
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF LABELING CHANGES IN MANUFACTURING SUPPLEMENTS

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I. PURPOSE

This document establishes procedures that assure the consistent, timely, and accurate review and processing of labeling changes included in the chemistry, manufacturing, and controls (CMC) supplemental applications described in 21 CFR 514.8(b)¹.

II. SCOPE

FDA's regulations and Guidance for Industry (GFI) #83 describe the types of reporting criteria for supplements and CMC changes to new animal drugs. Specifically, under 21 CFR 514.8(b), a drug sponsor must report a CMC change in a:

- Prior approval supplement (subclass code CP),
- 30-day changes being effected (CBE-30) supplement (subclass code CS),
- Immediate changes being effected (CBE) supplement (subclass code CI), or
- Minor changes and stability report (MCSR) (subclass code CA).

The type of submission is based on the change's potential to adversely affect the identity, strength, quality, purity, or potency of the drug, as these factors may relate to the safety or effectiveness of the drug.²

This document pertains only to CMC changes that require corresponding labeling changes to approved drugs and to CMC supplements with labeling, even if the sponsor is not actually requesting a labeling change in that supplement.³ Most CMC changes do not

¹ This applies only to CMC supplements reviewed by the Division of Manufacturing Technologies. Products where the CMC supplements are reviewed by the Division of Animal Bioengineering and Cellular Therapies will not follow this process.

² For multiple related changes, where the recommended reporting categories for the individual changes differ, CVM will ask the sponsor to submit a CMC supplement in accordance with the most restrictive of the reporting categories recommended for the individual changes.

³ This P&P applies only to manufacturing supplements that are reviewed by the Division of Manufacturing Technologies.

require changes to labeling. Some examples of CMC changes reported in supplemental applications that require labeling changes include:

- A change in the manufacturing facility for products where the manufacturing facility is identified on the labeling,
- A change in the size of the container resulting in a change to the labeled amount of drug,
- A change in the labeled storage conditions, or
- A change to in-use conditions, such as multiple entries or in-use stability.

If the drug sponsor provides updated labeling in an MCSR, the Division of Manufacturing Technologies (DMT) will request that the sponsor resubmit the updated labeling in an appropriate supplemental application.⁴

III. ORIGINAL CMC SUPPLEMENTS

A. Initial Screening Process

The DMT performs an initial screening and administrative review upon receipt of a CMC supplement.⁵ If the submission contains labeling:

1. The DMT issues a consult to the target animal division (TAD)⁶ through Appian. Per the procedure on requesting consulting reviews (see P&P 1243.3200), the consult request should be sent within 5 days of the submission being received. The DMT includes appropriate directions in the "Instructions for Consulting Reviewer(s)" section on the Appian form, for example, "Please review the labeling." If the submission is a CBE-30 supplement, the DMT also includes directions for the TAD to contact the DMT before the 30-day deadline to indicate whether the labeling changes can be placed into effect prior to receipt of a written notice of approval.⁷ This response prior to the 30-day deadline should be in an email and there is no expectation that the consulting review itself is completed within this time frame, nor that there will be any comments during the actual review of the label. If the TAD determines the labeling changes require approval prior to distribution, the TAD should request that the DMT designate the submission as CBE-30 unacceptable, which will change the supplement to a prior approval supplement. Submissions designated CBE-30 by the sponsor when submitted are given a subclass code of CS. Submissions determined to be unacceptable as a CBE-30 will require approval prior to distribution and the subclass code will change to CP.
2. The TAD determines, within 7 days of receipt of the consult, whether the TAD should be the primary reviewer for the submission. This is the case if the supplement requires a clinical assessment by the TAD and/or a Freedom of

⁴ Any labeling change must be reported in a supplemental application according to 21 CFR 514.8(c).

⁵ See P&P 1243.3020.

⁶ "Target animal division," means the Divisions of Companion Animal Drugs, Food Animal Drugs, and Generic Animal Drugs.

⁷ See 514.8(c)(2) and (3) for definitions of these changes.

Information (FOI) Summary, in addition to the labeling review. Examples of these types of submissions could include:

- a. Significant changes to the qualitative or quantitative formulation of a drug product that may affect the safety or effectiveness of the animal drug, or
- b. Changes to the primary container closure system that may affect the drug delivery volume.

If a clinical assessment by the TAD or an FOI Summary is required, the TAD notifies DMT that TAD should be the primary review group. The DMT will notify the sponsor to resubmit the supplement to the TAD with the correct submission code, new time frame (typically 180 days), and whether it will be a fee paying supplement because an eSubmitter submission cannot be recoded once it has been assigned to a reviewer. The DMT will also void the incorrectly coded submission in Appian, using the ONADE Void Submission function on the Actions tab.⁸ After the submission is resubmitted, the TAD follows P&P 1243.6020 or 1243.6040, as appropriate, and requests a consulting review from the DMT regarding the CMC information in the supplement.

