
POLICY AND PROCEDURES

OFFICE OF NEW DRUGS

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

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PURPOSE

- This MAPP describes the policies and procedures for staff in the Office of New Drugs (OND), Office of Generic Drugs (OGD), and other Center for Drug Evaluation and Research (CDER) offices when implementing section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which describes requirements for safety labeling changes (SLCs) for approved drugs¹ under the Food and Drug Administration Amendments Act of 2007 (FDAAA). For the purposes of this MAPP, these requirements are referred to as *FDAAA SLCs*.

¹ For the purposes of this MAPP, all references to *drugs* mean human drugs, including biological products, regulated by CDER.

BACKGROUND

- Per section 505(o)(4) of the FD&C Act, FDA is authorized to require and, if necessary, *order* (referred to as a FDAAA SLC order) application holders of certain approved drugs² to make FDAAA SLCs based on new safety information (NSI)³ that becomes available after approval of the drug. The statute imposes time frames for application holders to submit and for FDA staff to review such changes and gives CDER enforcement tools in instances of noncompliance.
 - Requirements under section 505(o)(4) apply to new drug applications (NDAs), biological licensing applications (BLAs), and abbreviated new drug applications (ANDAs) without a currently marketed reference listed drug (RLD) approved under an NDA, including discontinued drugs, unless approval of an application has been withdrawn in the *Federal Register* (FR).⁴ Therefore, the requirements apply unless approval of the application has been withdrawn after publication of an FR notice.⁵
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² Section 505(o)(4) does not apply to nonprescription (over-the-counter) drugs approved under a new drug application (NDA) or abbreviated new drug applications (ANDAs) that reference a marketed NDA reference listed drug. Additionally, section 505(o)(4) of the FD&C 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 OND will contact the unapproved drugs coordinator in the OND Immediate Office and the Office of Unapproved Drugs and Labeling Compliance to initiate appropriate actions.

³ Section 505-1(b)(3) of the FD&C Act.

⁴ For the purposes of this MAPP, discontinued drugs are referred to as *nonmarketed drugs*, to reflect that they include drugs that have been discontinued from sale and drugs for which approvals of the applications have been withdrawn. See the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) web page available at <https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book>.

⁵ See 21 CFR 314.152. Drugs are considered “withdrawn FR effective” 30 days after publication of the *Federal Register* notice.

POLICY**Requiring FDAAA SLCs**

- Generally, CDER will require FDAAA SLCs when CDER determines that NSI about a drug should be included in the labeling,⁶ in accordance with established FDA guidance on FDAAA SLCs.^{7,8} The designated signatory authority (OND deputy director for safety, division director or deputy division director) will make this determination. The Office of Regulatory Operations (or designee) in OGD will make this determination when the application for the NDA RLD is withdrawn FR effective.
- CDER staff will inform application holders in writing that FDAAA SLCs are required (see Attachment 1).
- OND staff may request other labeling changes at the same time FDAAA SLCs are required. Because requested labeling changes are not subject to FDAAA timelines, the requested labeling changes will be described in a separate section of the FDAAA SLC notification letter to distinguish them from required FDAAA SLCs.
- CDER staff will send all FDAAA SLC letters (notification, approval, and other) by both regular mail and a form of rapid communication (e.g., facsimile, email) to ensure that the application holder's receipt date is the same as or within 2 calendar days of the FDA letter date
- CDER staff will confirm that application holders have responded to a FDAAA SLC notification with either a labeling supplement (changes being effected or prior approval supplement) or rebuttal statement within 30 calendar days (see Definitions).

⁶ The term *labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce. The term *label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity. See 201(k) and 201(m) of the FD&C Act.

⁷ See the guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁸ The labeling change process under 21 CFR 314.70 and 601.12 continues to apply to application holders in situations in which the application holder independently becomes aware of newly acquired information and submits proposed labeling changes.

