



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993

The Honorable Joseph R. Pitts  
Chairman  
Subcommittee on Health  
Committee on Energy and Commerce  
House of Representatives  
Washington, D.C. 20515-6115

OCT 01 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the April 1, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on April 16, 2014.

If you have further questions, please let us know.

Sincerely,

A handwritten signature in black ink, appearing to read "Thomas A. Kraus".

Thomas A. Kraus  
Associate Commissioner  
for Legislation

cc: The Honorable Frank Pallone, Jr.  
Ranking Member  
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

**The Honorable John Shimkus**

- 1. Electronic distribution of prescribing information for drugs and biologics-known as e-labeling-would provide healthcare providers with access to the most up-to date safety and efficacy information for a prescription drug product, which is critical to enhancing patient safety. This policy has enjoyed broad support from this Committee in the past, and has heard from FDA that the agency also supports e-labeling policy.**

**In April 2013, the Subcommittee on Health held a hearing on securing the drug supply chain. At this hearing, Dr. Woodcock testified that e-labeling required a rule making process and noted that FDA planned to issue a proposed rule that year. It is my understanding that the proposed rule was submitted to OMB for review in August 2013, yet it still has not been published. Please share with the Committee the reasons for the delay in publishing this rule. Further, please provide a target date for publication of the proposed rule.**

FDA announced in the fall 2009 Unified Agenda of Regulatory and Deregulatory Action (Unified Agenda) its intention to publish a proposed rule, "Electronic Distribution of Content of Labeling for Human Prescription Drugs and Biological Products" (RIN: 0910-AG18), that would require electronic distribution of professional prescribing information for human drug and biological prescription products in lieu of paper, which is currently used. The information provided in the Unified Agenda presents a forecast of the rulemaking activities that the Agency expects to undertake in the foreseeable future. While we cannot provide you with a specific timeline and generally do not discuss details of a proposed rule's contents prior to the issuance of the proposed rule, this is an issue of importance.

FDA's impetus for a proposed rule for the electronic distribution of professional prescribing information is the need for more rapid distribution to health care professionals of the most up-to-date information about a prescription drug, including new warnings, contraindications, and directions for use, which would contribute to better care for patients, reduction in medication errors, and improved public health. Currently, the professional prescribing information, containing information for the safe and effective use of the product, is distributed in the form of paper leaflets. Although the information in the professional prescribing information is a valuable resource, it may not contain the most current information because the paper leaflets accompanying a particular drug may have been printed and distributed prior to more recent labeling changes. The printed professional prescribing information that is in the package on pharmacy shelves can be out of date because of any changes that have been made to the labeling subsequent to the distribution of the particular package of drug. Such changes can include new approved uses for a drug already on the market and new safety information detected from post-market use of the drug or from ongoing clinical trials.

FDA seeks to establish a modern and efficient process to distribute professional prescribing information to health care professionals. Because it takes time to prepare revised paper professional prescribing information, include it in the drug packages, and get those packages into distribution, the

electronic distribution of professional prescribing information would help ensure that health care professionals have immediate access to the most up-to-date information about the safety of marketed drugs. Drug products in distribution are rarely recalled by the manufacturer, solely because changes have been made to the labeling; accordingly “real-time” electronic distribution would foster use of the most up to date labeling information.

OMB review is generally the last significant step in the rulemaking process before publication. We are hopeful that the proposed rule will proceed promptly to publication after OMB’s review has been completed. OMB held meetings on this rule on November 7, 2013, January 13, 2014, and February 4, 2014. The public record of those meetings, including submissions provided by the meeting requestors, is available at ([http://www.whitehouse.gov/omb/oir/0910\\_meetings/](http://www.whitehouse.gov/omb/oir/0910_meetings/)).

- 2. Some have questioned whether FDA has the authority to require electronic distribution of prescribing information despite the fact that agency requires electronic submission for multiple filings coming to FDA, including new drug application, abbreviated new drug applications, among others. Do you believe that FDA has clear authority to require electronic labeling of prescribing information? If yes, please explain why.**

FDA generally cannot disclose the contents of a rulemaking document in advance of publication. As with any rulemaking, the proposed rule, when published, will set forth the basis of FDA’s authority to implement the proposed changes.

#### **The Honorable Tim Murphy**

- 1. One of the key principles of the Hatch-Waxman Act is the sameness principle. Under current law, the generic drug product must have the same active ingredient, dosage form, strength, route of administration, and labeling as the brand drug product. In practice this requires all labeling for generic drugs to be the same as labeling for brand products, meaning generic manufacturers are not permitted to make any changes to their labeling that is not consistent with labeling of a brand product. The proposed rule represents a shift in FDA's interpretation of this requirement. Will you please explain why FDA has changed its interpretation of the labeling requirements under Hatch-Waxman?**

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, because the generic drug industry has matured and captured an increasing share of the market, the proposal is based on the conclusion that an abbreviated new drug application (ANDA) holder should 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 brand drug manufacturers may discontinue marketing after generic drug entry. The proposed rule would

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. As described in the proposed rule, 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, if so, whether modifications to the labeling in the supplement 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.

