SOPP 8419: Section 505(o)(4) Required Safety Labeling Changes (SLCs)

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I. Purpose

This Standard Operating Policy and Procedure (SOPP) serves as a guide for Center for Biologics Evaluation and Research (CBER) staff for requiring a section 505(o)(4) required Safety Labeling Change (SLC).

II. Scope

A. This SOPP applies to new drug applications (NDAs) and biologics license applications (BLAs).

1. SLC authority does apply to abbreviated new drug applications (ANDAs) without a currently marketed reference listed drug (RLD) approved under an NDA, including discontinued drugs.

2. SLC authority does not apply if approval of the NDA has been withdrawn after publication of a Federal Register (FR) notice or if approval of the BLA has been withdrawn due to a license revocation.

III. Background

A. Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA obtained more authority over the labeling of prescription drugs and biologics.

1. Title IX, section 901 of FDAAA amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) with new section 505(o)(4) providing FDA authority to require applicants to amend the approved labeling for products in response to new safety information (NSI).

2. FDA can require and, if necessary, order (referred to as a FDAAA SLC order) application holders to make FDAAA SLCs based on new safety information that becomes available after approval of the drug.

a. Although NSI is typically the issue for SLCs, the statute states that this may also include information related to reduced effectiveness.

3. Upon FDA notification, the statute imposes time frames for application holders to submit either a labeling supplement or a rebuttal statement and for FDA staff to review all responses.

4. Failure to respond to a FDAAA SLC order is a violation of section 505(o)(4) and an application holder may be subject to civil monetary penalties, under section 303(f)(4) of the FD&C Act. A violation may also result in the drug being misbranded and subject the applicant to advisory or enforcement action.

a. Upon FDA issuance of a FDAAA SLC order letter, the application holder must submit a labeling supplement containing the required changes within 15 calendar days or should appeal the order within 5 calendar days of the date of the letter through FDA's formal dispute resolution process as described in 21 CFR 10.75 (also see *CBER SOPP 8005: Formal Dispute Resolution* and *Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level*).

IV. Definitions

A. New Safety Information (NSI) - As defined in section 505-1(b)(3) of the FD&C Act, includes information derived from a clinical trial, an adverse event report, a post-approval study, or peer-reviewed biomedical literature, data derived from the postmarketing risk identification and analysis system under section 505(k), or other scientific data deemed appropriate about (1) a serious risk or unexpected serious risk associated with use of a drug 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 (2) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

B. Changes Being Effected Supplement (CBE-0) - Changes that do not require FDA approval prior to distribution of the drug; for such changes, the applicant may distribute the drug with the changes upon FDA's receipt of the supplement. See 21 CFR 314.70(c)(6) and 601.12(f)(2).

C. SLC Notification Letter - The initial letter notifying the applicant that under section 505(o)(4) of the FDCA, FDA has determined, based upon new safety information (NSI), labeling changes are warranted. The applicant must either submit a labeling supplement or a rebuttal statement in response.

D. Rebuttal Statement - An applicant's formal written response statement to the FDA SLC Notification letter detailing the reasons/justification why the SLC is not warranted.

E. FDAAA SLC Order Letter - If an applicant fails to respond to an SLC Notification Letter or if, at the conclusion of the 30-day discussion period (or extension, if applicable), CBER determines that the applicant's labeling changes do not adequately address the new safety information or finds unacceptable the applicant's rebuttal as to why the labeling changes are not warranted, CBER will issue an order letter to **require** the change to the product labeling.

F. Discussion Period - CBER may initiate discussions with the applicant to reach agreement on whether the SLC labeling is needed after a rebuttal statement has been received or to review the applicant's modified labeling submitted as a PAS. These discussions are for a period of 30 calendar days. CBER may extend the discussion period for more than 30 calendar days, if warranted (e.g., more discussion time is needed to adequately address all complex/outstanding issues).

G. CBER Safety Communication - An important communication of postmarketing safety information to the public.

1. Typically, includes a summary of the safety issue and CBER's current understanding of the risk; a summary of information, including the source of the information, reviewed by FDA; information on the benefits and risks of the product involved; and when available and appropriate, recommendations for health care professionals and/or patients and caregivers.

2. CBER publishes important safety communications on the FDA.gov website.

V. Policy

A. FDAAA SLCs are required when NSI should be included in the labeling in accordance with Section 505(o)(4) and established FDA guidance.

B. The Office of Biostatistics and Pharmacovigilance (OBPV) and the drug's/biologic's relevant Product Office will work together to make any initial determination of a need for an SLC.

