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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Division of Drug Information at 855-543-3784 or 301-796-3400, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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)

September 2025
Labeling
Revision 1

Contains Nonbinding Recommendations

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

Guidance for Industry

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Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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)). Section 505(o)(4) authorizes FDA to require application holders for certain drugs[2] to make labeling changes based on new safety information (NSI) (including information related to reduced effectiveness) that becomes available after approval of the drug that FDA determines should be included in the labeling of the drug. This draft guidance revises the guidance for industry *Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* issued in July 2013. After it has been finalized, this guidance will replace the July 2013 guidance. Significant changes from the 2013 version include the addition of information related to Congress' 2018 changes to the statutory definition of ***adverse drug experience***[3] regarding reduced effectiveness, and a description of how FDA reviews and acts on safety labeling changes (SLCs) when NSI applies to multiple application holders and the SLC is issued to multiple applicants. Furthermore, the guidance clarifies when FDA may disclose SLC notification and order letters. Finally, additional changes were made to reflect current SLC processes and procedures that have been updated since the SLC guidance was issued in 2013.

Section 505(o)(4) of the FD&C Act authorizes FDA to require SLCs for:

- Prescription drug products with an approved new drug application (NDA) under section 505(b) of the FD&C Act

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drug* include drug products approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

[3] Terms that appear in ***bold italic*** type upon first use are defined in the Glossary section.

- Prescription drug products with an approved abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act, if the reference listed drug (RLD) is not currently marketed

- Biological products with an approved biologics license application (BLA) under section 351 of the Public Health Service Act (42 U.S.C. 262)

The SLC provisions in section 505(o)(4) apply to the above-listed drugs, including drugs that are not marketed, unless FDA has withdrawn approval of the NDA or ANDA and notice of the withdrawal has been published in the *Federal Register*, or, in the case of a BLA, the U.S. biologics license to manufacture the biological product has been revoked. Thus, even if an application holder is not actively marketing the drug(s) approved under its NDA, ANDA, or BLA, it is required to make the applicable SLCs under section 505(o)(4) unless and until approval of the application is effectively withdrawn in a *Federal Register* notice or the U.S. biologics license to manufacture the product has been revoked.

Section 505(o)(4) ***does not*** apply to nonprescription (over-the-counter) drugs regulated under the FD&C Act or to marketed unapproved drugs.[4]

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

FDA's guidance documents, in general, 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. IMPLEMENTATION OF SLCs UNDER SECTION 505(O)(4) OF THE FD&C ACT

The following sections answer key questions about the implementation of the SLC provisions in section 505(o)(4) of the FD&C Act.

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*** has the meaning given in section 505-1(b) of the FD&C Act, which

[4] 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.

defines *new safety information* 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) 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*
>
> (B) The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS].[5]

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 the Agency determines that such information should be included.

In 2018, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act) (Public Law 115-271) was enacted. Among other things, the SUPPORT Act changed the statutory definition of adverse drug experience in section 505-1(b)(1). It specified that the category of "any failure of expected pharmacological action of the drug" "*may include reduced effectiveness* under the conditions of use prescribed in the labeling of such drug, but which may not include reduced effectiveness that is in accordance with such labeling" (section 505-1(b)(1)(E) of the FD&C Act) (emphasis added). This modified definition clarified that reduced effectiveness of a drug, under certain circumstances, can form the basis for regulatory action under section 505(o)(4) if it meets the definition of ***serious adverse drug experience*** as defined in section 505-1(b)(4) (see also Glossary).[6]

[5] Section 505-1(b)(3) of the FD&C Act (emphasis added).

