Guidance for Industry

Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2012
Drug Safety

Guidance for Industry

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides information on the implementation of section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)), which was added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 505(o)(4) authorizes FDA to require certain drug and biological product application holders to make safety-related labeling changes based on safety information that becomes available after approval of the drug or biological product.

Section 505(o)(4) of the Act authorizes FDA to require safety labeling changes for the following products:

- Prescription drug products with an approved new drug application (NDA) under section 505(b) of the Act
- Biological drug products with an approved biologics license application (BLA) under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)
- Prescription drug products with an approved abbreviated new drug application (ANDA) under section 505(j) of the Act, if the NDA reference listed drug (RLD) is not currently marketed

The safety labeling changes provided for in section 505(o)(4) apply to the above-listed products, including products that are not marketed, unless approval of the NDA, BLA, or ANDA has been withdrawn in the *Federal Register*.

[1] This guidance has been prepared by the FDAAA Title IX Working Group in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

Section 505(o)(4) ***does not*** apply to nonprescription (over-the-counter) drugs approved under an NDA or to marketed unapproved drugs.[2]

This guidance does not address labeling supplements submitted voluntarily by an application holder. Application holders may submit labeling supplements for review at any time and without prior notification to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA has always had the ability to request safety-related changes to the labeling of approved medical products. However, until Congress passed and the President signed the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA's authority was relatively limited.

A. Past Practice

In the past, FDA has requested that holders of applications for approved products make labeling changes related to safety to address serious risks. FDA typically learned of the potential for such serious risks from a variety of sources, including FDA's adverse events reporting systems (see list of sources in Appendix A). In most cases, application holders responded to these requests for labeling changes by negotiating appropriate language with FDA staff to address the concerns and then submitting a supplement or amended supplement to obtain approval of the changes. Negotiations were often protracted, and FDA had few tools at its disposal to end negotiations and require the changes.

Before FDAAA, if the application holder did not respond to FDA's request or did not agree with the requested labeling changes, FDA could take the following actions:

- FDA could initiate proceedings to withdraw approval of the drug[3] — an action not normally desirable if some patients were benefitting from the drug despite its risks.

[2] Section 505(o)(4) of the FD&C Act does not apply to unapproved drugs, which do not, by definition, have approved labeling. However, FDA may prioritize action against unapproved drugs for which safety issues have been identified. When FDA becomes aware of the need for safety labeling changes that could affect unapproved drugs, the responsible review division in the Office of New Drugs (OND) will contact the Unapproved Drugs Coordinator in the Immediate Office, OND, and the Office of Unapproved Drugs and Labeling Compliance (OUDLC) to initiate appropriate actions.

[3] For the purposes of this guidance, all references to *drugs* mean human drugs, including biological drug products, regulated by CDER or CBER unless otherwise specified.

- FDA could notify the public about the safety information through mechanisms like Public Health Advisories or notification on the FDA web site describing the safety information and the need for labeling changes.
- If in FDA's judgment the absence of the new safety information from the drug's label rendered the product misbranded, FDA could take appropriate enforcement action.

Congress recognized the limitations of FDA's authority in this area and, in FDAAA, gave FDA new authorities to require safety labeling changes in certain circumstances.

B. New FDAAA Authorities and Requirements

On September 27, 2007, the President signed FDAAA (Public Law 110-85). Section 901 of Title IX of FDAAA amended the FD&C Act by adding new section 505(o). Section 505(o)(4) authorizes 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. 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.

III. IMPLEMENTATION OF SAFETY LABELING CHANGES UNDER FDAAA

The following sections answer key questions about the safety labeling changes that have been implemented under FDAAA.

A. What is *New Safety Information*?

*1. What Does **New Safety Information** Mean?*

Section 505(o)(2)(C) of the FD&C Act states that, for the purposes of section 505(o), the phrase *new safety information* is defined in section 505-1(b) (21 U.S.C. 355-1(b)) as "information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by [FDA]" about:

- "A serious risk or an unexpected serious risk associated with use of the drug that [FDA] 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 (REMS) was required, or since the last assessment of the approved [REMS] for the drug" (emphasis added), ***or***
- "The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]."