If the DMT remains the primary review group, the DMT and TAD personnel follow the procedures below.

B. TAD Consulting Review

1. The TAD reviews the submission as outlined in 1243.6020, sections V and VI. If an amendment is needed, the TAD should contact the DMT to discuss how the amendment request will be sent to the sponsor. In the consulting review, the TAD reviewer should:
 - a. Indicate any labeling changes that are being deferred to the DMT reviewer for determination of acceptability (e.g., changes to the storage condition statement, maximum puncture statements).
 - b. In the recommendations section, indicate whether a Green Book and Animal Drugs @ FDA (GBAAD) form is required for the change, whether the labeling submitted is final printed labeling (FPL), and whether the product is a nonsteroidal anti-inflammatory drug (NSAID).

If the labeling is an NSAID and included the package insert or client information sheet, the TAD and DMT reviewers should discuss how any forms will be provided to the Business Process Improvements (BPI) team for updating.

2. Closes out the consulting review as described in P&P 1243.3029.
3. After Appian notifies the TAD reviewer by email that the submission is acceptable and has been closed out, the TAD reviewer emails:

⁸ See P&P 1243.3011 and the Appian User Guide for instructions on voiding submissions.

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- a. The CVM Policy & Regulations Staff (HFV-6), using the Outlook Notification template on the ONADE Template page in SharePoint, regarding changes to the CFR, if applicable,
 - b. The BPI staff the GBAAD form, if necessary based on the change, at Internal information redacted, and
 - c. The Office of Surveillance and Compliance (OSC) Division of Pharmacovigilance and Surveillance regarding any labeling changes that should be made in a future supplement, if needed. If more information is needed, email DPS at Internal information redacted

C. CMC Review

1. The DMT prepares a review documenting whether the CMC information, including any CMC information on the labeling, is acceptable. If, during the course of review, an amendment is received that impacts labeling, that amendment will also be consulted to the TAD. Once the TAD consulting reviewer returns the consult, DMT determines and documents the approval status of the supplement.
2. The DMT prepares a letter appropriate for the final action status of the supplement, including the comments from the TAD reviewer's consulting review, if applicable.

IV. REACTIVATIONS OF SUPPLEMENTS

The DMT performs an initial screening and administrative review upon receipt of a reactivation of a CMC supplement. If the submission contains labeling, or the original supplement contained labeling even if the reactivation does not, the DMT reviewer sends a consult request to the TAD to confirm that the labeling submitted in the original supplement continues to be acceptable. The process proceeds as described in section III.B and III.C above for an original supplement with labeling.

V. ASSEMBLING AND ROUTING THE PACKAGE FOR FINAL CLEARANCE

The DMT reviewer completes the steps for final clearance in Appian, including:

1. Selects the appropriate final action code for the supplement.
2. Builds the clearance chain in Appian according to the longest chain needed for the package, which varies depending on the final action code.
3. Answers the questions under "Additional Actions" depending on the specific information in and the approval status of the supplement.
 - a. Select "Does this supplement contain acceptable labeling?", check yes ONLY if the supplement is being APPROVED. If the reactivation or original submission included labeling, even if the reactivation itself does not, choose yes to this question. If you check "yes" additional questions will appear:
 - Check "This submission contains FPL" ONLY if the TAD has indicated that the submission contains FPL.

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- Check “This submission contains NSAID labeling”. The DMT and TAD reviewers should discuss how any forms will be provided to the BPI team for updating.
 - Check “This CMC supplement contains labeling reviewed by a consultant” in ALL cases.
 - Check “This submission contains Blue Bird labeling” ONLY if the submission includes Blue Bird labeling.
 - Check “This submission includes labeling for a pioneer product” ONLY for pioneer products. If the submission is to a generic file but includes copies of the pioneer labeling for reference, do NOT check this box.
 - If the pioneer product is a Type A medicated article labeling, medicated feed labeling, or a veterinary feed directive (VFD) then select “This submission includes the approval of changes to Type A medicated article labeling, medicated feed labeling (e.g., Blue Bird or branded), and/or VFD(s)...”
 - If the labeling is for a pioneer dosage form that is not a medicated feed dosage form, select “This submission includes approval of changes to the labeling of a non-medicated feed dosage form...”
 - b. Select “Do you want to notify all consultants that the submission has been closed out?” in ALL cases, whether approved or incomplete.
 - c. Do not select “Do you want to notify someone else that the submission has been closed out?” unless you have discussed with your team leader.
4. Uploads the DMT review and appropriate letter. There may be other pertinent information that needs to be included (memos to file, copies of sponsor communication emails, etc.). The review is signed by the reviewer and team leader, and incomplete letter is signed by the reviewer and team leader, while a complete letter is signed by the reviewer, team leader, and the division director per division policy. The remaining documents do not require signature, but if they are part of the package, they will need to be uploaded into Appian with the above documents in order to get them correctly archived into FDA’s record.
5. Completes the Appian “Review Summary” field to indicate that the CMC supplement includes labeling in ALL cases.