C. The source data for the NSI will determine the primary discipline review lead. OBPV is primarily responsible for review of the NSI source data derived from a pharmacovigilance observational study, a study using population-based data sources, and spontaneous adverse event data. The Product Office is primarily responsible for review of the NSI source data from a clinical trial.

D. Regardless of the source of NS**I** and lead primary discipline review, the Product Office will administratively manage any SLC notification telecons, letters, needed SLC orders, applicant rebuttal statements or formal disputes, and SLC labeling supplements**.**

E. The CBER Safety-Related Working Group (CBER SWG) will provide Center level oversight and concurrence with all required SLCs. If there is disagreement between the Product Office and OBPV on the need for a SLC, the CBER SWG will serve to arbitrate and, if necessary, the Center Director will provide the final Center level decision**.**

Note: CBER's Office of Compliance and Biologics Quality (OCBQ) will provide compliance oversight of SLC Orders through participation at the CBER SWG.

F. CBER will inform applicants in writing of any SLC notifications or FDAAA SLC orders. CBER will attempt to communicate the issuance of such letters in advance with either a prior day or same-day teleconference.

G. New or revised labeling information that meets the standard of NSI should generally (but not limited to) be described in one or more of the following labeling sections: Boxed Warnings, Contraindications, Warnings and Precautions, Drug Interactions, Adverse Reactions.

1. CBER may request other labeling changes at the same time SLCs are required; however, any labeling changes not subject to FDAAA will be described in a separate section of the SLC notification letter to distinguish from required FDAAA SLCs.

H. CBER will confirm that an applicant has received and responded to a SLC notification within 30 calendar days. The applicant should submit one of the following:

1. A CBE-0 supplement with proposed labeling changes **identical** to those that FDA has required as indicated in the SLC notification letter.

2. A PAS to propose alternative labeling changes to those that FDA has required as indicated in the SLC notification letter.

3. A formal rebuttal statement and justification in lieu of a labeling supplement if the applicant does not believe a SLC is warranted.

I. CBER may issue a FDAAA SLC order after sending a SLC notification letter if:

1. CBER does not receive a labeling supplement or a rebuttal statement within the designated timeframe after SLC Notification.

2. CBER determines that the applicant's proposed PAS labeling changes do not adequately address the NSI, and further discussions do not lead to agreement.

3. CBER does not agree with the applicant's rebuttal statement, and further discussions do not lead to agreement.

J. FDAAA Safety Communications, SLC Notifications (only if a class) and all SLC Order letters will be posted on the CBER's Safety and Availability (Biologics) web page.

K. CBER will follow SLC notification and FDAAA SLC order timeframes as specified in *Guidance for Industry: Safety Labeling Changes- Implementation of the Section 505(o)(4) of the FD&C Act*.

L. If an SLC results in modification of an approved risk evaluation and mitigation strategy (REMS), the applicant may be informed of both requirements, generally in the same letter. The letter may instruct applicants to submit the SLC in a separate supplement from the REMS modification. If warranted, CBER may alternatively notify applicants of the need for a REMS modification after the SLC has been approved.

M. If the notification letter was issued for more than one application as part of a class labeling change, any labeling decisions should wait until all supplements and rebuttal statements submitted within 30 days of notification have been reviewed. FDA intends to:

1. Communicate SLC Notifications and approve SLC labeling supplements on the same day to all class members unless there is a well-justified, scientific rationale to support different wording for different drug labels.

2. Make public the SLC Notification if part of a class (SLC Notifications for a single product are considered confidential and not made public).

VI. Responsibilities

A. Pharmacovigilance Reviewer (OBPV)

1. Works with the Clinical Reviewer to identify the potential need for a SLC.
2. Participates in discussions on the need for a SLC.
3. Documents the postmarket safety issue triggering a SLC in a primary review memo if NSI derived by study/data overseen by OBPV.

B. Clinical Reviewer (Product Office)

1. Works with the Pharmacovigilance Reviewer (OBPV) to identify the potential need for a SLC.
2. Participates in discussions on the need for a SLC.
3. Documents the need for a SLC in a primary review memo if NSI derived by study/data overseen by Product Office.

C. Regulatory Project Manager

1. Facilitates and serves as primary point of contact with the applicant(s).
2. Drafts, circulates, obtains final concurrence of all SLC letters, and obtains sign-off.
3. Facilitates the discussion period.

D. CBER SWG Representative in Relevant Product Office and OBPV

1. Facilitates communication between the review team and the CBER SWG.
2. Serves as an office resource related to FDAAA safety provisions.

E. CBER SWG

1. Interprets the policies and procedures used by all CBER Offices pertinent to patient-related safety issues.
2. Provides decisional concurrence and compliance oversight of safety-issues at the Center Level.

