Guidance for Industry

Safety Labeling Changes — Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Kristen Everett at 301-796-5400, or (CBER) the Office of Communication, Outreach, and Development (OCOD) at 301-827-1800 or 800-835-4709.

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)

April 2011
Drug Safety

Guidance for Industry

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Office of Communications
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
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Development, HFM-40
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Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 (the Act) (21 U.S.C. 355(o)(4)) 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 upon new 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 section 505(o)(4) safety labeling changes provisions 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

A. Past Practice

In the past, FDA has requested that holders of applications for approved products make labeling changes related to safety after approval to address serious risks. FDA learned of the potential for such serious risks from a variety of sources (including but not limited to the sources listed 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, the Agency 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.
- FDA could notify the public about the safety information through mechanisms such as a Public Health Advisory or notification on the FDA Web site describing the safety information and the need for labeling changes.
- If in the Agency's judgment the absence of the new safety information from the drug's label rendered the product misbranded, FDA could take appropriate enforcement action.

[2] Section 505(o)(4) of the Act does not apply to unapproved drugs, which do not, by definition, have approved labeling. However, it may be important to 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 Compliance 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.

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

B. New FDAAA Authority and Requirements

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

A. What is *New Safety Information*?

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

Section 505(o)(2)(C) of the Act states that, for the purposes of section 505(o), the term *new safety information* has the meaning given in section 505-1(b). In section 505-1(b) of the Act (21 U.S.C. 355-1(b)), *new safety information* is defined 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", ***or***
- "The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]".

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

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.

Once FDA has learned about the potential for new safety information, FDA may derive new safety information through various means, including but not limited to:

- a new analysis of existing information

- 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 information that may be new safety information that should be incorporated into a drug's labeling under section 505(o)(4). If the safety information is relevant to more than one member of a drug class, FDA expects that review staff will identify the affected class members and review staff in all relevant review divisions and offices will be part of the team. Within CDER, the Office of Generic Drugs (OGD), the Unapproved Drugs Coordinator, and the Office of Compliance (OC) may also 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 Agency meetings, Drug Safety Oversight Board meetings, or Advisory Committee meetings.

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

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 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 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 professional labeling:

- BOXED WARNINGS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
- DRUG INTERACTIONS
- ADVERSE REACTIONS

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). 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).

FDA expects that all 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 Act.

If certain changes to the professional labeling 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.

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(s). If the new safety information applies to more than one application holder, FDA plans to send a letter to each holder of an approved NDA, BLA, and ANDA without a marketed NDA RLD on the same day. Holders of approved NDAs, BLAs, and ANDAs without a marketed NDA RLD will also be notified and required to make the changes if approval of the application has not been formally withdrawn by *Federal Register* notice.

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)
- Proposed labeling changes
- Instructions regarding the circumstances in which the application holder should respond by submitting proposed labeling changes as a *prior approval supplement*[4] or a *changes-being-effected supplement*[5]

B. How Do 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).

[4] 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).

[5] A *changes-being-effected supplement* 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).

If the notification letter applies to only one application and the application holder submits a supplement proposing the labeling changes identical to those that FDA included in the notification letter, the application holder should submit a changes-being-effected supplement. In all other situations, the application holder should submit a prior approval supplement to propose labeling changes that reflect the new safety information. As mentioned in section IV.A above, in the notification letter, FDA will provide information about whether application holders should submit proposed labeling changes as a prior approval or a changes-being-effected supplement.

It is FDA's view that the labeling changes process under 21 CFR 314.70 and 601.12 continues to apply to application holders[6] in situations in which the application holder is aware of newly acquired information. 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 plans to forward copies of safety labeling change letters (including notification letters and orders) via fax or e-mail so that they will be received on the date the document is issued.

The application holder's prior approval supplement may contain proposed edits or counterproposals to the language recommended by FDA, with the rationale for the changed wording.

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 will take, and the time frame in which FDA plans to take those actions.

[6] ANDA holders cannot make labeling changes through the formal supplement process under 21 CFR 314.70 in all circumstances in which NDA holders can, because all labeling changes for ANDA drug products must be consistent with section 505(j) of the Act, which requires that an ANDA's labeling be the same as the NDA RLD's labeling (with some exceptions, described in 21 CFR 314.98(a)(8)(iv)). Although the formal supplement process under 21 CFR 314.70 is not expressly available except to match the RLD labeling, ANDA holders are obligated to provide FDA with information about labeling concerns. See 57 FR 17961 (April 28, 1992). 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 Act. ANDA holders also have a duty to inform FDA of certain adverse events, and to annually report "information…that might affect the safety, effectiveness, or labeling of the drug product." 21 CFR 314.80, 314.81, and 314.98.

