Alerts and Updates

Labeling Changes For Prescription Drugs After New Safety Information: FDA's Draft Guidance

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The U.S. Food and Drug Administration (FDA) has issued a draft guidance detailing its current view on section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act. Section 505(o)(4) allows the FDA to require postapproval labeling changes to drug and biological-product labeling when the FDA has learned of new safety information.[1] The rule was enacted to modify the past practice of protracted labeling negotiations, which ultimately left the FDA with limited options if an application holder failed to comply.

Application of Section 505(o)(4)

Section 505(o)(4) applies to New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and Biologics License Applications (BLAs), but is separate and distinct from labeling supplements that may be submitted voluntarily by an application holder. The FDA's actions under 505(o)(4) are based on the potential for new safety information obtained from a source other than the application holder. Specifically, new safety information may be information from "a clinical trial, an adverse event report, a postapproval study. . . [or] peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system. . . or other scientific data deemed appropriate by [the Secretary]." That information is related to either:

(A) a serious risk or unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

When the FDA learns of the potential for new safety information, it will use a multidisciplinary team to review the information and determine whether a labeling change is necessary. The FDA anticipates that section 505(o)(4) will be implemented when a change to the boxed warnings, contraindications, warnings and precautions, drug interactions or adverse-reactions sections of the professional labeling is required. However, the FDA has indicated that if a change would be warranted only to the adverse-reactions section and to no other section, the FDA is unlikely to exercise its authority under section 505(o)(4).

Timing and Procedure Under Section 505(o)(4)

The FDA initiates an action under section 505(o)(4) by issuing a notification letter to the application holders. The notification letter will indicate:

- The source of the new safety information;
- A description of the new safety information;
- Proposed labeling changes; and
- Instructions for submitting a "prior approval supplement" or a "changes-being-effected supplement."

In response to the notification letter, an application holder has two options:

1. The application holder may submit one of two supplements, as provided in the notification letter. The FDA's guidance indicates that a "changes-being-effected supplement" does not require further agency approval. In contrast, a "prior approval supplement" requires further FDA review before the product may be distributed with the proposed labeling; or

2. If the application holder does not agree with the FDA's position, it may submit a rebuttal statement setting forth the reasons why a change to the labeling is not necessary. Either of these two responses must be submitted within 30 calendar days of the date on the notification letter.

The FDA's review of either a supplement or a rebuttal statement is similar in terms of timing. Upon receipt of a supplement, the FDA will first determine if the revised language can be approved without changes. If so, the FDA will attempt to approve the supplement within 30 calendar days. However, if changes are warranted, the FDA will open a 30-day discussion period, which may be extended under limited circumstances. Fifteen days after the 30-day discussion period has ended, the FDA will either send a supplement approval letter if an agreement was reached, or order the application holder to make the FDA's required labeling changes. Should an application holder not submit a labeling supplement or rebuttal statement, the FDA may issue an order for the labeling to be changed.

The timing outlined above is similar for all types of applications noted above with one exception: ANDA holders with a marketed NDA reference listed drug (RLD). In this case, the Office of Generic Drugs will notify the ANDA holder of the required labeling changes once it is approved for the NDA RLD. Within 30 days after this notification, the ANDA holder will then need to submit a "changes-being-effected supplement." This is consistent with the FDA's regulations, which require the ANDA's labeling to mimic that of the RLD in most circumstances.

The End Result: New Labeling, Appeals or Violations

The FDA's use of section 505(o)(4) may have one of several results: new labeling, an appeal of the FDA's order or an enforcement action if the application holder does not comply. With regard to revised labeling, the FDA's guidance indicates that it should be available on the application holder's website within 10 calendar days of approval. As for the timing of implementing revised labeling for package inserts and other printed materials, the FDA will issue a guidance on this topic. Alternatively, the FDA's guidance indicates that an appeals process is available for applicants who disagree with any

ordered labeling changes. Should an application holder not comply with the FDA's order, the application holder may face an enforcement action by the FDA. This may include unapproved new drug charges, misbranding charges, civil monetary penalties or seizure of the product and an injunction. Nonetheless, the FDA's guidance indicates a willingness to negotiate labeling changes using the platform provided by section 505(o)(4).

For Further Information

If you have any questions about this *Alert*, please contact Frederick (Rick) R. Ball, Elese Hanson, any member of the Pharmaceutical, Pharmacy & Food industry group or the attorney in the firm with whom you are regularly in contact.

Note

1. *See* Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(o)(4).