[6] FDA discusses the applicability of this provision to postmarketing studies or clinical trials (postmarketing requirements (PMRs)) in draft guidance for industry *Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019), explaining that PMRs need not be limited to safety endpoints. That draft guidance notes that efficacy endpoints may be appropriate, for example, to further assess whether a potential lack of expected pharmacological effect, including reduced effectiveness, may result in a *serious adverse drug experience*. When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

The SUPPORT Act added the following italicized language in the revisions to section 505(o)(4) regarding the standard for SLCs:

> If the Secretary becomes aware of *new information, including any* new safety information *or information related to reduced effectiveness*, that the Secretary determines should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under subsection (b) is not currently marketed, the holder of an approved application under subsection (j).

This additional statutory language related to reduced effectiveness clarifies that the Agency can require changes to labeling to include information about a serious risk that results from reduced effectiveness, including information that was derived from a postapproval study or clinical trial required under section 505(o)(3) of the FD&C Act.[7] FDA generally intends to require labeling changes only when the "new information" that the Agency becomes aware of is about a serious risk as defined in section 505-1.

2. How Does FDA Identify and Evaluate New Safety Information?

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) have defined policies and procedures for managing postmarketing safety signals, which include identifying safety signals and bringing together persons with relevant expertise to prioritize, evaluate, make timely decisions, and act to address identified concerns. CDER and CBER may learn about safety signals from many sources, including, but not limited to, postmarketing adverse event reports, postmarketing clinical trials or studies, the application holder's periodic safety reports, or published medical literature.

After evaluating the signal and its associated risk, the Agency determines whether regulatory action is warranted. Regulatory actions may include requiring that application holders make changes to a drug's labeling under section 505(o)(4) of the FD&C Act.

More information about CDER's and CBER's policies and procedures for managing drug safety issues is available in several Manuals of Policies and Procedures (MAPPs) and Standard Operating Policy and Procedure (SOPPs).[8]

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[7] Examples of information about a serious risk resulting from reduced effectiveness may include a potential drug-drug interaction that reduces the systemic exposure of a drug approved to reduce the risk of cardiovascular events, or a signal that a subgroup of patients with a life-threatening cancer may not respond to a drug that had been approved based on a clinically meaningful effect in the overall patient population with the cancer. See Postmarketing Studies and Clinical Trials Guidance at 14−15.

[8] See, for example, MAPP 6004.3 *Safety Labeling Changes Under Section 505(o)(4) of the FD&C Act*; MAPP 4121.3 *Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)*, CBER's SOPP 8419. *Section 505(o)(4) Required Safety Labeling Changes (SLCs),* and MAPP 6700.9 *FDA Posting of Potential Signals of Serious Risks Identified by the FDA Adverse Event Reporting System*. FDA MAPPs are available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp. FDA SOPPS for biologics are available at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps.

B. What Types of SLCs Could Be Required Under Section 505(o)(4) of the FD&C Act?

Information that meets the standard of new safety information that FDA determines should be included in labeling, thereby triggering the SLC process under section 505(o)(4) of the FD&C Act, can be described in new or revised language in any section of the Prescribing Information, or in other types of prescription drug labeling (e.g., FDA-approved patient labeling, carton or container label or labeling).

Changes to Prescribing Information required under section 505(o)(4) of the FD&C Act may necessitate changes to REMS documents and REMS materials. When that is the case, the application holder should submit the REMS changes as REMS modifications under section 505-1 of the FD&C Act.[9]

Not all labeling changes that may be related to safety (including those related to reduced effectiveness) will be required and reviewed under section 505(o)(4) of the FD&C Act. For example, new information about a *nonserious* risk would not be required to be added to labeling through an SLC because it would not meet the criteria described in section 505(o)(4). For labeling changes that do not meet the SLC criteria, application holders may continue to submit labeling supplements using standard procedures (see 21 CFR 314.70 and 601.12).

III. PROCEDURES

A. How Will FDA Notify Application Holders of Required SLCs?

Once FDA has determined that there is new safety information that should be included in labeling, FDA sends an SLC notification letter to the application holder(s). A holder of an approved NDA, BLA, or ANDA (if the RLD is not currently marketed) will be notified of the requirement to make the SLC, unless approval of the application has been formally withdrawn in a *Federal Register* notice or the U.S. biologics license to manufacture the product is revoked.[10] If the new safety information applies to more than one application holder, FDA intends to send a letter on the same day to each holder of an approved NDA, BLA, and/or ANDA (if the RLD is not currently marketed).

