly tests and clinical trials the branded drug already underwent, and thus offer the same drug at a lower price to patients. For two decades FDA itself has determined that it would violate the statute if generic manufacturers were allowed to deviate from the FDA-approved labeling of the branded drug.[3] Congress has also embraced this settled rule, as we have declined to change it in every food and drug law we have passed since 1992.

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[1] FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products—Proposed Rule*, 78 Fed. Reg. 67985 (Nov. 13, 2008).

[2] The Act requires a generic drug to have the same label, the same active ingredient, the same route of administration, dosage, and strength, and to be bioequivalent to its brand name counterpart. Regarding the generic drug's labeling, the statute requires "the same as the labeling approved for the listed drug referred to in" the sponsor's ANDA. FDCA §§ 505(j)(2)(A)(ii)-(v).

[3] FDA, *Abbreviated New Drug Application Regulations—Final Rule*, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992); FDA, *Guidance for Industry: Changes to an Approved NDA or* ANDA, at 24 (Apr. 2004). *See also* 21 C.F.R. § 314.150(b)(10) (stating that FDA approval of an ANDA will be withdrawn if the agency finds that "the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug.").

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The proposed rule undermines this sameness requirement by allowing generic drug manufacturers to unilaterally revise their safety-related labeling upon submission to the FDA of a "changes being effected" (CBE-0) supplement including the newly acquired information the company believes warranted the changes.[4] After the CBE-0 supplement is submitted, the FDA will evaluate the underlying information submitted, along with other relevant safety data the agency has compiled, and decide whether to officially approve the same labeling changes for the branded product. If approved, all other generics on the market would have 30 days to revise their labeling accordingly. Therefore, multiple FDA-approved, therapeutically equivalent products will at least temporarily be permitted to have different safety-related labeling prior to the FDA determining whether such changes are adequately tailored or warranted at all.

FDA's proposed rule is not only inconsistent with the sameness requirement in the text of the Hatch-Waxman Act, it also threatens to undermine the law's purpose. As the FDA itself has recognized, "Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart."[5] Allowing generic manufacturers to unilaterally change their labeling means potentially dozens of drugs that are chemically and biologically identical might nonetheless bear different safety information, confusing patients and prescribers alike. The labeling on the generic products should be identical to the labeling on the branded product so providers and patients are comfortable with the risks and benefits of the product they are using regardless of the name of the company on the bottle or vial.

The Hatch-Waxman law strikes a very important balance between protecting valuable incentives for research and innovation while also encouraging competition in the market. The proposed rule could change that balance and increase the cost of generic and branded drugs. The proposed rule would require generic manufacturers to comply with the new labeling rules without access to the innovator's clinical trial data or the FDA's files, and thus manufacturers cannot possibly know whether the FDA has considered or rejected prior labeling changes. This could result in costly, duplicative testing. Moreover, FDA acknowledges that the proposed rule could increase manufacturer exposure to state tort lawsuits. These costs could be in the billions, and surely will be passed on to the consumer in the form of higher prices. However, the proposed rule estimates the annual cost to be between $4,237 to $25,852. No explanation is given as to how the FDA derived such a low estimate.

To assist the Committee(s) in better understanding the decision making process that led to this proposed rule and to determine whether there are better ways of ensuring patients and providers have timely access to consistent drug safety information, please provide answers to the following questions by no later than February 5, 2014:

1. For the period of time after a generic drug has submitted a CBE-0 supplement, please explain how the generic drug's label will be "the same as the labeling approved for the

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[4] Currently, a generic drug manufacturer can only use the CBE-0 supplement process to make changes to its labeling in conformance with the FDA-approved labeling of the branded product.
[5] 57 Fed. Reg. at 17961.

requirements included in sections 505(j)(2)(A)(i)-(v) of the Hatch-Waxman Act extend beyond the date of approval?

2. Please explain the benefit of having proposed label changes published on a public website before FDA consideration, undermining FDA's current role as the gatekeeper and deciding authority for changes to a drug's label.

3. Please provide the names of any executive branch employees outside the FDA who were involved in the decision to proceed with this proposed rule or who participated in drafting or reviewing it.

4. What is FDA's policy on when an adverse event needs to be listed on the label? Are there standards around the prevalence or severity of the adverse event that are necessary before it rises to a labeling change?

5. What is the expected cost to the FDA to review the CBE-0 submissions in a timely manner and establish and update the website, and from where does the FDA propose drawing resources to meet these costs? How will the agency prioritize submissions and what is the estimated time of review?

6. Please describe in detail how FDA arrived at the estimated cost of the rule of $4,237 to $25,852 per year and estimates it will receive 20 CBE-0 supplements annually from approximately 15 ANDA holders. Please explain how the agency derived these estimates. Did FDA conduct any analysis of how long it takes a manufacturer to prepare a CBE supplement and how much it costs? Did FDA conduct any analysis of what it will cost manufacturers to institute new procedures for monitoring safety and effectiveness of drugs? Did FDA conduct any analysis of the effect the proposed rule will have on drug prices? Please provide all documents and communications regarding the cost-benefit analysis.

7. Generic drug manufacturers can currently propose labeling changes with FDA as a result of newly acquired safety information. Please provide statistics for how many times this is done in comparison to brand name manufacturers and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug manufacturers are not submitting required adverse event reports or otherwise not meeting their post-market surveillance requirements

8. The proposed rule notes a 2010 study of FDA safety-related drug labeling changes that found the median time from initial approval of the drug product to label change was 11 years. Please provide this study and all supporting documentation to the Committee(s). Please also provide statistics showing how long it takes FDA to make a decision once a label change is suggested.

9. Please explain why the prior approval supplement process alone cannot be used effectively to change generic and brand drug labels, and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug

manufacturers are not updating their label upon FDA approval of a change to the label of the reference brand drug.

10. As an alternative approach, did the FDA consider permitting generic drug manufacturers to use a modified CBE process by which the agency has an opportunity to assess a proposed labeling change before introducing it into the market? What does the agency believe would be the pros and cons of using this approach as opposed to the CBE-0? Did the agency conduct a cost benefit analysis of such an approach?

11. Did the agency consider the impact the proposed rule would have on over-the-counter (OTC) drugs? If so, please submit any such analysis and explain how FDA envisions the proposed regulation applying to OTC drugs.

A number of processes already exist through which generic drug manufacturers can share new safety information and propose a label change to FDA without disrupting the market. If the agency believes those methods are inadequate, it cannot simply ignore written statute. FDA has an obligation to share those concerns with Congress and work together on a legislative solution.

Thank you for your prompt consideration of this important matter. If you have any questions, please have your staff contact Stacy Cline or Grace Stuntz with the Health, Education, Labor, and Pensions Committee at (202) 224-6770 and John Stone, Paul Edattel or Carly McWilliams with the Energy & Commerce Committee at (202) 225-2927.

Sincerely,

Lamar Alexander
Ranking Member
Health, Education, Labor
and Pensions Committee

Fred Upton
Chairman
Energy and Commerce Committee

Michael B. Enzi
United States Senator

Marsha Blackburn
Member of Congress

Richard Burr
United States Senator

John Shimkus
Member of Congress

Johnny Isakson
United States Senator

Joseph R. Pitts
Member of Congress

Orrin G. Hatch
United States Senator

Greg Walden
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Pat Roberts
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Tim Murphy
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Lisa Murkowski
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Michael C. Burgess
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Mark Kirk
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Bob Latta
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