DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

FEB 26 2014

The Honorable Joseph R. Pitts
House of Representatives
Washington, D.C. 20515-3816

Dear Mr. Pitts:

Thank you for your letter of January 22, 2014, cosigned by several of your colleagues, to the Food and Drug Administration (FDA or the Agency), expressing concern with the proposed rule, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," published in the *Federal Register* on November 13, 2013, and available online at *http://federalregister.gov/a/2013-26799*. I should emphasize at the outset that this is a proposed rule and that FDA will be receiving comments on the proposal until March 13 of this year. We will consider those comments carefully and, as with any proposed rule, it is of course possible that FDA might adopt an alternative regulatory approach or that the final rule may differ in some respects from the proposal to reflect points made in the comments. We appreciate your interest in this matter.

We have restated each of your questions below in bold, followed by FDA's responses. Because we have a pending proposed rule concerning these issues, our responses are limited, reflecting statements made publicly in the preamble to the proposed rule.

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 [brand name] drug" as required by the Hatch Waxman Act? Do the sameness requirements included in sections 505(j)(2)(A)(i)-(v) of the Hatch Waxman Act extend beyond the date of approval?**

At the time of FDA's adoption of the generic drug regulations in 1992, which included the current rules relating to generic drug labeling, FDA believed it was important that product labeling for the reference listed drug (RLD or brand drug) and any generic drugs be the same to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. However, as the generic drug industry has matured and captured an increasing share of the market, tension has grown between FDA's requirement that a generic drug have the same labeling as its RLD, which facilitates substitution of a generic drug for the prescribed product, and the need for an abbreviated new drug application (ANDA) holder to be able to independently update its labeling as part of its independent responsibility to ensure that the labeling is accurate and up to date.

In the current marketplace, approximately 80 percent of drugs dispensed are generic and, as we have learned, brand drug manufacturers may discontinue marketing after generic drug entry. FDA believes it is time to provide ANDA holders with the means to update product labeling to reflect data obtained through post-market surveillance, even though this may result in temporary labeling differences among products while FDA reviews the proposed labeling change. During its review of a generic drug manufacturer's changes being effected (CBE-0) supplement, FDA would consider submissions by the brand drug manufacturer and other generic drug manufacturers related to the safety issue and determine whether the labeling update is justified and whether modifications are needed. FDA would make an approval decision on proposed labeling changes for the generic drug and the corresponding brand drug at the same time, so that brand and generic drug products have the same FDA-approved labeling.

The proposed rule would likely reduce the variation between brand and generic drug labeling that currently takes place. Under current regulations, only brand drug manufacturers can independently update product labeling with certain newly acquired safety information and distribute revised labeling, before FDA reviews or approves the labeling change, by submitting a CBE-0 supplement. Under the current regulation, FDA generally has advised that a generic drug manufacturer may use the CBE-0 supplement process only to update its product labeling to conform to the FDA-approved labeling for the corresponding brand drug or to respond to FDA's specific request to submit a labeling change through the CBE-0 process. Accordingly, while FDA reviews a brand drug manufacturer's CBE-0 supplement, there currently is a difference between the brand drug labeling and generic drug labeling. Once FDA approves a change to the brand drug labeling, the generic drug manufacturer is required to revise its product labeling to conform to the approved labeling of the corresponding brand drug. FDA advises that this update should occur at the very earliest time possible; however, FDA has determined that there is often a delay, of varying lengths, between the date on which revised brand drug labeling is approved and the date on which the generic drug manufacturer submits such labeling updates.

The proposed rule, if finalized, generally would reduce the time in which all generic drug manufacturers make safety-related labeling changes by requiring generic drug manufacturers to submit conforming labeling changes within a 30-day time frame. Please see response to Question 9, for additional information on FDA's examination of the time between approval of an NDA holder's labeling change to include a new boxed warning and submission of the ANDA holder's labeling supplement for conforming changes.

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.

If finalized, this rule would help ensure that health care practitioners and the public have access to the most current drug safety information, which may be used to inform treatment decisions based on the balance of potential benefits and risks of the drug product for each patient. The need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for the "changes being

effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers supports FDA's public health mandate and, as discussed below, does not undermine FDA's authority to decide on whether a labeling change proposed in the CBE-0 supplement should be approved.

The proposed FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: the active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement).

It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the corresponding brand drug manufacturer, as well as other generic drug manufacturers. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page through a link to FDA's online labeling repository at *http://labels.fda.gov*. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at *http://labels.fda.gov.*

The proposed FDA Web page is expected to enhance transparency and facilitate public access to new safety-related information for all products—biological products licensed under the Public Health Service Act as well as drug products approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The public may subscribe to FDA's free e-mail subscription service to receive an e-mail message each time there is an update to this proposed FDA Web page.

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.

In the course of developing and reviewing FDA proposed regulations, the documents go through a standard clearance review with the Department of Health and Human Services and the Office of Management and Budget, as was the case here.

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?