The phrases *serious risk* and *unexpected serious risk* are also defined in section 505-1(b) of the FD&C Act and are included in the Glossary at the end of this guidance.

It is FDA's view that the statutory definition of *new safety information* is broad to enable FDA to require application holders to add information about serious risks to the labeling of a drug when necessary.

2. How Does FDA Learn About New Safety Information?

FDA may learn about new safety information from many sources, including, but not limited to those listed in Appendix A. FDA may derive new safety information through various means, including, but not limited to the following:

- A new analysis of existing information (under section 505-1(b); see guidance section III.A.1)
- An assessment of the risks and benefits of the drug as it pertains to a new use of the drug, a new indication for the drug, or the use of the drug in a new population
- Information on the effectiveness of a previously approved REMS obtained since the last assessment of that REMS

3. How Will FDA Evaluate the New Safety Information?

FDA will form a multidisciplinary team to evaluate new safety information for possible incorporation into a drug's labeling under section 505(o)(4).[4] The composition of the team will vary depending on the nature of the safety concern. Within CDER, the Office of Generic Drugs (OGD), the Unapproved Drugs Coordinator, and the Office of Unapproved Drugs and Labeling Compliance (OUDLC) may be notified, as appropriate. The team's discussions and evaluations of the new safety information may include, but are not limited to, presentations at internal FDA meetings, Drug Safety Oversight Board meetings, or Advisory Committee meetings. Established CDER policies and procedures, including notification as appropriate of application holders, will be followed.[5] Public communication about drug safety issues is further described in a separate guidance.[6]

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[4] If the safety information is relevant to more than one member of a drug class, the multidisciplinary review team will identify the affected members of the class and include staff from all relevant review divisions and offices. Review of new safety information for a drug class will follow the same procedures as for individual drugs.

[5] See Manual of Policies and Procedures (MAPP) 6700.7, Safety Labeling Changes Under Section 505(o)(4) of the FDCA; MAPP 4121.2, Tracking of Significant Safety Issues in Marketed Drugs — Use of the DARRTS Tracked Safety Issue (TSI), and MAPP 6700.9, FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System. FDA MAPPs are available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[6] See FDA guidance for industry on *Drug Safety Information—FDA's Communication to the Public*. FDA guidances are available on FDA's guidance web page at http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm.

We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidances (Drug) Web page.

B. What Types of Safety Labeling Changes Could Be Required Under Section 505(o)(4)?

FDA expects that information that meets the standard of new safety information that should be included in labeling, thereby triggering safety labeling changes under section 505(o)(4), generally will include, but is not limited to, 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

FDA expects that labeling changes that address new safety information about serious risks that affect a class of drugs will be required under the authority of section 505(o)(4) of the FD&C Act.

If certain changes to the prescribing information are required under section 505(o)(4), other changes to the product labeling, including changes to an existing Medication Guide or creation of a new Medication Guide, may also be required 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 REMS.

If FDA notifies an application holder that, under section 505(o)(4), a new Medication Guide must be created (and a class Medication Guide does not already exist), the application holder must submit a draft of the Medication Guide within 30 days, as required by section 505(o)(4)(B).

FDA recognizes that if a new Medication Guide is required and a Medication Guide for the class does not already exist, it could be challenging to create a Medication Guide that adequately describes risks and benefits in patient friendly language within the submission time frame required under section 505(o)(4) of the FD&C Act. (Medication Guide language is generally derived from approved prescribing information.) Therefore, upon request from the application holder, FDA may consider exercising enforcement discretion on a case-by-case basis to allow additional time with regard to the submission of a new Medication Guide.

Changes to prescribing information required under section 505(o)(4) may affect REMS documents and REMS materials other than a Medication Guide or patient package insert. These changes are managed under section 505-1 as REMS modifications and are not part of required safety labeling changes.

FDA does not anticipate that all labeling changes that may be related to safety will be required and reviewed under section 505(o)(4) of the FD&C Act. For labeling changes that are not required and reviewed under section 505(o)(4), application holders may continue to submit labeling supplements using standard procedures (See 21 CFR 314.70 and 601.12).