Note: This committee is overseen by the Associate Director for Policy and the Associate Director for Review Management.

F. CBER SWG Executive Secretary - Manages the CBER SWG Meeting and is the point of contact for discussing regulatory issues and clearance of SLC related submissions.

G. Clinical and Pharmacovigilance Supervisors - Participates in discussions on the potential need for a SLC.

H. Director, Division of Pharmacovigilance

1. Participates in the discussion on the need for a SLC.
2. Reviews the SLC Notification Letter and/or FDAAA SLC Order Letter.

I. Division Director or Designee in Relevant Product Office

1. Participates in the discussion on the need for a SLC.
2. Reviews the SLC Notification Letter and/or FDAAA SLC order Letter.

J. Office Director in OBPV - Participates in discussions on the need for a SLC.

K. Office Director or Designee in Relevant Product Office - Participates in discussions on the need for a SLC.

L. Office of Communication, Outreach and Development/Division of Disclosure and Oversight Management/Electronic Disclosure Branch (OCOD/DDOM/EDB) - Performs a disclosure review of the approved SLC Order Letter and any needed safety communication and coordinates posting to FDA's website.

M. Office of Compliance and Biologics Quality (OCBQ)

1. Provides compliance oversight of SLC Orders.
2. The Advertising and Promotional Labeling Branch (APLB) in the Division of Case Management (DCM) participates, as necessary, in discussions on the content and context of information included in the prescribing information (PI) under a SLC Order.

VII. Procedures

A. SLC Notification to Applicant

1. Discuss the source of NSI (see definition above) and the potential need for a SLC during review team meetings. **[Pharmacovigilance Reviewer and/or Clinical Reviewer and/or Pharmacovigilance and Clinical Supervisors]**

Note: The SLC Notification to the applicant must not occur until there is concurrence at the CBER SWG.

2. Alert the Office SWG Representative for a need to present the potential SLC at an upcoming CBER SWG meeting. **[Pharmacovigilance Reviewer and/or Clinical Reviewer]**

3. Notify the Executive Secretary of the CBER SWG for scheduling. **[Office SWG Representative]**

4. One week prior to the scheduled CBER SWG meeting, send the SLC background materials (which will provide an overview of the product, source of NSI, safety risk that the SLC will mitigate, and proposed safety labeling changes) to the CBER SWG Executive Secretary. **[Clinical and/or Pharmacovigilance Reviewers]**

   Note: The CBER SWG meeting provides Center decisional concurrence on the need for a SLC and is documented in the minutes.

5. Create a pre-assigned Submission Tracking Number (STN) per *SOPP 8416: CBER Initiated Second Level STNs*. **[Product Office RPM]**

   Note: For class labeling changes across several applicants, all communications and actions should occur on the same day.

6. Coordinate a brief teleconference with the applicant(s) on the day before/day of the planned letter issuance as a courtesy to explain the SLC Notification and source of NSI. **[Product Office RPM]**

   Note: Clinical and Pharmacovigilance Reviewers and Supervisors could attend depending on the situation.

7. Complete the review memo for the SLC Notification justification based upon the source of the NSI. **[Clinical Reviewer or OBPV Reviewer]**

8. Draft, circulate, obtain final concurrence of the SLC Notification Letter(s), and sign-off by designated signatory. Send the letter to the applicant by rapid communication (secure email or fax) and confirm receipt. **[Product Office RPM]**

B. Failure of Applicant to Respond to SLC Notification Letter

1. Draft, circulate, and obtain final concurrence of the FDAAA SLC order letter. Send the letter to the applicant by rapid communication and confirm receipt. **[Product Office RPM]**

2. Submit the letter to OCOD/DDOM/EDB for a disclosure review and posting to FDA webpage. **[Product Office RPM]**

C. Applicant Submission of Rebuttal Statement to SLC Notification

1. Upon receipt (day of formal submission) of the rebuttal statement, initiate a 30-day discussion period with applicant. By rapid communication

(secure email, fax, or telecon), notify the applicant of receipt and the end date of the discussion period. If an extension of the discussion period is warranted, issue a discussion extension letter.

2. Within 15 days of end of the 30-day or extended discussion period, if OBPV and Product Office:

a. Accept applicant's SLC rebuttal:

i. Present at an upcoming CBER SWG meeting to obtain Center concurrence (follow general SWG steps in A. above).

ii. Draft, circulate, and obtain final concurrence of the Rebuttal agreement letter. Send the letter to the applicant by rapid communication and confirm receipt. **[Product Office RPM]**

b. Do not accept applicant's SLC rebuttal:

i. Notify CBER SWG Executive Secretary of Product Office's decision to reject applicants SLC rebuttal. **[Product Office RPM]**

ii. Coordinate a brief teleconference with the applicant to:

(1) obtain agreement to submit a labeling supplement **[Product Office RPM]**

OR

(2) notify applicant that an SLC order letter will be sent (have letter ready for that day).