In general, FDA intends to include the following information in the SLC notification letter:

- The source from which the new safety information was derived, unless such information is the confidential commercial information of another application holder

[9] See the guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (June 2020).

[10] Requirements under section 505(o)(4) of the FD&C Act apply to NDAs, BLAs, and ANDAs (if the RLD is not currently marketed), *including discontinued products*, unless approval of an application has been withdrawn in the *Federal Register* or, in the case of biological products, all aspects of the license for the biological product have been revoked. Therefore, requirements described in an SLC notification letter apply unless approval of the application has been withdrawn in the *Federal Register*.

- A brief description of the new safety information (e.g., 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 (PAS)[11] or as a changes being effected (CBE-0 supplement)[12]

In general, FDA intends to forward courtesy copies of SLC letters (including SLC notification letters and orders) using a form of rapid communication (e.g., fax, email) so that an application holder receives the SLC letter within 2 days[13] of the date the document is issued.

B. How Should an Application Holder Respond to an SLC Notification Letter?

Section 505(o)(4)(B)(i) and (ii) of the FD&C Act states that, after receiving notification of the required SLC, 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).

Following notification, the labeling supplement or rebuttal statement must be submitted within 30 days.[14] If the application holder submits a supplement proposing labeling changes identical to those that FDA included in the SLC notification letter, it may be appropriate for the application holder to submit a CBE-0 supplement. However, when NSI exists that affects multiple applications and the SLC is issued to multiple application holders, application holders should be aware that changes to the language or placement of the proposed labeling changes can occur during discussion periods with the application holders, and the required labeling approved for multiple applications may differ from the initial proposed labeling changes included in the SLC notification letter.

[11] A PAS proposes changes that require supplement submission and approval before the distribution of the product with those changes (see 21 CFR 314.70(b) and 601.12(f)(1)).

[12] A CBE-0 supplement proposes changes that do not require FDA review or approval before distribution of the product with the change; 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)(iii) and 601.12(f)(2)).

[13] All references to "days" in this guidance are calendar days.

[14] Section 505(o)(4)(B) of the FD&C Act. FDA has interpreted within 30 days to mean within 30 calendar days of the date that the SLC notification letter is issued.

To propose alternative labeling changes that reflect the new safety information in response to the SLC notification letter, the application holder should submit a PAS. Whether the application holder submits a CBE-0 supplement or a PAS, to facilitate the review of the supplement, FDA recommends that the application holder provide a clean version (in Microsoft Word file format) of the labeling (i.e., no redline/strikeout and no annotations) containing the proposed changes and a marked-up version (in Microsoft Word file format) of the labeling. The latter should include all proposed changes (those made by FDA and the application holder) in tracked changes, as well as annotations to provide explanations that support all proposed revisions for counterproposals or proposed edits to the language included in the SLC notification letter.[15]

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

Section 505(o)(4)(C) of the FD&C Act directs FDA to "promptly review and act upon" a labeling supplement or rebuttal statement responding to an SLC 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 expects to take those actions. This section first describes this process for an SLC for a single application holder, and then for multiple application holders.

a. Single application SLC

Labeling Supplements

When an application holder submits a labeling supplement in response to an SLC notification letter, FDA's review team intends to proceed as follows:

- If the proposed labeling can be approved without discussion with the application holder, FDA will approve the labeling supplement promptly and notify the application holder by sending a supplement approval letter. In general, supplements can be approved without discussion with the application holder if the proposed labeling revision is identical to the FDA-proposed labeling included in the SLC notification letter. The Agency's goal is to act on such labeling supplements within 45 days of receipt.