- 2. Like brand drug manufacturers, generic drug manufacturers are required under current law to share information with FDA about adverse events resulting from use of their drug product. When this information is reported to FDA, does FDA have the authority currently to require a labeling change for brand and generics if the agency believes an update to the safety information is in the interest of public health? Do you have any reason to believe that generic drug manufacturers are not reporting adverse events to FDA as required by current law? If a generic drug manufacturer does not report adverse events in a timely manner, what penalties are available to FDA to enforce this requirement?**

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.

FDA assesses compliance with the requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA and submission of adverse drug experience reports to FDA through inspections of selected drug manufacturers and contractors working on their behalf. FDA may issue Warning Letters, Untitled Letters, or take other appropriate action based on inspectional observations.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes FDA to require certain drug and biological product application holders to make safety-related labeling

changes based on “new safety information” that becomes available after approval of the drug or biological product. “New safety information” is defined in section 505-1(b) of the FD&C Act. However, it is FDA’s view that, notwithstanding the section 505(o)(4) process, the labeling changes process under 21 CFR 314.70 and 601.12 continues to apply to application holders in situations in which the application holder becomes aware of newly acquired information, including in circumstances that meet the criteria for submission of a CBE-0 supplement.

### The Honorable Renee Ellmers

- 1. The sameness principle is one key tenants of the Hatch-Waxman Act. The generic product must be the same as the innovator product when it comes to active ingredient, dosage form, strength, route of administration, and labeling. Congress put these requirements into place to ensure the public trust in the nation's pharmaceutical supply so that patients who took a generic drug would know that the drug would produce the same clinical effect as the originator product. It appears that the proposed rule guts the fundamental idea of sameness by allowing brands and generics to have different labeling.**

**As a nurse, administering life saving medications to patients can be a matter of proper timing. I am concerned that multiple different versions of labeling, for the same drug, will lead to confusion among practitioners. I am also concerned about the welfare of patients. How would you respond to these concerns?**

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.

- 2. Some commentators have recommended that FDA address the Mensing issue by moving to a prior approval system for safety labeling changes for all drugs, both New Drug Applications (NDA's) and Abbreviated New Drug Application (ANDA's), in the**

**multisource environment. What do you think of that approach? Did FDA consider it in the course of formulating this proposal?**

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 considered several alternatives that would allow certain requirements of the proposed rule to vary. However, FDA proposed the regulatory change that it believed 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 received a great deal of public input from various stakeholders during the comment period on the proposed rule. FDA is carefully reviewing the comments that have been submitted to the public docket and will determine next steps based on our analysis of the comments.

**3. Under current law, generic drug manufacturers are required to report serious adverse events regarding their drug products to FDA within 15 days. Is that correct?**

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.

**4. Has it been brought to your attention that generic drug manufacturers are not meeting their obligations to report adverse events? If yes, what enforcement authority does FDA have currently to ensure that generic drug manufacturers comply with adverse event reporting requirements?**

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.

FDA seeks to ensure compliance with the requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA and submission of adverse drug experience reports to FDA through inspections of selected drug manufacturers and contractors working on their behalf. FDA may issue Warning Letters, Untitled Letters, or take other appropriate action based on inspectional observations. Failure to comply with the adverse event reporting requirements violates Sections 301(e) and 505(k) of the FD&C Act.

5. **As you know, generic manufacturers only have access to scientific and medical evidence for their own products. Generic manufacturers do not have access to clinical trial and post market surveillance data for the brand drug product or another drug manufacturer's product because it is proprietary information. Is it correct that only FDA is in possession of all relevant scientific, clinical information related to the safety and efficacy of any drug product, whether brand or generic? If yes, isn't FDA then best positioned to determine whether an update to the safety information of a brand or generic product is in the interest of public health?**

The need to communicate certain safety-related labeling changes as promptly as possible based on newly acquired information available to manufacturers 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. 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.

As described in the proposed rule, during FDA’s review of a generic drug manufacturer’s 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. FDA has received a great deal of public input from various stakeholders during the comment period on the proposed rule. FDA is carefully reviewing the comments that have been submitted to the public docket and will determine next steps based on our analysis of the comments.