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- If CDER does not receive a labeling supplement or a rebuttal statement within 30 calendar days, CDER staff will consider the application holder to have forfeited the review and discussion period and may issue a FDAAA SLC order (see Policy – FDAAA SLC Orders).

FDAAA SLC Discussion Periods

- CDER staff will decide whether to approve the supplement or initiate a 30-day discussion period to review the application holder's proposed changes or rebuttal statement detailing why labeling changes are not warranted.
- If an extension of the discussion period is warranted, CDER staff will issue a labeling discussion extension letter, which will include the date that the extended discussion period will end. In general, an extension should not exceed 30 calendar days (see Policy – FDAAA SLCs for Drug Classes) and must be granted by the signatory authority by the end of the first discussion period. Any subsequent extensions must be discussed with CDER's Safety Requirements Team.

FDAAA SLCs for Drug Classes

- CDER staff will require FDAAA SLCs for each drug in a class when NSI exists that affects the entire class. The FDAAA SLC notification letters will explicitly state which class of drugs the NSI applies to and why the information can be generalized to the entire class.
- CDER staff will apply policies for FDAAA SLCs for individual drugs to drug classes as described above. In addition, the following will also apply:
 - CDER staff will send all FDAAA SLC letters (notification, approval, and other) to application holders within a drug class on the same calendar day or within 2 calendar days of the FDA letter date.
 - If the FDAAA SLC notification letter to an NDA RLD application holder also includes other requested labeling changes of an NDA RLD application holder, CDER staff will not include the requested labeling changes in the FDAAA SLC notification letter to ANDA application holders.
 - CDER staff may, in the FDAAA SLC notification letters involving a drug class, notify application holders that an extension of the discussion period will be necessary and include the anticipated discussion period end date in the letter. CDER staff may further extend discussions, if warranted (see Policy – FDAAA SLC Discussion Periods). CDER will conclude the discussion period(s) on the same calendar day for all application holders of the drug class.

- CDER staff will decide on the final labeling language after reviewing *all* responses received within the 30 calendar day time frame. CDER staff will approve a labeling change common to all class members unless there is a well-justified scientific rationale to support different wording for different drug labeling across the class.

FDAAA SLC Orders

- CDER staff will issue a FDAAA SLC order after sending a FDAAA SLC notification letter and one of the following occurs:
 - CDER staff determines that the application holder’s proposed labeling changes do not adequately address the NSI, and further discussions will not lead to agreement
 - CDER staff does not agree with the application holder’s rebuttal statement, and further discussions will not lead to agreement
 - CDER staff does not receive the application holder’s supplement or rebuttal statement within 30 calendar days of the FDAAA SLC notification letter
- CDER staff will post all FDAAA SLC order letters on FDA’s website.⁹
- If an application holder formally disputes a FDAAA SLC order, CDER staff will follow standard dispute resolution procedures.¹⁰
- CDER staff will not delay approval of labeling changes for the rest of a drug class because of an order or dispute resolution process involving one or more application holders.

FDAAA SLCs and Drugs With Pending New or Supplemental Applications

- OND will act on pending labeling supplements concurrently with or after approval of a supplement submitted in response to a FDAAA SLC requirement. OND will generally approve pending supplemental efficacy applications, or new marketing applications for other drugs in the class,¹¹ with labeling that reflects the

⁹ Ibid.

¹⁰ See the guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level*.

¹¹ Includes BLAs for biosimilar drug products.

NSI that formed the basis for the FDAAA SLC requirement. Depending on the time frames for action on the application, this approval may occur before approval of the FDAAA SLC.

- OGD will approve pending original and supplemental ANDA applications with the last approved labeling of the RLD. OGD action on the FDAAA SLCs will not affect the approvability of ANDAs within time frames agreed to under the Generic Drug User Fee Amendments.

FDAAA SLCs That Require Modifications of an Approved REMS

- If FDAAA SLCs result in modification of an approved risk evaluation and mitigation strategy (REMS),¹² CDER staff will notify application holders of both requirements, generally in the same letter. The letter may instruct application holders to submit the FDAAA SLCs in a separate supplement from the REMS modifications.¹³
 - Alternatively, CDER staff may notify application holders of the REMS modifications after the FDAAA SLCs have been approved.