- If the labeling supplement proposes changes to the language or placement of the proposed labeling changes to what was provided in the SLC notification letter, and the Agency disagrees with or needs time to further consider the proposed changes, the Agency will initiate a discussion period with the application holder to review and discuss the proposed revisions.[16] The discussion period will begin on the date FDA receives the

[15] Including the proposed text of the labeling as a clean copy and as a marked-up or tracked-change version facilitates timely review and discussion of the counterproposal or proposed edits to the language.

application holder's submission and last no more than 30 days (unless an extension is warranted).[17] The Agency will issue an action letter 15 days after the end of the discussion period as described below.

Rebuttal Statements

If the application holder submits a rebuttal statement and FDA accepts the reasons why labeling changes are not warranted, FDA intends to promptly notify the application holder. In such situations, FDA's goal is to send such notification within 45 days of receipt of the rebuttal statement.

If the application holder submits a rebuttal statement and FDA does not accept the reasons why labeling changes are not warranted, FDA will initiate a discussion period with the application holder.[18] The discussion period would begin on the date that FDA receives the application holder's rebuttal statement and last no more than 30 days (unless an extension is warranted).[19] If the application holder agrees to submit a labeling supplement during the discussion period, the supplement should be submitted before the end of the discussion period (and any extension period, if applicable), and FDA will follow the procedure as outlined in the previous section.

SLC Actions and Time Frame

Within 15 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 agreement 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 or rebuttal statement and FDA and the application holder cannot reach agreement, FDA can order the application holder to make the required labeling changes under section 505(o)(4)(E) of the FD&C Act (see section III.D for further discussion of SLC orders).

b. SLC for multiple application holders

This section applies when NSI exists that affects multiple applications and SLCs are issued to multiple application holders in the same action.

Labeling Supplements

[16] Section 505(o)(4)(C) of the FD&C Act.

[17] Section 505(o)(4)(D) of the FD&C Act.

[18] Section 505(o)(4)(C) of the FD&C Act.

[19] Section 505(o)(4)(D) of the FD&C Act.

When SLCs are issued to multiple application holders, FDA may receive multiple labeling supplements with potentially differing revisions. To provide the opportunity to review all labeling supplements and harmonize the language and placement for the new safety information among all applications, FDA generally intends to initiate a discussion period automatically and prespecify an end date for the discussion period that is common to all application holders, regardless of when in the 30-day time frame the application holders submit their labeling supplements.[20] In other words, the Agency may include in the SLC notification letter a date when the discussion period will end for all affected applications. The Agency will strive to act on all the labeling supplements on the same day.

Based on the discussion period, the Agency may revise the proposed labeling changes from what was included in the original SLC notification letter. The Agency intends to inform all application holders of any change in the proposed labeling, and application holders should submit that revised proposed labeling for approval before the end of the discussion period. The proposed labeling should be in the form of an amendment to their previously submitted supplement or, if they previously submitted a rebuttal statement, a labeling supplement. If any application holder fails to submit the final proposed labeling before the end of the discussion period, the Agency can order that application holder to make the changes under section 505(o)(4)(E) of the FD&C Act and as described in section III.D of this guidance. An order issued to one or more application holders will not delay approval of labeling changes for the rest of the application holders.

For safety labeling changes that were issued to multiple application holders, FDA intends to send approval letters and/or SLC order letters, as needed, to all application holders of NDAs, BLAs, and ANDAs (if the RLD is not currently marketed) on the same day.

Rebuttal Statements

If an application holder submits a rebuttal statement with a rationale for why the labeling change is not warranted for its particular application and FDA agrees, FDA will accept the rebuttal for that application holder and intends to promptly notify the application holder while continuing the process with the rest of the application holders.

If an application holder-submits a rebuttal statement and FDA does not agree, the Agency will use the open discussion period to address the rebuttal.[21]

SLC Actions and Time Frame

[20] See section 505(o)(4)(D) of the FD&C Act (allowing FDA to extend the discussion period if the Agency determines it is warranted).