VI. FINALING OUT PACKAGES

A. Appian Sign-off

It is the responsibility of the DMT reviewer to make sure that the correct personnel are available and entered into the Appian concurrence chain and that the package moves through Appian for concurrences in a timely manner. The DMT reviewer should initiate communication with the appropriate individuals when the package is stalled.

B. Document Control Unit/Business Informatics (BI) Team

The BI Team updates Animal Drugs @ FDA (ADAFDA) as appropriate when the approval is finalized, as part of the GBAAD monthly update process.

VII. UPDATING VOLUME 0

When new labeling is approved, the TAD updates the Volume 0.^{9,10} When labeling is submitted in a CMC supplement, the labeling is not considered approved until the CMC supplement is approved. When closing out the submission in Appian, the DMT reviewer will select to notify all consulting reviewers that the submission is closed out.

A. If the CMC supplement is approved:

Within two weeks of receiving the Appian notification, the TAD will update the Volume 0 with the information for the approved submission and check the Volume 0 back into SharePoint.

B. If the CMC supplement is incomplete:

The TAD checks the Volume 0 back into SharePoint without updating.

VIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 - New Animal Drug Applications

§ 514.8, Supplements and other changes to an approved application

CVM Guidance for Industry #83 - Chemistry, manufacturing and controls changes to an approved NADA or ANADA

CVM Program Policy and Procedures Manual – ONADE Reviewer's Chapter

1243.3011 – Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications

1243.3020 - Managing the Review of Submissions in the Submission Tracking and Reporting System (STARS) Queue

1243.3026 - Amending and Resetting the Clock on Submission Tracking and Reporting System (STARS) Submissions

1243.3029 - Closing Out a Consulting Review for Submission Tracking and Reporting System (STARS) Submissions

⁹ See P&P 1243.3810 for updating the Volume 0.

¹⁰ If the labeling is incomplete, regardless of whether the CMC portion of the supplement is acceptable or not, no changes are made to the Volume 0.

1243.3030 - Completing Final Action Packages for Submission Tracking and Reporting System (STARS) Submissions

1243.3200 – Routing a Request to Obtain a Consulting Review of a Submission Tracking and Reporting System (STARS) Submission

1243.3801 – Completing the Green Book and Animal Drugs at FDA (GBAAD) Form

1243.3810 - Creating and Maintaining a Reference Copy of the Currently Approved Labeling for an Application (Volume 0)

1243.6020 - Review of New Animal Drug Application and Abbreviated New Animal Drug Application Supplements (NL Subclass)

ONADE Office Policy Page

Initial Recommendations for the Addition of Approved by FDA Statements to Labeling

Appian User Guide

Internal information redacted

Volume 0

Internal information redacted

IX. VERSION HISTORY

October 1, 2007 - original version

November 12, 2008 - This update adds clarifications to Section III of this document to facilitate the initial screening process of CMC supplements. Members of the ONADE Team Leader Working Group expanded and approved the content of this section to specify the number of days that each division has in the routing of the supplement and each division's role in searching for Volume 0.

June 16, 2009 - Revised to instruct reviewers on using the DCU2 Outlook mailbox.

August 28, 2014 - Revised to incorporate a new process for updating Volume 0 and publishing FR notices

September 16, 2014 - Revised to correct minor editorial issues.

June 22, 2016 - Updated formatting and redact internal information that made up the appendix.

February 9, 2018- Updated the process to reflect that labeling is requested in all reactivations, regardless of whether there were incomplete comments on the labeling following the initial review. Clarification added on the interaction between DMT and the TAD reviewers regarding the GBAAD form. Added the sections for routing the final action and finalizing in Appian.

August 1, 2018 – Clarify that reactivations where the original supplement contained labeling, whether the reactivation contains labeling or not, are consulted to the TAD. Update the Appian process for voiding a submission to reflect the new names of functions and tabs in Appian Tempo.

April 15, 2019 – updated to add instructions on when and how to ask for addition of “Approved by FDA...” statements to labeling.

June 22, 2020 - Updated all internal links for SharePoint sites because FDA has migrated this information to a new version of SharePoint.

September 17, 2020 – Revised to include instructions related to applications containing OSC-initiated labeling changes.