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 revised language in the supplement can be approved or requires further discussion, and proceed as follows:

- If the proposed revised language can be approved without changes, FDA will approve the supplement promptly and notify the application holder by sending a supplement approval letter. For supplements that propose 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 discuss the proposed revisions (section 505(o)(4)(C)). The discussion period will begin on the date that FDA receives the application holder's submission and will last no more than 30 calendar days (unless an extension is warranted) (section 505(o)(4)(D)).

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.
- 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 may order the application holder to make the required labeling changes (see section IV.E for further discussion of safety labeling changes orders).

If more than one drug in a class is affected, including ANDA products, FDA will send approval letters to all affected application holders of NDAs, BLAs, and ANDAs without a marketed NDA RLD, on the same day.

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 notify the application holder.
- 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 will begin on the date that FDA receives the application holder's rebuttal statement and will 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, and FDA will follow the procedure as outlined above in IV. C. 1. a.

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 may order the application holder to make the required labeling changes (see section IV.E 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 will be warranted when a 30-day discussion period may not suffice to adequately address all outstanding issues. For example, the labeling change may involve a drug class or the supplement may contain 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 other advisory committees.

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 commonality between products, FDA anticipates that a 30-day extension of the discussion period may be warranted.

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 prior approval 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 may 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 will 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 *changes-being-effected supplement*[7] ***within 30 days*** of the date of the written notification from FDA.

D. How Will FDA Issue Orders 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 may 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
- A Complete Response action for the sections of labeling on which the application holder and FDA cannot agree
- 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)

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

[7] A *changes-being-effected supplement* identifies changes for which distribution may occur when FDA receives the supplement (in this case, labeling changes that FDA specifically requests) (21 CFR 314.70(c)(6) and 601.12(f)(2)).

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.

Alternatively, instead of submitting a changes-being-effected supplement, the application holder may appeal the order through formal dispute resolution procedures ***within 5 calendar days*** of the date of the order (section 505(o)(4)(F)) (see section V for further discussion of the dispute resolution procedures).

Under Section 505(o)(4)(F), if the application holder does not submit a supplement within 15 calendar days of the date of the order and does not initiate dispute resolution within 5 calendar days of 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. 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, PPIs, 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 the FDA 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 the FDA Web site.

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*)[8] (see section 505(o)(4)(F) of the Act).

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." 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

[8] 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.

determination. The dispute process will be considered to be concluded if an appeal of a written determination is not received within this timeframe.

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. ENFORCEMENT OF 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[9] or, when applicable, the holder of the approved application under section 505(j), does not submit a supplement within 15 calendar days of the date of a safety labeling change order or initiate dispute resolution within 5 days, the responsible person or 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 holder will be in violation of section 505(o)(4) of the Act.

Enforcement action for a violation of 505(o)(4) could result in one or more of the following:

- Violations of the requirements for safety labeling changes may result in unapproved new drug charges. 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 Act).

- Violations of the requirements for safety labeling changes may result in misbranding charges. Failure to comply with section 505(o)(4) causes a product to be misbranded under section 502(z) of the Act (21 U.S.C. 352(z)).

- Under section 303(f)(4) of the Act (21 U.S.C. 333(f)(4)(A)), an application holder 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 application holder 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 application holder's efforts to correct the violation (see section 303(f)(4)(B) of the Act).

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

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

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 licensing application (BLA), supplements, or investigational new drug application (IND)
- FDA inspections and investigations, including postmarketing adverse drug experience (ADE) inspections
- Reports received via established drug quality reporting systems
- Medical literature submitted by application holders or external stakeholders or identified by Agency staff
- Submissions from an application holder, including:
  - — Periodic safety reports, including periodic adverse drug experience reports (21 CFR 314.80(c)(2)), 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 postmarketing requirements or commitments or with the Agency's knowledge
  - — REMS assessments as required under section 505-1 of the Act
  - — Field alert reports (FARs) as required under 21 CFR 314.81(b)(1) or Alert reports as required under 21 CFR 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)
- 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 postmarketing analysis of adverse events 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.

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.