RESPONSIBILITIES AND PROCEDURES

The procedures for FDAAA SLCs are also summarized in Chart 1 in Attachment 2.

1. Reviewing NSI and Deciding to Require FDAAA SLCs

- **The Multidisciplinary Review Team will:**
 - Review the safety information to determine if it meets the statutory definition of NSI
 - Recommend to the OND deputy director for safety (DDS) (or the OND division director/OND deputy division director (DD/DDD)) that FDAAA SLCs should be required

¹² See the guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*.

¹³ See MAPP 4191.1 *Risk Evaluation and Mitigation Strategies Modifications and Revisions*. MAPPs can be found on the Manual of Policies and Procedures web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>.

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- Upon DDS (or DD/DDD) concurrence, provide the OND safety regulatory project manager/regulatory health project manager (SRPM/RPM) with at least one of the following:
 - The proposed language for inclusion in labeling
 - If inclusion of specific language is not possible, description of the types of required labeling changes and the sections of the labeling that should be changed
 - **The OND DDS (or DD/DDD) will:**
 - Decide whether the criteria for FDAAA SLC have been met
 - If the FDAAA SLC involves more than one OND review division, work with other DDS's to identify a lead division and coordinate communication to the application holders, multidisciplinary submission review, and action

2. Preparing and Issuing the FDAAA SLC Notification Letter(s)

For all FDAAA SLCs

- **The OND SRPM/RPM will:**
 - Draft the FDAAA SLC notification letter(s) to the applicable NDA/BLA application holder(s), including nonmarketed NDA drugs (see Attachment 1).
 - Determine whether the application holder of an NDA/BLA drug discontinued from sale previously submitted a request for withdrawal of FDA approval of the application per 21 CFR 314.150(c), and determine if the FR notice announcing the withdrawal of the approval has published and is effective per 21 CFR 314.162.
 - When FDA review of FDAAA SLC submissions is expected to exceed 30 calendar days, include a statement in the notification letter that FDA has determined that a discussion extension will be warranted, and insert the date that accounts for the statutory 30 calendar day review plus the additional discussion period extension.
 - FDAAA SLC notification letters that involve drug classes generally should include a discussion extension period to allow for coordination of review and action for multiple products.

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- Monitor for and track the application holder’s response(s) to the FDAAA SLC notification letter to ensure that responses are received within 30 calendar days.
 - If the response is not received within 30 calendar days, follow the responsibilities and procedures in section 10.
 - Determine whether the FDAAA SLC requirement potentially affects any pending supplements or original applications. Work with responsible SRPMs/RPMs to coordinate appropriate approval timelines.
 - If the FDAAA SLC involves more than one OND review division, work with other SRPMs/RPMs to coordinate communication to the application holders, multidisciplinary submission review, and action.
 - **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee),¹⁴ if applicable, will:**
 - Review and sign the FDAAA SLC notification letter in the appropriate document archiving system

For FDAAA SLCs involving drug classes

- **The OND SRPM/RPM will:**
 - Identify all NDAs/BLAs in the drug class (i.e., all *active* applications, including drugs that have been discontinued from sale), with input from other OND RPMs
 - Determine if there is at least one approved ANDA in the drug class and notify the OGD SLC coordinator¹⁵ that a FDAAA SLC notification letter will be issued for a drug class that includes a nonmarketed NDA RLD and an approved generic
 - Provide the list of all NDA RLDs in the class, including nonmarketed NDAs, to the OGD SLC coordinator

¹⁴ The designee serves as the signatory for FDAAA SLC notification and actions that do not involve a combined REMS action. The director of the Office of Bioequivalence will serve as the signatory for actions that involve both FDAAA SLC and REMS modifications.