FDA expects that information that results in changes made only to the ADVERSE REACTIONS section, but does not warrant inclusion in other sections of labeling (such as WARNINGS AND PRECAUTIONS), would not normally trigger required safety labeling changes under section 505(o)(4). In addition, minor revisions to risk information that is already in the labeling (e.g., updating the risk of neutropenia in the label of a cytotoxic chemotherapy drug or updating information about the risk of hypoglycemia for an antidiabetic agent) may not trigger required safety labeling changes under section 505(o)(4) in all circumstances. FDA also anticipates that minor editorial changes to any part of the labeling would not trigger required safety labeling changes under section 505(o)(4).

IV. PROCEDURES

A. How Will FDA Notify Application Holder(s) of Required Safety Labeling Changes?

Once FDA has determined that there is new safety information that should be included in labeling, FDA plans to send a safety labeling change notification letter (notification letter) to the application holder.[7] Under section 505(o)(5), a holder of an approved NDA, BLA, or ANDA without a marketed NDA reference listed drug (RLD) will be notified and required to make the changes, unless approval of the application has been formally withdrawn in a *Federal Register* notice.[8] If the new safety information applies to more than one application holder, FDA plans to send a letter on the same day to each holder of an approved NDA, BLA, and/or ANDA without a marketed NDA RLD.

FDA will include the following information in the notification letter:

- The source from which the new safety information was derived
- A brief description of what the new safety information is about (a serious risk or an unexpected serious risk associated with the use of the drug, or the effectiveness of the REMS)
- A statement that the new safety information applies to a drug class, if relevant
- Proposed labeling changes
- Instructions regarding the circumstances in which the application holder should respond by submitting proposed labeling changes as a *prior approval supplement*[9] or as *changes-being-effected supplements*[10]

[7] FDA will generally send all letters by electronic mail or facsimile in addition to sending a hard copy to ensure that the application holder's receipt date is identical or similar to the FDA letter date.

[8] Requirements under section 505(o)(4) apply to NDAs, BLAs, and ANDAs without a currently marketed reference listed drug approved under an NDA, ***including discontinued products***, unless approval of an application has been withdrawn in the *Federal Register*. Therefore, requirements described in a safety labeling change notification letter apply unless approval of the application has been withdrawn in the *Federal Register*.

[9] A *prior approval supplement* proposes changes that require supplement submission and approval prior to the distribution of the product with those changes. See 21 CFR 314.70(b) and 601.12(f)(1).

[10] FDA regulations provide for two types of changes-being-effected supplements. A *supplement - changes-being-effected* proposes changes that do not require FDA approval prior to distribution of the product; for such changes, the application holder may distribute the product with the changes upon FDA's receipt of the supplement (see 21 CFR 314.70(c)(6) and 601.12(f)(2)).

B. How Should Application Holders Respond to a Notification Letter?

Section 505(o)(4)(B)(i) and (ii) states that, 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; 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).

If the notification letter applies to only one application, and the application holder submits a supplement proposing labeling changes identical to those that FDA included in the notification letter, the application holder may submit a *supplement - changes-being-effected*, and the changes will be effective upon FDA's receipt of the supplement.

If the notification letter is for class labeling changes involving more than one application, and the application holder submits a supplement proposing labeling changes identical to those that FDA included in the notification letter, the application holder may submit a *supplement - changes-being-effected in 30 days*. Changes will be effective 30 days after FDA's receipt of the supplement unless FDA informs the application holder that the discussion period must be extended to review and consider alternative wording from other class members. In all other situations, the application holder(s) should submit a *prior approval supplement* to propose alternative labeling changes that reflect the new safety information.

It is FDA's view that the labeling changes process under 21 CFR 314.70 and 601.12 continues to apply to application holders[11] in situations in which the application holder becomes aware of

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A *supplement - changes-being-effected in 30 days* proposes changes that do not require FDA approval prior to distribution of the product; however, the application holder may not distribute the product with the changes until 30 days following FDA receipt of the supplement, and, may not distribute the product with the changes if within 30 days following FDA's receipt of the supplement, FDA directs the application holder otherwise (see 21 CFR 314.70(c)(3)).

