4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0849]

Establishing Timeframes for Implementation of Product Safety Labeling Changes; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is seeking comments on specific issues related to its authority under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to require or order safety labeling changes for approved prescription drug products based on new safety information that becomes available after a drug product is approved. The FD&C Act specifies the timeframes within which a safety labeling change must be submitted when required or ordered by the FDA, and timeframes for FDA to conclude its review and take regulatory action regarding safety labeling changes. FDA's regulations also provide procedures by which labeling changes that do not qualify as changes based on new safety information can be requested by FDA or by the holder of the drug approval. FDA is seeking public input to assist the Agency in establishing specific timeframes for implementing both types of labeling changes.

DATES: Submit either electronic or written comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit electronic comments on this document to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug

Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted. Title IX, Subtitle A, section 901 of FDAAA added to the FD&C Act new section 505(o) (21 U.S.C. 355(o)), which authorizes FDA to require labeling changes when the Agency becomes aware of new safety information it believes should be included in the labeling of an approved drug product. [1]

Before the enactment of FDAAA, if FDA believed that a labeling change was necessary to address safety information newly identified after approval of a drug product, the Agency would ask the application holder to make the appropriate labeling changes. In most cases, application holders responded to FDA's requests for labeling changes by negotiating appropriate language with FDA staff to address the concern, and then submitting a supplement or amended

[1] For purposes of this notice, drug product means a human drug product including a biological drug product. Labeling includes the carton or other container or packaging labels, the prescribing information, patient package inserts, and Medication Guides.

supplement to obtain approval of the changes. FDA routinely asked applicants to submit supplemental applications to revise the labeling of approved products, but the Agency lacked the authority to compel changes to product labeling based on new safety information. At times, FDA and application holders discussed the appropriate timeframe by which new labeling would be made available. Typically products that had already moved beyond the manufacturing line were not withdrawn from distribution to change existing labeling under the timeframes.

Under FDAAA, FDA is now authorized to require and, if necessary, order application holders to implement safety labeling changes to reflect new safety information (section 505(o)(4) of the FD&C Act). Although the statute provides specific and relatively short timelines for submission and review of FDAAA-required safety labeling changes following a notification or order from FDA, the statute does not include specific deadlines for how soon the revised labeling must be incorporated into the packaging of the product that is offered for sale, or into other labeling (section 505(o)(4) of the FD&C Act).

In an effort to make revised safety labeling available as soon as possible after the changes required under FDAAA are approved, FDA has recommended that application holders post the revised labeling on their Web sites within 10 days of approval. (See draft guidance for industry entitled "Safety Labeling Changes--Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act" (76 FR 20686, April 13, 2011)). In letters approving supplements with safety labeling changes, FDA has also recommended that revised labeling accompany the product within "a reasonable amount of time" and has occasionally suggested specific timeframes when this could occur. However, we have not yet announced general timeframes in which we expect new labeling to be disseminated nor have we established the timeframe for when product packaging needs to reflect the revised label.

In addition to safety labeling changes that may be required under FDAAA, FDA may continue to request safety labeling changes under existing regulations and application holders may continue to propose labeling changes on their own initiative (§§ 314.70 and 601.12 (21 CFR 314.70 and 601.12)). Existing regulations in §§ 314.70 and 601.12 describe several mechanisms for effecting proposed labeling changes to approved drug applications including the following: (1) A prior approval supplement (PAS) is used for changes that must receive approval before being implemented; (2) a changes-being-effected supplement (CBE) is used for other kinds of labeling revisions that must be received by the Agency prior to distribution of the drug with the revised labeling; and (3) the annual report for the drug product is used for certain minor changes that need only be described in the next annual report.

Current labeling regulations do not provide specific timeframes for implementing other safety labeling changes--changes not required under FDAAA--that are made by submitting a PAS or CBE, or by reporting the change in the annual report.

II. Purpose of Request for Comments

Because safety labeling changes may be related to serious risks, this information must be promptly communicated to prescribers and patients. Thus, it is important for FDA to clarify its expectations regarding the timeframes for applicants to implement safety labeling changes to ensure that the labeling is updated in a timely manner. FDA anticipates that in most cases, as in the past, it will not be necessary for products with existing labeling to be withdrawn from distribution and that under certain circumstances it may be appropriate for products with existing labeling to remain in distribution until the current product inventory is exhausted.

FDA is interested in hearing from application holders, manufacturers, distributors, and other stakeholders about their experience with and views on the practical implementation of

revised product labeling, including their views as to how factors in the following three categories may affect implementation: (1) Drug manufacturing and packaging, and printing labels and other labeling; (2) supply chain issues; and, (3) other issues. FDA may use the information received to develop draft guidance for industry regarding timeframes for revising product labeling following the approval of safety labeling changes, and may apply these timeframes to particular safety labeling changes.

III. Questions Posed by FDA

With this notice, FDA is soliciting comments from application holders, manufacturers, distributors, and other stakeholders on the following questions:

A. Considerations Related to Drug Manufacturing and Packaging, and to Printing Labeling

1. What are the considerations related to drug manufacturing and packaging, of which FDA should be aware, as they relate to implementation of revised product labeling?

2. What are the considerations related to printing labels and other types of labeling of which FDA should be aware, as they relate to implementation of different types of revised product labeling?

B. Supply Chain Issues

3. What are the supply chain factors (including storage, shipping, and distribution factors) of which FDA should be aware that limit or otherwise affect how quickly a labeling change can be implemented?

C. Other Considerations

4. What alternative labeling mechanisms (e.g., having labeling available on a product Web site) could be used to disseminate new safety information quickly to patients and health care providers?

5. How should the relative seriousness of the new safety information, or whether the new safety information describes a newly identified risk, or strengthens a risk already identified in current labeling, affect timelines for implementing revised product labeling?

6. What are the implementation considerations when the safety labeling change is to prescriber versus patient labeling (or both)?

7. What would be a reasonable timeframe following approval of revised safety related labeling changes for applicants to implement the revised labeling? Please relate this timeframe to the optimal point in the supply chain (e.g., newly manufactured product, newly shipped product) and the type of labeling change.

8. Are there other considerations or options related to implementing safety labeling changes of which FDA should be aware?

IV. Comments

Interested persons may submit either electronic or written comments regarding this document to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, as well as at http://www.regulations.gov.

Dated: December 14, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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