¹⁵ Notify the OGD SLC coordinator only if an OGD representative is not already part of the multidisciplinary review team evaluating the safety issue that is the basis of the FDAAA SLC.

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- Determine with the OGD SLC coordinator the expected duration of the extended discussion period, based on the scope of the drug class and complexity of the FDAAA SLCs
 - Work with the DDS, OGD SLC coordinator, and the SRPMs/RPMs from other OND review divisions (if applicable) to develop a representative FDAAA SLC notification letter *template* for drafting letters to ANDA application holders.
 - Coordinate issuing the FDAAA SLC notification letters with the OGD SLC coordinator (and other OND SRPMs/RPMs, if the drug class includes applications from other OND review divisions)
 - If other public communications about the drug class FDAAA SLC requirement are planned (e.g., Drug Safety Communications), provide a copy of the representative FDAAA SLC notification letter to the CDER Office of Communications (OCOMM)
- **The OGD SLC Coordinator will:**
 - Identify all ANDA drugs that reference nonmarketed NDA RLDs and that the FDAAA SLC requirement applies to
 - Share that list with the OND DDS, the OND SRPM/RPM, and the Office of Generic Drug Policy (OGDP) and note in the list sent to OGDP all nonmarketed NDA RLDs for which the reason for nonmarketing (including for reasons of safety or effectiveness) has not been documented
 - Determine with the OND SRPM/RPM the expected duration of the extended discussion period for the drug class, based on the scope of the drug class and extensiveness of the labeling changes
 - Draft the FDAAA SLC notification letters to the application holders of ANDAs that reference a nonmarketed NDA RLD (see Attachment 1)
 - Coordinate drafting and issuing the ANDA FDAAA SLC notification letters with the OND SRPM/RPM
 - Use the representative FDAAA SLC notification letter *template* received from the OND SRPM/RPM to draft the ANDA FDAAA SLC notification letter(s)
 - Monitor for and track the ANDA holder's response(s) to the FDAAA SLC notification letter to ensure that responses are received within 30 calendar days

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- If the response is not received within 30 calendar days, follow the responsibilities and procedures in section 10
 - **The OGD Staff will:**
 - If the FDAAA SLCs involve ANDAs, and if the reason is not documented, initiate consults to the OND review division and other offices as needed to determine the reason(s) by the end of the FDAAA SLC discussion period

For FDAAA SLCs involving drugs for which the application holder has previously requested withdrawal of approval of the NDA/BLA/ANDA but the withdrawal is not yet effective

- **The OND SRPM/RPM will:**
 - Check whether application holders for a discontinued drug submitted a request for withdrawal of FDA approval of the application, but the request has not been acted on
 - Notify the Office of Regulatory Policy (ORP) of the planned FDAAA SLC requirement and obtain information about the status of the *final withdrawal of approval* action(s)
- **The OGD SLC Coordinator will:**
 - Contact OGD Staff to check whether application holders for a discontinued drug submitted a request for withdrawal of FDA approval of the application, but the request has not been acted on
 - Inform OGD Staff of the planned FDAAA SLC requirement and obtain information about the status of the final withdrawal of approval action(s)

3. Reviewing Labeling Supplements Received in Response to a FDAAA SLC Notification Letter

- **The Multidisciplinary Review Team will:**
 - Determine if the labeling supplement can be approved without changes
 - If the supplement cannot be approved without changes, initiate a discussion period

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- Recommend discussion period extensions, as appropriate, to the DDS (DD/DDD) (see section 5)