August 16, 2022 – Revised to include instructions for using checkboxes in Appian appropriately, including to communicate to consulting reviewers that the submission has been closed out. Additional clarification was added to the boilerplate language for the TAD reviewer to ensure the DMT reviewer has the information to accurately fill out the checkboxes in Appian during the close out process. Editorial changes and reorganization were made to the TAD and DMT review sections for clarity. Instructions for paper submissions were removed as we no longer have paper CMC supplements.

February 9, 2023 – Updated to to reflect a recent change in Appian wording regarding labeling.

April 24, 2023 - Section III B 1 c was updated contact info for OSC Division of Pharmacovigilance and Surveillance.

APPENDIX 1

In the “Recommendations” section of their review, the TAD CR should include the following language (modified as applicable for the submission) for the DMT reviewer to use in completing the final action package for the CMC supplement:

The labeling <(pick one) is/is not> FPL.

The labeling <(pick one) is/is not> for an NSAID product.

The labeling change <(pick one) does/does not> require a GBAAD form.

If this submission is approved, then please transmit the following to the sponsor:

<The TAD CR should include the following paragraph if applicable:>

We identified additional changes in your submitted labeling that differ from the last approved labeling. We considered these additional changes in our approval decision.

<The TAD CR should include the applicable labeling paragraph depending on the type of labeling submitted (and delete the others):>

<Use this paragraph for a dosage form product (non-feed product) if some or of all the labeling does not meet CVM's eFPL standards [see P&P 1243.5725].> Your final printed labeling must be identical to the facsimile labeling submitted <Month DD, YYYY (X-0000, labeling component(s)), and Month DD, YYYY (X-0000, labeling component(s)).> *<If applicable, include a description of typographical changes needed for the final printed labeling.>* Please submit a single copy of each component of the final printed labeling to us within six months of the date of this letter or at the next printing of this labeling, whichever comes first. The labeling should be provided in Portable Document Format (.pdf) files, which are an exact electronic representation of the final labeling. Address the labeling to the Division of <(pick one) Companion Animal Drugs, Food Animal Drugs, Generic Animal Drugs>. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

OR

<Use this paragraph for a dosage form product (non-feed product) if any or of all the labeling meets CVM's eFPL standards [see P&P 1243.5725].> Your final printed labeling submitted <Month DD, YYYY (X-0000, labeling component(s)), and Month DD, YYYY (X-0000, labeling component(s))> is acceptable. It is not necessary to resubmit this labeling. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

OR

<Use this paragraph if labeling for a medicated feed product was submitted and it does not meet CVM's eFPL standards [see P&P 1243.5725].> Your final printed labeling of the Type A medicated article must be identical to the approved labeling submitted <Month DD, YYYY (X-0000, labeling component(s)), and Month DD, YYYY (X-0000, labeling component(s)).> *<If applicable, include a description of typographical changes needed for the final printed labeling.>* It is not necessary to <(pick one) submit/resubmit> your

<(choose applicable) representative Type B and Type C medicated feed labels (Blue Bird labels) or veterinary feed directive(s).> Please submit a single copy of each component of the final printed labeling to us within six months of the date of this letter or at the next printing of this labeling, whichever comes first. The labeling should be submitted via eSubmitter in Portable Document Format (.pdf) files, which are an exact electronic representation of the final labeling. Address the labeling to the Division of <(pick one) Companion Animal Drugs, Food Animal Drugs, Generic Animal Drugs>. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

OR

<Use this paragraph if labeling for a medicated feed product was submitted and it meets CVM's eFPL standards [see P&P 1243.5725].> Your <(choose applicable) final printed labeling, representative Type B and Type C medicated feed labels (Blue Bird labels), veterinary feed directive(s)> submitted <Month DD, YYYY (X-0000, labeling component(s)), and Month DD, YYYY (X-0000, labeling component(s))> is acceptable. It is not necessary to resubmit this labeling. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

<The TAD CR should include applicable language from Section X of the "Initial Recommendations" Office Policy requesting addition of the "Approved by FDA..." statement by September 30, 2023, if not already included on the labeling>

If this submission is not approved, then please transmit the following to the sponsor:

<The TAD CR should include this language if the labeling is not acceptable:>

We have reviewed the <(pick one) facsimile labeling/final printed labeling> submitted with this supplement and have the following comments: <include comments>.

Please resubmit the revised labeling when the supplement is reactivated.

<The TAD CR should include this language if the labeling is acceptable:>

We have reviewed the <(pick one) facsimile labeling/final printed labeling> submitted with this supplement and have no required or suggested revisions at this time. The CMC supplement must be reactivated (i.e., resubmitted) and approved by CVM before the labeling is approved. Resubmit the labeling when the supplement is reactivated.

< The TAD CR should include applicable language from Section X of the "Initial Recommendations" Office Policy requesting addition of the "Approved by FDA..." statement by September 30, 2023, if not already included on the labeling>