FDA/CDER
SMALL BUSINESS CHRONICLES
SEPTEMBER 20TH, 2013

July 2013 Guidance for Industry:
Safety Labeling Changes - Implementation of Section 505(o)(4) of the FD&C Act

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Safety Labeling Changes for Prescription Drugs

FDA is committed to protecting and promoting public health by ensuring the quality, safety, and effectiveness of medical products. Thus, it would make sense that FDA has the authority to require drug labeling changes when new safety issues are of concern. In fact, until passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA) FDA's authority was limited to ***requesting*** labeling changes. With the passage of FDAAA, FDA can ***require*** safety labeling changes in certain circumstances.

New Requirements Section 505(o)(4) of the Federal Food, Drug, and Cosmetic (FD&C) Act, added by FDAAA, authorized FDA to require and, if necessary, ***order*** labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug. It also imposed 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.

FDA may require safety labeling changes for:

- Prescription drug products with an approved new drug application (NDA)
- Biological products with an approved biologics license application (BLA)
- Prescription drug products with an approved abbreviated new drug application (ANDA), if the NDA reference listed drug (RLD) is not currently marketed

The requirement applies to products that are not marketed, unless approval of the NDA, BLA, or ANDA has been withdrawn in the *Federal Register*. This ***does not*** apply to nonprescription (over-the-counter) drugs approved under an NDA or ANDA. It also does not apply to unapproved drugs, which do not, by definition, have approved labeling. However, FDA may take other regulatory actions against unapproved drugs for which safety issues have been identified.

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New Safety Information FDA may learn about new safety information from many sources. Once FDA becomes aware of new safety information, FDA then evaluates the information and determines whether it should be included in the labeling for a drug or class of drugs.

Information that may trigger safety labeling changes under section 505(o)(4) includes:

- information that would be described in new or revised language in the following sections of the prescribing information: Boxed Warnings; Contraindications; Warnings and Precautions; Drug Interactions ; Adverse Reactions

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Note that certain safety-related label changes may warrant changes to an existing Medication Guide or creation of a new Medication Guide to ensure that all labeling for the product is consistent. Medication Guides are part of the product labeling and are also potential elements of a Risk Evaluation and Mitigation Strategy (REMS). Thus, labeling changes may also necessitate changes to REMS documents and REMS materials.

In addition, the following changes *may not* trigger safety labeling changes under section 505(o)(4):

- changes made only to the Adverse Reactions section, but do not warrant inclusion in other sections of labeling (such as Warnings and Precautions)
- minor revisions to risk information that is already in the labeling
- minor editorial changes to any part of the labeling

Note that application holders may continue to submit labeling supplements using standard regulatory processes when they learn about information that they believe should be included in their product's labeling.

Procedures Once FDA has determined that there is new safety information that should be included in labeling, FDA sends a safety labeling change notification letter to the application holder(s). After receiving notification of the required safety labeling changes, the application holder(s) must either:

- submit a supplement with proposed labeling changes to reflect the new safety information [a *changes-being-effected supplement* (CBE-0) if the labeling changes are identical to those that FDA requested, or a *prior approval supplement* if alternative labeling changes are proposed]; or

- notify FDA that it does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted (a rebuttal statement).

Following notification, the labeling supplement or rebuttal statement must be submitted within 30 calendar days. FDA will promptly review and act upon a safety labeling changes supplement or rebuttal statement. For supplements that propose acceptable wording, FDA's goal is to act within 30 calendar days of receipt of the supplement. If the proposed revised language cannot be approved without changes FDA will initiate a 30-day discussion period. At the end of this period (plus any applicable extension period), FDA has 15 calendar days to either send a supplement approval letter to the applicant, or order the application holder to make the required labeling changes.

Enforcement If the responsible person or application holder does not comply with the requirements for section 505(o)(4), they would be in violation of the FD&C Act and may be subject to enforcement actions including charges under section 505 of the FD&C Act; misbranding charges; civil monetary penalties; seizure and injunction.

You may find details and additional information on safety-labeling changes in FDA's Guidance for Industry – Safety Labeling Changes —Implementation of Section 505(o)(4) of the FD&C Act.

Until next time,
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