[21] Section 505(o)(4)(C) of the FD&C Act.

Within 15 days of the conclusion of the 30-day discussion period (and any extension period, if applicable), FDA will proceed with either or both of the following actions:

- FDA will issue a supplement approval letter to any application holder with which FDA has reached agreement on the proposed labeling.

- If FDA does not agree with the application holder's proposed labeling changes or rebuttal statement and FDA and that application holder cannot reach agreement, FDA can order the application holder to make the required labeling changes under section 505(o)(4)(E) (see section III.D of this guidance for further discussion of SLC orders).

2. Additional Information on Review Procedures

The following sections provide additional information on FDA's review procedures for labeling supplements or rebuttal statements responding to SLC notification letters.

a. Discussion period extensions

As explained above, if FDA does not agree with the language or placement of the proposed labeling change in the submitted labeling 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, unless FDA determines that an extension of the discussion period is warranted.[22]

Under section 505(o)(4)(D) of the FD&C Act, 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. FDA's reasons may include, but are not limited to, the labeling change involves a large number of applications, the supplement contains significantly revised labeling, the need to consider and discuss an application holder's alternative labeling revision, consider additional information, obtain consensus at a higher level within CDER or CBER or among involved offices, or receive input from the Drug Risk Management Board or an advisory committee. In such cases, before the conclusion of the discussion period, FDA may notify the application holder(s) in writing that the discussion period has been extended and, when possible, briefly state the reason(s) for the extension.

b. Failure to respond to an SLC notification letter

If the application holder does not submit a labeling supplement or a rebuttal statement within 30 days of the date of the SLC notification letter, the application holder will be considered to have forfeited the discussion period, and FDA can issue an SLC order directing that the labeling be changed.

[22] Section 505(o)(4)(C) and (D) of the FD&C Act.

c. Labeling change notifications for ANDAs with a marketed NDA RLD

Holders of ANDAs with a marketed NDA RLD would usually be notified by the Office of Generic Drugs (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 (CBE-0) supplement within 30 days of the date of the written notification from FDA.

D. How Will FDA Issue an SLC Order?

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 SLC order to change the product labeling.[23] FDA can also issue an SLC order if a labeling supplement or rebuttal statement is not submitted within 30 days of the date of the SLC notification letter.

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

When FDA issues an SLC order letter, it will do so within 15 days of the conclusion of the 30-day discussion period (or extension, if applicable).[24] All SLC order letters issued are posted on FDA's website.[25] FDA includes the following in the SLC order letters:

- Reiteration of all the labeling changes the application holder must make, including any language about which the Agency and application holder reached agreement during the discussion period

- A brief explanation why the application holder's proposed labeling changes or rebuttal statement do not adequately address the new safety information

- An order to submit a CBE-0 supplement within 15 days of the date of the SLC order for specified changes to the labeling (FDA plans to include specific wording and location for these required labeling changes in the SLC order letter)

- Brief instructions explaining that within 5 days of the date of the SLC order letter, instead of submitting a CBE-0 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

[23] Section 505(o)(4)(E) of the FD&C Act.

[24] Ibid.

[25] SLC order letters are available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm189280.htm for CDER or at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics for CBER.

for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (November 2017).[26]

After the application holder submits the CBE-0 supplement, FDA intends to promptly review the labeling supplement, and if it addresses the new safety information adequately as directed, FDA will approve the supplement, generally ***within 15 days*** of receipt.

Under section 505(o)(4)(F) of the FD&C Act, if the application holder neither submits a labeling supplement within 15 days of the date of the SLC order nor initiates dispute resolution within 5 days of the date of the SLC order, the application holder will be in violation of the statute. This may result in enforcement actions, which are described in section V of this guidance.