(a) Draft, circulate, and obtain final concurrence of the FDAAA SLC order letter. Send the letter to the applicant by rapid communication and confirm receipt. **[Product Office RPM]**

(b) Submit the letter to OCOD for a disclosure review and posting to FDA webpage. **[Product Office RPM]**

D. Applicant responds within 30 calendar days with CBE-O supplement.

1. Ensure that the labeling changes are identical to those communicated in the SLC Notification letter (in order for the supplement to be properly categorized as a CBE-0). **[Product Office RPM]**

2. Complete the primary review memo as soon as possible. Ensure that the proposed labeling is identical to those changes required in the notification

letter and notify OBPV Reviewer if SLC was based upon OBPV NSI source. **[Clinical Reviewer]**

3. Determine if there is a need for a CBER Safety Communication to be issued at the time of SLC supplement approval. **[Review Team]**

4. Finalize the primary review memo and obtain final concurrence. **[Clinical Reviewer]**

5. Draft, circulate, and obtain final concurrence of the CBE-0 supplement approval letter. Send the letter to the applicant by rapid communication. **[Product Office RPM]**

E. Applicant responds within 30 calendar days with PAS supplement.

1. If the proposed alternative language cannot be approved without changes, initiate a 30-day discussion period with applicant. By rapid communication (secure email, fax, or telecon), notify the applicant of receipt and the end date of the discussion period. **[Review Team]**

   a. If an extension of the discussion period is warranted for an additional 30-days, issue a labeling discussion extension letter. **[Product Office RPM]**

2. Within 15 calendar days of the conclusion of the 30-day discussion period (and any extension period, if applicable), if CBER and the applicant:

   a. Reach consensus on the proposed labeling:

      i. Determine if there is a need for a CBER Safety Communication to be issued at time of SLC supplement approval. **[Review Team]**

      ii. Ensure the completion and concurrence of the final review memo. **[Clinical Reviewer]**

      Note: If OBPV issued the SLC Notification Letter based on the source of NSI, the OBPV Reviewer will also provide a review memo in addition to the Clinical Reviewer in order to concur on the alternative labeling language proposed by the applicant.

      iii. Draft, circulate, and obtain final concurrence of the PAS supplement approval letter. Send the letter to the applicant by rapid communication. **[Product Office RPM]**

   b. Do not reach consensus on the proposed labeling:

i. Ensure the completion and concurrence of the final review. **[Clinical Reviewer]**

Note: If OBPV issued the SLC Notification Letter based on the source of NSI, the OBPV Reviewer will also provide a review memo in addition to the Clinical Reviewer.

ii. Draft, circulate, and obtain final concurrence of the FDAAA SLC Order Letter. Send the letter to the applicant by rapid communication. **[Product Office RPM]**

iii. Submit letter to OCOD/DDOM/EDB for a disclosure review and posting to FDA webpage. **[Product Office RPM]**

F. Applicant responds to FDAAA SLC Order letter.

1. If the applicant disagrees with the SLC Order and requests formal dispute resolution, follow *CBER SOPP 8005: Formal Dispute Resolution Process* for procedures. **[Product Office]**

a. If the applicant loses the formal dispute; the applicant must submit the ordered labeling supplement within 15 calendar days of the determination. When submitted, follow the supplement review process under D., above.

Note: CBER will not delay approval of a product class SLC if there is a formal dispute under review for any one applicant.

b. If the applicant wins the formal dispute, a SLC labeling supplement is no longer required.

VIII. Appendix

A. Safety Labeling Change (SLC) Process Overview and Important Time Frames for Review Staff

IX. References

A. The reference below is CBER Internal:

1. SOPP 8416: CBER Initiated Second Level STNs

B. References below may be found on the Internet:

1. Guidance for Industry: Safety Labeling Changes -- Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act

2. Guidance for Industry and Review Staff: Formal Dispute Resolution: Sponsor Appeals Above the Division Level
3. Drug Safety Communications | FDA web page
4. SOPP 8005: Formal Dispute Resolution Process
5. Safety & Availability (Biologics) web page

X. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
Erik Laughner	Sonday Kelly, MS, RAC, PMP, Director, DROP/ORO	February 12, 2024	2	Clarifies review responsibilities
Erik Laughner	Christopher Joneckis, PhD	February 10, 2022	1	First Issuance

SOPP 8419: Appendix A Safety Labeling Change (SLC) Process Overview and Important Time Frames for Review Staff