6. **It has come to my attention that back in September, the FDA created a \$20 million program to test the safety and quality of generic products. What was the reason for the creation of this program? One of the news articles mentioned that your agency has "acknowledged reports that some people may experience an undesired effect when switching from some brand name drugs to generic versions." FDA's acknowledgement regarding this problem is very troubling to me, particularly from a patient and provider perspective. I am interested in your thoughts on this important patient safety issue.**

A generic drug is the same as a brand-name drug in active ingredient, dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. FDA requires generic drugs to meet the same high standards for quality, strength, purity, and stability as brand-name drugs.

Regarding your assertion that “FDA created a \$20 million program to test safety and quality of generic drugs,” you may be referring to FDA’s generic drug regulatory science initiative. In July 2012, Congress passed GDUFA (Title III of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144)). GDUFA is designed to enhance public access to safe, high-quality generic drugs and reduce costs to industry and patients. To support these goals, FDA agreed in the GDUFA commitment letter to work with industry and interested stakeholders on identifying regulatory science research priorities specific to generic drugs for each fiscal year covered by GDUFA. The commitment letter outlines FDA’s performance goals and procedures under the GDUFA program for the years 2012–2017. The commitment letter can be found at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

The FY 2013 regulatory science research priorities list was developed by FDA and industry and included in the GDUFA commitment letter. To implement the FY 2013 priorities list, the Office of Generic Drugs awarded \$17 million in external contracts and grants to initiate new research studies during FY 2013. Four million dollars were allocated to support internal research related to generic drugs. This includes rapid response capabilities through equipment for FDA labs and support for laboratory research fellows at FDA, as well as research fellows to work on data analysis and coordination of internal activities with external grants and contracts.

On June 21, 2013, the Office of Generic Drugs held a public hearing to gain input in developing the FY 2014 regulatory science priorities list. This list was prepared based on internal Center for Drug Evaluation and Research discussions, comments received from this public hearing, and comments submitted to the public docket. The FY 2014 Regulatory Science Priorities are as follows: 1) Postmarket evaluation of generic drugs, 2) Equivalence of complex products, 3) Equivalence of locally acting products, 4) Therapeutic equivalence evaluation and standards, and 5) Computational and analytical tools.

On May 16, 2014, FDA hosted a public hearing to obtain input from industry and other interested stakeholders on the identification of regulatory science priorities for FY 2015. To help fulfill FDA’s mission, FDA sought input on the following topics: 1) Current regulatory science challenges that limit the availability of generic drugs, 2) Regulatory science approaches to improve the preapproval evaluation of therapeutic equivalence of generic drugs, 3) Post-approval regulatory science approaches to ensure the therapeutic equivalence of approved generic drugs, 4) Prioritization of FY 2015 regulatory science research topics for generic drugs based on public health impact, and 5) The need for additional or revised draft guidance to clarify FDA’s scientific recommendations related to generic drug development. FDA is considering all comments made at this hearing and received through the docket as it develops its FY 2015 GDUFA Regulatory Science Plan. Additional information concerning GDUFA, including the text of the law and the commitment letter, can be found on the FDA web site at <http://www.fda.gov/gdufa>.

## Attachment 2 – Member Requests for the Record

*During the hearing, Members asked you to provide additional information for the record and you indicated that you would provide that information. For your convenience, descriptions of the requested information are provided below,*

### The Honorable Joseph R. Pitts

- 1. In February of 2013 while FDA was drafting this proposed rule, agency officials met with several plaintiffs lawyers, including at least one representative from the American Association for Justice, also known as the Association of Trial Lawyers of America. In fact, according to FDA's public calendar, one of the agency participants in this meeting was Daniel Siegelman from the Office of the Commissioner, who is himself a former prominent member of trial bar. Would you please provide the Committee with the minutes from this February 2013 meeting?**

On May 6, 2014, FDA provided responsive documents to the Committee, regarding the Committee's requests on the February 2013 meeting. FDA has identified no record of minutes having been recorded for this meeting.

### The Honorable Gus Bilirakis

- 2. The FDA frequently issues guidance better informing industry of FDA's expectations. How many guidance documents has FDA issued related to updating of generic drug labeling in the past decade?**

Guidance documents represent the Agency's current thinking on a particular subject, and are one means by which FDA informs industry of acceptable approaches to comply with applicable statutory and regulatory requirements. Documents related to updating generic drug labeling include the following: Guidance for Industry on Revising ANDA Labeling Following Revision of the RLD Labeling (May 2000), Guidance for Industry on Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 2013), and Guidance for Industry on Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act (July 2013). FDA also discusses its interpretation of statutory and regulatory requirements and explains its policies regarding compliance with such requirements in preambles to a proposed or final regulation and other Agency statements.