[11] To implement the statutory prohibition against marketing a misbranded product, 21 CFR 201.57(c)(6) requires that prescription drug labeling be "revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with the drug" (see also sections 502(a),(f),(j), and (n) of the FD&C Act).

ANDA holders cannot, however, make labeling changes through the formal supplement process under 21 CFR 314.70 in all circumstances in which NDA holders can because an ANDA's labeling must be the same as the NDA RLD's labeling (with some exceptions, as described in 21 CFR 314.94(a)(8)(iv)). Accordingly, the *changes-being-effected* supplement process under 21 CFR 314.70(c) is not expressly available except to match the RLD labeling or to respond to FDA's specific request to submit a labeling change under this provision. ANDA holders are obligated to provide FDA with information about labeling concerns. See 57 FR 17950, 17961 (April 28, 1992). An ANDA holder may submit a prior approval supplement to request a change to product labeling, and "FDA will determine whether the labeling for the generic and [reference] listed drugs should be revised" (57 FR at 17961). ANDA holders also have a duty to inform FDA of certain adverse events in compliance with postmarket reporting requirements, to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarket

newly acquired information independent of an FDA notification. However, in situations in which FDA becomes aware of new safety information that it believes should be included in the labeling and notifies an application holder, the process established by section 505(o)(4) applies; in such situations, an application holder should submit proposed labeling changes as described above.

Following notification, the labeling supplement or rebuttal statement must be submitted within 30 days (section 505(o)(4)(B)). FDA has interpreted ***within 30 days*** to mean within 30 calendar days of the date that the notification letter is issued. FDA will forward copies of safety labeling change letters (including notification letters and orders) by fax or e-mail so that they will be received on the date the document is issued.

An application holder's prior approval supplement may contain proposed edits or counterproposals to the language recommended by FDA. When FDA notifies an application holder that safety labeling changes are needed, FDA is aware of the new safety information that the changes are intended to address. Therefore, application holders should provide explanations (often referred to as "annotated labeling") only for counterproposals or proposed edits to the language recommended by FDA in the notification letter.[12]

C. How Will FDA Review the Required Labeling Supplement or Rebuttal Statement?

Section 505(o)(4)(C) of the Act directs FDA to "promptly review and act upon" a safety labeling changes supplement or rebuttal statement responding to a notification letter.

*1. Meaning of **Promptly Review and Act***

This section describes the process FDA intends to use to review labeling supplements and rebuttal statements, the actions that FDA can take, and the time frame in which FDA expects to take those actions.

a. Labeling Supplements

When an application holder submits a labeling supplement, FDA's review team will conduct a preliminary review of the supplement, consider whether the proposed language in the supplement can be approved or requires further discussion, and proceed as follows:

- If the proposed language, either identical to the language in the notification letter or revised, can be approved without changes, FDA will approve the supplement promptly and notify the application holder by sending a supplement approval letter.[13] For supplements that propose

adverse drug experiences and to annually report "information…that might affect the safety, effectiveness, or labeling of the drug product" (see 21 CFR 314.80, 314.81, and 314.98).

[12] Including the proposed text of the label as a clean copy and as a marked up or track changes version facilitates timely review and discussion of the counter proposed or edited language.

[13] Supplement approval letters for required safety labeling changes are posted on FDA's web site, consistent with FDA's policy for all approval letters.

acceptable wording, FDA's goal is to take action within 30 calendar days of receipt of the supplement.

- If the proposed revised language cannot be approved without changes, the Agency will initiate a discussion period to review and discuss the proposed revisions (section 505(o)(4)(C)). The discussion period would begin on the date that FDA receives the application holder's submission and last no more than 30 calendar days (unless an extension is warranted) (section 505(o)(4)(D)).
- If it is class labeling, and one or more members of the class submit proposed revised language, FDA will inform any application holder(s) that have submitted a supplement-changes being effected in 30 days that changes will not be effective 30 days after FDA's receipt of the supplement and that the discussion period must be extended to review and consider alternative wording from other class members.