E. When Should New Labeling with SLCs Be Available?

FDA expects that new approved labeling with SLCs will be available on the application holder's website within 10 days of the date listed on the approval of the labeling supplement. In addition, approved updates to NDA and BLA labeling with SLCs are posted on FDA's website.[27]

F. Will SLC Letters Be Disclosed?

FDA does not intend to routinely post SLC notification letters but may, at its discretion, post letters that apply to more than one application (e.g., when FDA anticipates significant public interest). SLC notification letters that apply to a single application are considered confidential commercial information and are not posted; however, the resulting NDA and BLA labeling and supplement approval letters are posted. All SLC order letters are posted on FDA's website.[28]

[26] See section V of this guidance for further discussion of dispute resolution procedures.

[27] See the Drugs@FDA: FDA-Approved Drugs web page at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm for CDER-regulated products and the Biologics Products & Establishments web page at https://www.fda.gov/vaccines-blood-biologics/biologics-products-establishments for CBER-regulated products. See also, the draft guidance for industry *Public Availability of Labeling Changes in "Changes Being Effected" Supplements* (September 2006). When final, this guidance will represent FDA's current thinking on this topic.

[28] SLC order letters are available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm189280.htm for CDER or at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics for CBER.

IV. DISPUTE RESOLUTION

An application holder may appeal an SLC order using formal dispute resolution procedures.[29] The appeal should be submitted as correspondence to the NDA, BLA, or ANDA.

Under section 505(o)(4)(F) of the FD&C Act, the application holder must make its appeal of the SLC 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 days after the date the SLC order letter was received will not be considered. 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 days of receiving that determination. FDA will consider the dispute resolution process to be concluded if an appeal of a written determination is not received within this time frame.

At the conclusion of the dispute resolution process, if FDA determines that a labeling supplement is required, the application holder must submit the labeling supplement within ***15 days*** of the date of that determination.[30] If the labeling supplement is not submitted within 15 days, the application holder will be in violation of the statute.

V. ENFORCING REQUIREMENTS FOR SLCs

If the application holder neither submits a labeling supplement within 15 days of the date of an SLC order nor initiates dispute resolution within 5 days, the application holder will be in violation of section 505(o)(4) of the FD&C Act. In addition, if at the conclusion of the dispute resolution process, FDA determines that a labeling supplement must be submitted and such supplement is not submitted within 15 days of the date of the determination, the application holder will be in violation of section 505(o)(4) of the FD&C Act.

It is a prohibited act under section 301(d) (21 U.S.C. 331(d)) of the FD&C Act to introduce or deliver for introduction into interstate commerce a drug if the application holder for the drug is in violation of SLC requirements under section 505(o).[31] In addition, a drug is misbranded under section 502(z) of the FD&C Act (21 U.S.C. 352(z)) if the application holder for that drug is in violation of SLC requirements under section 505(o)(4).[32] Under section 303(f)(4) of the FD&C Act (21 U.S.C. 333(f)(4)), an application holder that is in violation of SLC requirements is

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[29] See the guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level*.

[30] Section 505(o)(4)(G) of the FD&C Act. FDA has interpreted within 15 days to mean within 15 calendar days of the date that FDA determines a labeling supplement is required.

[31] See also sections 505(o)(1) and (4) of the FD&C Act.

[32] Section 301 of the FD&C Act describes certain prohibited acts with respect to misbranded drugs.

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.[33]

Violations of these requirements may be subject to additional enforcement action, including but not limited to, seizure of the product and injunction.

[33] Section 303(f)(4)(B) of the FD&C Act.

GLOSSARY

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

Adverse drug experience

> [M]eans 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, which may include reduced effectiveness under the conditions of use prescribed in the labeling of such drug, but which may not include reduced effectiveness that is in accordance with such labeling.

New safety information

> [W]ith respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) [of the FD&C Act]), 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 the Department 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

> [A]n 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

[M]eans a risk of a serious adverse drug experience.

Unexpected serious risk

[M]eans 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.