For FDAAA SLCs involving drug classes

- **The Multidisciplinary Review Team will:**
 - After all labeling supplements are submitted, initiate discussions with the application holders as necessary
 - Review submitted proposals for alternative labeling language and determine the language that best communicates the serious risk information
 - Negotiate labeling language with all application holders in the drug class, as informed by the *best* proposed language
- **The OND SRPM/RPM will:**
 - Notify the OGD SLC coordinator (and the other OND SRPMs/RPMs, if applicable) if an NDA application holder submits proposed language that is different from what was specified in the FDAAA SLC notification letter
 - If the multidisciplinary review team revises the labeling language during the discussion period,
 - Notify the OGD SLC coordinator and provide the revised language
 - Send the revised labeling language to the application holder(s) via email or facsimile, and upon reaching agreement on the proposed language, instruct the application holder(s) to submit the revised labeling as an amendment to the labeling supplement
- **The OGD SLC Coordinator will:**
 - Notify the OND SRPM/RPM if an ANDA application holder submits proposed language that is different from what was specified in the FDAAA SLC notification letter
 - If the multidisciplinary review team revises the labeling language during the discussion period,
 - Send the revised labeling language to the application holder(s) via email or facsimile and instruct the application holder(s) to submit the revised labeling as an amendment to the labeling supplement

- As applicable for nonmarketed NDA RLDs, work with OGD to confirm that the FDA's determinations of the reason(s) for discontinuation are completed by the end of the FDAAA SLC discussion period
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Oversee the management and coordination of OND review division activities regarding labeling supplement review
 - Work with the OND SRPM/RPM or OGD SLC coordinator, if applicable, to ensure adherence to statutorily mandated FDAAA SLC time frames for FDA review and action on the submission

4. Reviewing Rebuttal Statements Received in Response to a FDAAA SLC Notification Letter

- **The Multidisciplinary Review Team will:**
 - Review the rebuttal statement
 - If the multidisciplinary review team accepts the application holder's rebuttal, follow the responsibilities and procedures in section 7
 - If the multidisciplinary review team does not accept the application holder's rebuttal, initiate a discussion period (and extensions as appropriate) to discuss the rebuttal with the application holder
 - If the application holder submits a labeling supplement after communication from CDER staff that the rebuttal is not accepted, review the labeling supplement before the end of the discussion period (or applicable extensions)
- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - If the multidisciplinary review team accepts the application holder's rebuttal, follow the responsibilities and procedures in section 7
 - If the multidisciplinary review team does not accept the application holder's rebuttal and the discussion period needs to be extended, follow the responsibilities and procedures in section 5
 - If the multidisciplinary review team does not accept the application holder's rebuttal after discussions,

- Notify the Office of Compliance Office of Unapproved Drugs and Labeling Compliance (OUDLC)
- Draft a FDAAA SLC order letter (see section 9)
- If the application holder submits a labeling supplement after notification from CDER staff that the rebuttal is not accepted but before the FDAAA SLC order letter issues, follow the responsibilities and procedures in section 3
- If, during the discussion period, the labeling language that was included in the SLC notification letter is revised and the application holder agrees to submit a labeling supplement that reflects the agreed-upon language, send the revised language to the application holder(s) via email or facsimile with the instruction to submit the revised, agreed-upon language in a labeling supplement

5. Extending the Discussion Period

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Before the conclusion of the discussion period, discuss with the multidisciplinary review team and the DDS (and/or the director of the Office of Regulatory Operations in OGD or designee) whether extension of the discussion period is warranted¹⁶
 - Issue a labeling discussion extension letter to the application holder(s) stating that an extension is needed
 - If a second or subsequent extension of the discussion period is anticipated, discuss the appropriateness of the extension with the Safety Requirements Team
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Review and sign the labeling discussion extension letter(s)

¹⁶ Reasons for extension of the discussion period include, but are not limited to, the need to: consider the application holder's alternative language; consider additional information about the safety issue; consider an application holder's request for additional time to submit a new Medication Guide when an individual or a class Medication Guide does not already exist; obtain consensus at a higher level within CDER or among involved offices about the proposed safety labeling; or receive input from additional groups about the proposed safety labeling.