Within 15 calendar days of the conclusion of the 30-day discussion period (and any extension period, if applicable), FDA will proceed as follows:

- If FDA and the application holder reach consensus on the proposed labeling, FDA will notify the application holder by sending a supplement approval letter.[14]
- If FDA does not agree with the application holder's proposed labeling changes and FDA and the application holder cannot reach consensus, under section 505(o)(4)(E), FDA can order the application holder to make the required labeling changes (see section IV.E for further discussion of safety labeling changes orders).

b. Rebuttal Statements

Similar to the process for supplements, when an applicant submits a rebuttal statement, FDA's review team will conduct a preliminary review of the rebuttal statement, consider whether FDA accepts the application holder's reasons why labeling changes are not warranted or whether the rebuttal statement requires further discussion, and proceed as follows:

- If FDA accepts the application holder's reasons why labeling changes are not warranted, FDA will promptly notify the application holder. In such situations, FDA's goal is to take action within 30 calendar days of receipt of the rebuttal statement.
- If FDA does not accept the application holder's reasons why labeling changes are not warranted, the Agency will initiate a discussion period (section 505(o)(4)(C)). The discussion period would begin on the date that FDA receives the application holder's rebuttal statement and last no more than 30 calendar days (unless an extension is warranted) (section 505(o)(4)(D)). If the sponsor agrees to submit a labeling supplement during the discussion period, the supplement should be submitted before the end of the discussion period or any extension period, if applicable, and FDA will follow the procedure as outlined above in IV.C.1.a.

[14] Supplement approval letters for required safety labeling changes are posted on FDA's Web Site, consistent with FDA's policy for all approval letters.

Within 15 calendar days of the conclusion of the 30-day discussion period (and any extension period, if applicable), FDA will proceed as follows:

- If FDA and the application holder reach consensus on the reasons why labeling changes are not needed, FDA will notify the application holder.
- If FDA does not agree with the application holder's rebuttal statement and FDA and the application holder cannot reach consensus on the submission of a labeling supplement, under section 505(o)(4)(E), FDA can order the application holder to make the required labeling changes (see section IV.D for further discussion of safety labeling changes orders).

2. Additional Information on Review Procedures

The following sections provide additional information on FDA's review procedures for safety labeling changes supplements or rebuttal statements responding to a notification letter.

a. 30-Day Discussion Periods and Extensions

As explained above in IV.C.1, if FDA does not agree with the wording in the submitted supplement or the reasoning of the rebuttal statement, FDA must initiate discussions that do not extend for more than 30 days after the receipt of the submission (section 505(o)(4)(C) and (D)).

Under section 505(o)(4)(D), FDA may extend the discussion period for more than 30 days, if FDA determines that an extension of the discussion period is warranted. FDA expects that an extension of the discussion period (usually for another 30 days) will be warranted when a 30-day discussion period may not suffice to adequately address all outstanding issues (e.g., the labeling change involves a drug class or the supplement contains significantly revised language). In such cases, before the conclusion of the discussion period, FDA may notify the application holder in writing that the 30-day discussion period has been extended and, when possible, briefly state the reason(s) for the extension. FDA's reasons may include, but are not limited to, the need to consider and discuss the application holder's alternative language, consider additional information, obtain consensus at a higher level within CDER or CBER or among involved offices, or receive input from the Drug Safety Oversight Board or an Advisory Committee.

FDA does not anticipate more than one extension to the 30-day discussion period for most labeling changes.

b. Failure to Respond to a Notification Letter

If the application holder does not submit a labeling supplement or a rebuttal statement within 30 calendar days of the date of the notification letter, the application holder will be considered to have forfeited the review and discussion period, and FDA can issue an order directing that the labeling be changed (see section IV.D for further discussion of safety labeling changes orders).

c. Labeling Change Notifications for ANDAs with a Marketed NDA RLD

Holders of ANDAs with a marketed NDA RLD would usually be notified by OGD of the required safety labeling changes after approval of the labeling supplement for the NDA RLD. ANDA holders should submit the required labeling changes as a *supplement- changes-being-effected* ***within 30 days*** of the date of the written notification from FDA.