The requirements for the content and format of labeling for human prescription drug and biological products are described in FDA's regulations (see 21 CFR 201.56, 201.57, and 201.80; see also the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006) commonly referred to as the "Physician Labeling Rule" (PLR)). FDA's considerations and criteria for inclusion of adverse reactions in the labeling are outlined in two of FDA's guidances for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format;* and *Adverse Reactions sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format.*

As described in FDA guidance, the WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards (e.g., clinically significant drug interference with laboratory tests with subsequent inaccurate test results) that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in this section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established. The BOXED WARNING is ordinarily used to highlight for prescribers those adverse reactions that are so serious in proportion to the potential benefit from the drug that it is essential that they be considered in assessing the risks and benefits of using the drug; *or* those adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug. Boxed warnings are most likely based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate.

Adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable, are listed in the ADVERSE REACTIONS section of labeling. FDA's regulations require a separate list for adverse reactions identified from clinical trials and those identified from spontaneous reports after a drug has been marketed. Various factors such as seriousness, severity, frequency, and strength of causal association are used in determining which adverse reactions to include in the ADVERSE REACTIONS section and in characterizing those reactions. Typically, adverse reactions for a given drug will have varying clinical significance (ranging from serious to minor) and certain adverse reactions that have relatively serious clinical implications will be discussed, often in greater detail, in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS).

The PLR and guidances are available at
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf.

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?

In the Preliminary Regulatory Impact Analysis, the Agency made assumptions regarding the number of safety-related labeling changes that will be submitted in CBE-0 supplements. These assumptions were necessary due to the uncertainty about how the proposed rule will alter industry behavior. We assumed that FDA would receive all reports of adverse events required to be submitted and that all drug labeling is eventually updated to reflect important drug safety information, either through a CBE-0 supplement or a prior-approval supplement. We did not estimate the cost to FDA to review a CBE-0 submission, because we view any labeling change initiated by an ANDA holder for a generic drug (rather than a new drug application (NDA) holder for a brand drug) as a transfer across time instead of a change in net cost. Thus, it is a resource-neutral transfer within FDA.

In the Preliminary Regulatory Impact Analysis, we conclude, based on consultations with IT and Communication specialists within FDA, that the creation and maintenance of the Web page devoted to providing information on the CBE-0 supplements for safety-related labeling changes for ANDAs, NDAs, or biologics license applications (BLAs) that are pending FDA action would be routine for FDA staff and would use already established resources. Therefore, we did not include costs to FDA to create or maintain the Web page in the analysis. We acknowledge, however, that if additional resources are needed, the burden to FDA could be between $5,000 and $10,000 to create the page in the first year. We estimate the maintenance burden to be an additional $6,500 to $13,000 per year.

The Agency intends to assess and enhance current procedures for coordinating review of submitted CBE-0 supplements by the relevant review offices to ensure that the proposed labeling changes are acted on in a timely manner, as resources allow. In general, with regard to drug safety issues, FDA prioritizes among these based on factors that include, but are not limited to, the seriousness of the risk; the estimated size of the population exposed to the risk of the drug; the suspected frequency of harm to patients exposed to the drug; the context of the drug's use; the quality of the data suggesting the risk; and the plausibility of a causal relationship between the drug and the risk. FDA anticipates that these and/or similar factors will be considered when prioritizing among the CBE-0 supplement submissions.

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.

The estimates are fully explained in the Preliminary Regulatory Impact Analysis *http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm375128.pdf* and in the Paperwork Reduction Act of 1995 section of the proposed rule, *http://www.gpo.gov/fdsys/pkg/FR-2013-11-13/pdf/2013-26799.pdf*, at pp. 67996-97.

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.**

FDA cannot readily identify recent examples in which a generic drug manufacturer contacted FDA to propose labeling changes as a result of newly acquired safety information related to the active ingredient. Accordingly, we cannot provide the requested statistics.

We do wish to clarify that the proposed rule focuses on the obligation to update labeling to reflect newly acquired information, not on the legal duties to report adverse drug events to FDA or more generally to meet post-market surveillance requirements associated with adverse event reporting obligations. The proposed rule neither cites nor is based on evidence that generic drug manufacturers are not submitting to FDA required reports of spontaneous adverse event reports that they receive.

Brand and generic drug manufacturers currently have the same requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA. All drug manufacturers (both brand and generic) must promptly review all adverse drug experience information obtained or otherwise received from any source, including published literature, and comply with applicable reporting and recordkeeping requirements. Reporting requirements include submission of 15-day alert reports for serious and unexpected adverse drug experiences, periodic reports, an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling.

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.

The 2010 FDA study, "Evaluation of FDA Safety-Related Drug Label Changes," was reported in Pharmacoepidemiology Drug Safety (vol. 22, pp. 302-302, 2013) and is enclosed for your reference.

The Agency relied on the publicly available FDA MedWatch website to obtain a comprehensive list of approved safety-related labeling changes, including drug name, safety issue, and sections of the drug label that were modified between January 1, 2010, and December 31, 2010.

The data to calculate median time to a label change relative to product approval was obtained by retrieving the product approval date and the date of the labeling change for each drug from FDA databases.