6. Approving a FDAAA SLC Supplement

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Draft the supplement approval letter(s)
 - If the supplement approval letter involves NDAs/BLAs, append the final, agreed-upon labeling to the approval letter
 - For drug class FDAAA SLC actions, coordinate with the OND SRPMs/RPMs and OGD SLC coordinator the issuing of the supplement approval letters to ensure that the approval actions are taken concurrently for the drug class
- **The OGD SLC Coordinator will:**
 - If the FDAAA SLC involves ANDAs, before issuing the supplement approval letters confirm with OGD completion of any consults issued to determine the reason(s) for nonmarketing (including for reasons of safety or effectiveness) for nonmarketed NDA RLDs (see section 2)
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Review and sign the supplement approval letter(s)

7. Accepting a FDAAA SLC Rebuttal

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Draft a rebuttal acceptance letter and issue the letter within 30 calendar days of receipt of the rebuttal statement (unless extension of the discussion period was warranted)
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Review and sign the rebuttal acceptance letter

8. Acting When a Submission Is Not Received in Response to a FDAAA SLC Requirement

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**

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- Contact the Document Room to determine whether a submission was received
 - If a submission was received, complete the responsibilities and procedures in section 3
 - If no submission was received,
 - Notify OUDLC of the application holder’s failure to respond to the FDAAA SLC notification letter
 - Complete the responsibilities and procedures in section 9

9. Ordering a FDAAA SLC

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Draft the FDAAA SLC order letter and ensure that the letter is reviewed and cleared by the appropriate groups
 - Issue the FDAAA SLC order letter within **15 calendar days** of the conclusion of the discussion period (or extension, if any)
 - Also, send the FDAAA SLC order letter via email or facsimile on the same day, to ensure rapid receipt by the application holder, and confirm the application holder’s receipt of the letter via email
 - If the FDAAA SLC order follows discussion of a supplement, ensure that the FDAAA SLC order letter includes
 - Description of the sections of labeling on which the application holder and the multidisciplinary review team agree
 - An order to submit a supplement that includes changes to the sections of labeling that are agreed upon, changes on which the application holder and FDA cannot agree, and specific wording for all changes, listed in an appendix to the letter and separated into sections that delineate *agreed-upon* language and *ordered* language
 - Rationale for the ordered labeling changes that were not agreed upon
- **The OND SRPM/RPM will:**
 - If the FDAAA SLC order letter involves NDAs/BLAs, notify the OND Operations and CDER Formal Dispute Resolution program about the FDAAA

SLC order and the potential for a formal dispute resolution request by the NDA or BLA application holder(s)

- **The OGD SLC Coordinator will:**
 - If the FDAAA SLC order letter involves ANDAs, notify the OGD Immediate Office and CDER Formal Dispute Resolution program about the FDAAA SLC order and the potential for a formal dispute resolution request by the ANDA application holder(s).
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Inform the CDER senior managers who oversee the review division or office (i.e., OND office director and OGD director) of the recommendation to order SLCs
 - Review the FDAAA SLC order letter
- **The OND Office Director and the OGD Director, if applicable, will:**
 - Sign the FDAAA SLC order letter

10. Acting on Responses to a FDAAA SLC Order

When a labeling supplement is received

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Together with the DDS or director of the Office of Regulatory Operations in OGD, ensure that the multidisciplinary review team promptly reviews the supplement
- **The OND DDS (or DD/DDD) and the Director of the Office of Regulatory Operations in OGD (or designee), if applicable, will:**
 - Approve the supplement, generally **within 15 calendar days** of receipt

When a labeling supplement is not received

- **The OND SRPM/RPM and OGD SLC Coordinator, if applicable, will:**
 - Notify OUDLC of noncompliance with the FDAAA SLC order, including if the application holder

- Submitted a supplement in response to the FDAAA SLC order that does not adequately address the NSI
 - Failed to submit a required labeling supplement **within 15 calendar days** of a dispute that was denied
 - Did not submit a supplement **within 15 calendar days** of the FDAAA SLC order (and for NDAs/BLAs/ANDAs, did not initiate dispute resolution **within 5 calendar days** of the FDAAA SLC order)
- **The Office of Compliance OUDLC will:**
 - Advise OND and OGD staff if the application holder does not respond to a FDAAA SLC notification or order letter
 - Initiate appropriate enforcement action against an application holder that is in violation of section 505(o)(4) of the FD&C Act