3. Additional Information on Review Procedures for a Drug Class

a. Labeling Supplements and Discussion Period(s)

For class labeling changes, it is FDA's policy that labeling decisions should wait until all supplements submitted within 30 days of notification have been reviewed. FDA intends to approve a labeling change common to all class members on the same day unless there is a well-justified, scientific rationale to support different wording for different drug labels. To carefully review supplements from all application holders and to consider the differences and commonalities between products, FDA anticipates that a 30-day extension of the discussion period may be warranted.

To enable consensus on wording of the labeling change, FDA may propose to the application holders specific language to include in the labeling during the discussion period. If agreement is reached, application holders should submit an amendment to their supplement with the agreed-upon wording before the end of the discussion period.

If FDA does not agree with one or more application holder's proposed labeling changes and FDA and the application holder(s) cannot reach agreement, under section 505(o)(4)(E), FDA can order the application holder(s) to make the required labeling changes (see section IV.D for further discussion of safety labeling changes orders).

If FDA and the remaining application holders agree on the proposed labeling, FDA will notify these application holders by sending supplement approval letters. An order issued to one or more application holder(s) will not delay approval of labeling changes for the rest of the class.

For class labeling changes, FDA will send approval letters or Order letters, as needed, to all affected application holders of NDAs, BLAs, and ANDAs without a marketed NDA RLD, on the same day.

b. Rebuttal Statements and Failure to Respond to a Notification Letter

One or more application holders in a class may submit a rebuttal statement or fail to respond, while others submit labeling supplements within the required 30-day time frame. FDA will follow the processes described in IV. C.1.b. and C.2.b. for the application holders who submit a rebuttal or do not respond, respectively. FDA will follow previously described processes for application holders who submit labeling supplements in response to the notification letter. If one or more application holders in a class submit rebuttal statements or fail to respond, it will not delay approval of required safety labeling changes that other application holders in the class submit within the required time frame.

D. How Would FDA Issue an Order for Labeling Changes?

If, at the conclusion of the 30-day discussion period (or extension, if applicable), FDA determines that the application holder's proposed labeling changes do not adequately address the new safety information or finds unacceptable the application holder's reasons why the labeling changes are not warranted, FDA can issue an order to change the product labeling (section 505(o)(4)(E)). FDA may also issue an order if a supplement or rebuttal statement is not submitted within 30 calendar days of the date of the notification letter.

FDA anticipates that orders for labeling changes will be rare and that such actions will first involve discussion with the appropriate CDER or CBER senior managers.

Order letters will be issued within 15 calendar days of the conclusion of the 30-day discussion period (or extension, if applicable) (section 505(o)(4)(E)). FDA plans to include the following in the order letters:

- Approval of any sections of labeling on which the application holder and FDA reached agreement during a discussion period triggered by a supplement submission
- A Complete Response action for the sections of labeling on which the application holder and FDA could not agree during the discussion period
- A brief explanation why the application holder's proposed labeling changes or rebuttal do not adequately address the new safety information
- An order to submit a changes-being-effected supplement within 15 calendar days of the date of the order for specified changes to the sections of labeling on which the application holder and FDA cannot agree (FDA plans to include specific wording for these required labeling changes in the order letter)
- Instructions to the application holder that within ***5 calendar days*** of the date of the order letter, instead of submitting a changes-being-effected supplement, the application holder may appeal the order, through FDA's formal dispute resolution process as described in 21 CFR 10.75 and the guidance for industry on *Formal Dispute Resolution: Appeals Above the Division Level*[15] (section 505(o)(4)(F)) (see section V for further discussion of dispute resolution procedures).

After the application holder submits the changes-being-effected supplement, FDA intends to promptly review the supplement, and if it addresses the new safety information adequately as directed, FDA will approve the supplement, generally ***within 15 calendar days*** of receipt (section IV.D.1). As with other approval letters, the document will be posted on the FDA Web site.