The published manuscript of the study contains the basic data and the analyses. Our finding that the median time from approval to a safety-related labeling change in 2010 of 11 years is consistent with that of independent researchers (see Moore TJ, Singh S, Furberg CD. The FDA and New Safety Warnings. Arch Intern Med 2012; 172: 78–80). As we note in the manuscript:

> A recent paper by Moore et al. on 2009 FDA safety warnings found (i) adverse event reports were the most frequent evidence source that supported new regulatory actions and boxed warnings and (ii) the median time from approval to major safety-related regulatory action was 11 years.[] Although Moore et al. reviewed only boxed warnings, warnings, and contraindications for 2009 data and excluded some safety-related regulatory actions and OTC drugs, their findings regarding evidence sources were consistent with our more comprehensive analysis of the data in 2010.

It is important to note that the focus of the FDA study was to characterize the types of drug safety data sources that give rise to post-market safety-related label changes (adverse event reports, clinical trials, observational studies, etc.). It was not to find out the median time from initial approval of a drug product to a label change for all drug products, or a first-time label change for the products reviewed. The 11 years was applicable only to the drug products reviewed in this study.

Because this was a cross-sectional study (i.e., it examined all label changes in calendar year 2010) and not a longitudinal study, the median time to a label change presented in the manuscript is not the median time to the first safety-related labeling change, which may have occurred earlier than the year 2010; this study was just looking at the label changes occurring in 2010. Similarly, it is not a measure of how long it took the company to implement the labeling change. We did not collect information that would allow us to make these measurements.

At this time, we do not have readily available statistics showing how long it takes FDA to make an approval decision on a labeling change proposed in a supplement. In general, FDA aims to review and take action on a supplement submitted by the application holder for a proposed labeling change within 180 days of receipt of the supplement (see regulatory review goals described in 21 CFR 314.100). In certain circumstances, FDA may require certain drug and biological product application holders to make safety-related labeling changes based on new safety information that becomes available after approval (see section 505(o)(4) of the FD&C Act). Section 505(o)(4) of the FD&C Act imposes time frames for application holders to submit and for FDA staff to review such changes, and gives FDA new enforcement tools to bring about timely and appropriate safety labeling changes.

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.

The need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for the "changes being effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Currently, if a generic drug manufacturer believes that newly acquired safety information should be added to drug product labeling, it must provide supporting information to FDA, and FDA determines whether labeling for both the brand and generic drugs should be revised, which results in a delay in updating generic drug labeling and getting new information to prescribers and patients. FDA's proposed revisions to its regulations, if finalized, would enable generic drug manufacturers to update product labeling promptly to reflect certain types of newly acquired information related to drug safety.

FDA examined new boxed warnings approved during the 2009-2010 time period and found that the time between approval of the NDA holder's labeling change and submission of the ANDA holder's labeling supplement for conforming changes varies, and the majority of ANDA supplement submissions occur after 30 days. [1] Roughly half (30 of 61)[2] of the ANDA supplement submissions for a boxed warning labeling change occurred over 100 days after the NDA's labeling change FDA had approved. ANDA holders currently are advised to submit a CBE-0 supplement to revise product labeling to conform to an approved revision to the reference listed drug's labeling "at the very

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[1] Boxed warning labeling changes were the only labeling changes in this review because they represent the strongest labeling changes and we would expect to see the quickest changes to labeling by ANDA holders once the NDA holder's labeling has been changed to reflect the new boxed warning. This is the same time period from which the baseline conditions in the Preliminary Regulatory Impact Analysis are drawn.

[2] Our sample includes 61 approved CBE-0 supplements for changes to the boxed warning of brand drugs for which there was a marketed generic drug at the time of the approved labeling change. Of the 61, there were only seven times where an ANDA holder submitted a labeling supplement to FDA for conforming labeling revisions to the boxed warning within 30 days of the approval of the labeling change supplement submitted by the NDA holder.

earliest time possible" (see guidance for industry on "Revising ANDA Labeling Following Revision of the RLD Labeling" (2000)). The proposed rule would require ANDA holders to submit their revised labeling within 30 days of FDA's posting of the approval letter for the RLD's labeling change on its website.

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?

FDA considered several alternatives that would allow certain requirements of the proposed rule to vary, such as proposing a new category of supplements for certain labeling changes being effected in 30 days. However, FDA proposed the regulatory change that it believes would most likely benefit the public health by improving communication of important drug safety information to health care professionals and consumers. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers may improve communication of important, newly acquired drug safety information to prescribing health care professionals and the public. FDA has noted that the U.S. Supreme Court's decision in *Pliva v. Mensing* 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.

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.

The proposed rule applies to over-the-counter (OTC) drug products that are approved in NDAs and ANDAs, but does not apply to OTC drug products marketed under an OTC monograph. The Agency considered the impact that the proposed rule would have on both prescription and OTC drug products approved in NDAs and ANDAs and on biological products licensed in BLAs. FDA's analysis is described in the Preliminary Regulatory Impact Analysis, available at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*

Thank you, again, for contacting us concerning this important matter. Please let us know if you have further questions. The same letter has been sent to your cosigners.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

Enclosure