11. Posting FDAAA SLC Order Letters

- **The ORP Division of Information Disclosure Policy will:**
 - Automatically receive a copy of the FDAAA SLC order letter and enclosures once the letter is signed by the signatory in DARRTS
 - Within 2 business days of receipt, perform a disclosure review of the FDAAA SLC order letter and enclosures per established procedures
 - Within 1 business day after completion of the disclosure review, provide the redacted FDAAA SLC order letter to OCOMM's Division of Online Communications
- **The OCOMM Division of Online Communications will:**
 - Within 1 business day of receipt, post the redacted the FDAAA SLC order letter on FDA's website¹⁷

¹⁷ See the FDA web page Postmarket Drug Safety Information for Patients and Providers available at <https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers>.

REFERENCES¹⁸

- Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). (<https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>)
 - FDA’s Postmarketing Drug Safety Information for Patients and Providers web page (<https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers>)
 - Guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act*
 - Guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*
 - MAPP 4191.1, *Risk Evaluation and Mitigation Strategies Modifications and Revisions*
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DEFINITIONS

- **Changes being effected supplement (CBE-0):** Changes that do not require FDA approval prior to distribution of the drug; for such changes, the application holder 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).
- **New safety information (NSI):** “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)[of the FD&C Act]; 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

¹⁸ MAPPs can be found on the Manual of Policies and Procedures web page at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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.” (505-1(b) of the FD&C Act (21 U.S.C. 355-1(b))

NSI may be based on a new analysis of existing information or a different assessment of the risks and benefits of the drug (e.g., in relation to use in a new population).

- **Rebuttal statement:** An application holder’s statement to FDA detailing the reasons why the application holder believes a safety labeling change is not warranted.
- **Representative letter:** A de-identified sample letter that is drafted when FDAAA SLCs are issued for a drug class. The representative letter serves as a template for drafting SLC notification letters to other members in the class (e.g., ANDA application holders).

The representative letter is derived from the FDAAA SLC notification letter that is being issued to the individual NDA/BLA application holder(s) in the class. The representative letter includes the specifics of the SLC requirement (i.e., the new safety information and the label changes to be made). The representative letter excludes any information identifying the application holder and drug product (e.g., name, address, specific drug name) and other information that may be specific to the individual NDA/BLA.

More than one representative letter may be needed if the FDAAA SLC notification letters to the individual NDA/BLA application holder(s) in the class vary in the following content:

- The description of the source of the NSI
 - The description of the nature of the serious risk(s) of concern, including the populations affected
 - The revised labeling language and/or sections of labeling that are to be changed
- **Prior Approval Supplement (PAS):** Changes that require supplement submission and approval before the distribution of the drug with those changes. See 21 CFR 314.70(b) and 601.12(f)(1).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
7/10/2019	Initial	New MAPP Posting
11/7/24	N/A	Recertified via H. Edelberg's authority.

ATTACHMENT 1

Table 1: Applications for Which FDAAA SLC Notification Letters Are Issued

NDA* status	FDAAA SLC* Notification Letter Issuance	
	OND* to NDA holder	OGD* to holder of ANDA* that references the NDA
Active, marketed	X	Not applicable
Active, not marketed	X	Not applicable
Active, not marketed, withdrawal pending	X	X
Effectively withdrawn (30 days after publication of <i>Federal Register</i> notice) per 21 CFR 314.152	Not applicable	X

* New drug application (NDA); FDA Amendments Act of 2007 (FDAAA); safety labeling change (SLC); Office of New Drugs (OND); Office of Generic Drugs (OGD); and abbreviated new drug application (ANDA)

ATTACHMENT 2

Chart 1: Overview of FDAAA SLC Process and Time Frames (only applicable for SLC involving a single drug product)