Under section 505(o)(4)(F), if the application holder neither submits a supplement within 15 calendar days of the date of the order nor initiates dispute resolution within 5 calendar days of

[15] This guidance is available on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*. We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the Guidances (Drug) Web page.

the date of the order, the application holder will be in violation of the statute. This may result in enforcement actions, which are described in section VI.

E. When Should New Labeling Be Available?

FDA expects that new approved labeling will be available on the application holder's Web site within 10 calendar days of approval of the labeling supplement, or FDA's receipt of a changes-being-effected labeling supplement. In addition, updates to labeling are posted on FDA's Web site.[16]

FDA acknowledges that incorporating labeling changes into printed material included in new drug shipments usually requires more time than incorporating changes to a Web site. FDA intends to issue guidance outlining its expectations regarding time frames for the availability of labeling changes for package inserts, patient package inserts, and Medication Guides.

F. Will Safety Labeling Changes Letters Be Disclosed?

Safety labeling changes notification letters that apply to more than one application may be posted on FDA's Web site to provide rapid communication to the public of a serious safety risk. Notification letters that apply to a single application are considered confidential commercial information until the resulting supplement is approved.

All safety labeling changes order letters may be posted on FDA's Web site.[17]

V. DISPUTE RESOLUTION

An application holder may appeal an order to make a safety labeling change using the usual dispute resolution procedures (guidance for industry on *Formal Dispute Resolution: Appeals Above the Division Level*)[18] (see section 505(o)(4)(F) of the Act). The appeal should be submitted as correspondence to the NDA, BLA, or ANDA. The application holder should identify the submission as a **Formal Dispute Resolution Request** both on the cover letter and on the outside envelope.

Under section 505(o)(4)(F), the application holder must make its appeal of the order ***within 5 days*** of receiving that order. FDA has interpreted "5 days" to mean "5 calendar days." Appeals received by FDA later than 5 calendar days after the date that the order letter was received will not be entertained. Similarly, for appeals to higher levels, such as the Center Director, application holders should appeal a written determination made by a previous level within 5 calendar days of receiving that determination. The dispute process will be considered to be concluded if an appeal of a written determination is not received within this time frame.

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[16] See http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.

[17] Safety labeling changes order letters are available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm189280.htm.

[18] This guidance is available on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*.

At the conclusion of the dispute resolution process, if FDA determines that a labeling supplement is required, the labeling supplement must be submitted within ***15 days*** of the date of that determination (section 505(o)(4)(G)). FDA has interpreted "15 days" to mean "15 calendar days." If the labeling supplement is not submitted within 15 days, the application holder will be in violation of the statute.

VI. ENFORCING REQUIREMENTS FOR SAFETY LABELING CHANGES

Section 902 of FDAAA gave FDA authority to enforce the section 505(o)(4) requirements for safety labeling changes. If the responsible person[19] or, when applicable, the holder of the approved application under section 505(j) neither submits a supplement within 15 calendar days of the date of a safety labeling change order nor initiates dispute resolution within 5 days, the responsible person or application holder will be in violation of section 505(o)(4) of the Act. In addition, if at the conclusion of any dispute resolution process, the Secretary determines that a supplement must be submitted and such supplement is not submitted within 15 days of the date of the determination, the responsible person or application holder will be in violation of section 505(o)(4) of the Act.

Enforcement action could include one or more of the following:

- Charges under section 505 of the FD&C Act. A responsible person may not introduce or deliver into interstate commerce the drug involved if the applicant is in violation of section 505(o) safety labeling changes requirements (see section 505(o)(1) of the FD&C Act).

- Misbranding charges. A drug is misbranded under section 502(z) of the FD&C Act (21 U.S.C. 352(z)) if the applicant for that drug violates safety labeling change requirements.

- Civil monetary penalties. Under section 303(f)(4) of the FD&C Act (21 U.S.C. 333(f)(4)(A)), an applicant that violates safety labeling changes requirements may be subject to civil monetary penalties of up to $250,000 per violation, but no more than $1 million for all violations adjudicated in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the applicant of the violation. The penalties double for the following 30-day period and continue to double for subsequent 30-day periods, up to $1 million per period and $10 million for all violations adjudicated in a single proceeding. In determining the amount of a civil penalty, FDA will consider the applicant's efforts to correct the violation (see section 303(f)(4)(B) of the FD&C Act).

Such violations may also be subject to additional enforcement action, including but not limited to, seizure of the product and injunction.

[19] Defined at section 505(o)(2)(A) of the Act.

APPENDIX A: EXAMPLES OF SOURCES OF NEW SAFETY INFORMATION

FDA may learn of new safety information from various sources including, but not limited to:

- Routine monitoring of Adverse Event Reporting System (AERS) or Vaccine Adverse Event Reporting System (VAERS) in-boxes (by the CDER Office of Surveillance and Epidemiology (OSE) or CBER Office of Biostatistics and Epidemiology (OBE) Safety Evaluators)
- Data mining of AERS or VAERS databases, either through routine practice or triggered by a specific issue, by OSE and OBE
- Systematic data mining of all division products
- Safety-related data in a new drug application (NDA), biologics license application (BLA), supplements, or investigational new drug application (IND)
- FDA inspections and investigations, including postmarket adverse drug experience (ADE) inspections
- Reports received through established drug quality reporting systems
- Medical literature submitted by application holders or external stakeholders or identified by FDA staff
- Submissions from an application holder, including but not limited to:
  - Periodic safety reports, including periodic adverse drug experience reports (21 CFR 314.80(c)(2), 314.98(a)), periodic adverse experience reports (21 CFR 600.80(c)(2)), and periodic safety update reports (PSURs)
  - Reports of preclinical, toxicological, or pharmacokinetic studies, clinical trials, or observational studies
  - Studies and clinical trials that may or may not have been conducted as postmarket requirements or commitments or with FDA's knowledge
  - REMS assessments as required under section 505-1 of the FD&C Act
  - Field alert reports (FARs) as required under 21 CFR 314.81(b)(1) and 314.98(c) or Postmarketing 15-day Alert reports as required under 21 CFR 314.80(c)(1), 314.98(a), and 600.80(c)(1)
  - Reports of fatalities related to blood collection or transfusion, as required under 21 CFR 606.170(b)
  - Biological product deviation reports as required under 21 CFR 600.14 and 606.171
  - Annual reports as required under 21 CFR 314.81(b)(2) and 314.98(c)
- Communications with Centers for Disease Control and Prevention (CDC) about CDC's analysis of VAERS reports and the Vaccine Safety Datalink database
- Communications with foreign regulatory authorities regarding postmarket analysis of adverse reactions associated with drugs approved in their countries
- Meta-analyses of safety information, or new analyses of previously submitted information

GLOSSARY

The following definitions of terms are from section 505-1(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355-1(b)).

New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate by the Secretary (of Health and Human Services) about —

(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.

Adverse drug experience means any adverse event associated with the use of a drug in humans, whether or not considered drug related, including—

(A) an adverse event occurring in the course of the use of the drug in professional practice;
(B) an adverse event occurring from an overdose of the drug, whether accidental or intentional;
(C) an adverse event occurring from abuse of the drug;
(D) an adverse event occurring from withdrawal of the drug; and
(E) any failure of expected pharmacological action of the drug.

Serious adverse drug experience is an adverse drug experience that —

(A) results in —

(i) death;

(ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);

(iii) inpatient hospitalization or prolongation of existing hospitalization;

(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or

(v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

Serious risk means a risk of a serious adverse drug experience.

Signal of a serious risk means information related to a serious adverse drug experience associated with use of a drug and derived from —

(A) a clinical trial;
(B) adverse event reports;
(C) a postapproval study, including a study under section 505(o)(3);
(D) peer-reviewed biomedical literature;
(E) data derived from the postmarket risk identification and analysis system under section 505(k)(4);
(F) other scientific data deemed appropriate by the Secretary.

Unexpected serious risk means a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically or pathophysiologically related to an adverse drug experience identified in the labeling, but differs because of greater severity, specificity, or prevalence.