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OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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**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).

**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,
- 30-day changes being effected (CBE-30) supplement,
- Immediate changes being effected (CBE) supplement, or
- Minor changes and stability report (MCSR).

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.<sup>1</sup>

This document pertains only to CMC changes that require corresponding labeling changes to finished drugs and to CMC supplements with labeling, even if the sponsor is not actually requesting a labeling change in that supplement.<sup>2</sup> Most CMC changes

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<sup>1</sup> 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.

<sup>2</sup> This P&P applies only to manufacturing supplements that are reviewed by the Division of Manufacturing Technologies.

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do not 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.<sup>3</sup>

### III. ORIGINAL CMC SUPPLEMENTS

#### A. Initial Screening Process

The DMT performs an initial screening and administrative review upon receipt of a CMC supplement.<sup>4</sup> If the submission contains labeling:

1. The DMT issues a consult to the target animal division (TAD)<sup>5</sup> through Appian. Per our procedure on requesting consulting reviews (see P&P 1243.3200), the consult request should be sent within 5 days of the submission being logged into STARS. 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 are of a type that can be placed into effect prior to receipt of a written notice of approval.<sup>6</sup> This response prior to the 30-day deadline can be in an email and there is no expectation that the consulting review itself is completed within this time frame. If the TAD determines the labeling changes require approval prior to distribution, the TAD requests 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

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<sup>3</sup> Any labeling change must be reported in a supplemental application according to 21 CFR 514.8(c).

<sup>4</sup> See P&P 1243.3020.

<sup>5</sup> "Target animal division," means the Divisions of Therapeutic Drugs for Non-Food Animals, Production Drugs, and Therapeutic Drugs for Food Animals, and the Division of Generic Animal Drugs.

<sup>6</sup> 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 affect the safety or effectiveness of the animal drug, or
- b. Changes to the primary container closure system that affects the drug delivery volume.

If a clinical assessment by the TAD or an FOI Summary is required, the TAD notifies the DMT to reassign the CMC supplement to the TAD as the primary review group. If the submission was received by our Document Control Unit in paper, to reassign a paper submission, the DMT submits a Submission Tracking and Reporting System (STARS) Correction Request Form to the Document Control Unit (DCU) to change the primary review division and the sub-class code of the supplement. If the change in sub-class code will affect the STARS due date of the submission, the DMT notifies the sponsor of the new due date. See P&P 1243.3002 for handling and rejecting paper applications and submissions received after October 1, 2018. If the submission was made using eSubmitter, the DMT will notify the sponsor to resubmit the supplement to the TAD with the correct submission code. DMT will do this because we cannot recode an eSubmitter submission. The DMT will also void the incorrectly-coded submission in Appian, using the ONADE Void Submission function on the Actions tab.<sup>7</sup> After the submission is reassigned or resubmitted, the TAD follows P&P 1243.6020, 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 in section IV, below.

#### **B. TAD consulting review**

The TAD consulting review process for labeling changes in CMC supplements is similar to the labeling review process described in P&P 1243.6020, sections V.A. and V.B.

The TAD determines if a Volume 0 exists. If a Volume 0 does not exist, the TAD will follow the procedures for creating a Volume 0.<sup>8</sup> The TAD determines if a consult to the Office of Surveillance and Compliance (OSC) is needed and issues the appropriate sub-consult(s)<sup>9</sup>, if necessary.

The TAD determines the acceptability of the submitted labeling.

We are now requesting the addition of an "Approved by FDA" labeling statement based on the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (H.R. 5554). These amendments added a section to the Federal Food, Drug,

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<sup>7</sup> See P&P 1243.3011 and the Appian User Guide for instructions on voiding submissions.

<sup>8</sup> See P&P 1243.3810 Creating and Maintaining a Reference Copy of the Currently Approved Labeling for an Application (Volume 0).

<sup>9</sup> See P&P 1243.3200

and Cosmetic Act (FD&C Act) that requires the addition of the statement "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX" to labeling (except representative [Blue Bird] labeling) of approved new animal drugs and generic new animal drugs, respectively, by September 30, 2023. We are requesting the addition of the labeling statement to all approved and marketed labeling components of these products. We are also encouraging the addition of the statement to Blue Bird labeling to clearly identify that the medicated feed was manufactured in accordance with FDA-approved Blue Bird labeling. If the labeling included in the CMC supplement does not include the applicable labeling statement, the TAD reviewer should refer to the ONADE Policy 'Initial Recommendations for the Addition of Approved by FDA Statements to Labeling' found on the ONADE Policy SharePoint page for information on when and how to ask the sponsor to add the statement to the labeling.<sup>10</sup> Section X of the Policy provides boilerplate language for the TAD's review when it is appropriate to ask that the statements be added to the labeling.

1. If the labeling is acceptable, the TAD:
  - a. Prepares a consulting review incorporating information described in P&P 1243.6020, including specific language regarding the submission of final printed labeling for DMT to include in the approval letter (see Appendix) and identification of any labeling changes we want to instruct the sponsor to make in a future supplement. If the applicable "Approved by FDA..." statement is not already included on the labeling, include applicable language from Section X of the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling.
  - b. Closes out the consulting review as described in P&P 1243.3029.
  - c. Prepares the Green Book and Animal Drugs @ FDA (GBAAD) form.<sup>11</sup> A GBAAD form is only prepared if necessary for the specific change in the supplement, and is prepared when requested by the DMT reviewer during the notification email that we are approving the supplement. The TAD reviewer emails it to the DMT reviewer to upload into Appian during the close out process.
  - d. Emails the CVM Policy & Regulations Staff (HFV-6), using the Outlook Notification template on the ONADE Template page in SharePoint, regarding changes to the CFR and OSC regarding any labeling changes that should be made in a future supplement, if needed. This should be conducted after

<sup>10</sup> Link to ONADE Policy on "Approved by FDA..." labeling statements  
Internal information redacted.

<sup>11</sup> See P&P 1243.3801

being notified that the submission is acceptable and has been closed out by the DMT reviewer.

2. If the labeling is not acceptable as submitted, the TAD and DMT will:
  - a. Determine whether there is sufficient time to amend the application to correct the observed deficiencies and who will contact the sponsor to request the amendment.<sup>12</sup> If the applicable "Approved by FDA..." statement is not already included on the labeling, include applicable language from Section X of the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling.
  - b. The DMT creates consulting review requests for any labeling amendments to the TAD for review and the TAD again determines the acceptability of the submitted labeling.
3. If the labeling is not acceptable, and we determine we will not ask for an amendment to correct the deficiencies, the TAD:
  - a. Prepares a consulting review stating that the labeling is incomplete and provides specific comments for DMT to send to the sponsor. If the applicable "Approved by FDA..." statement is not already included on the labeling, include applicable language from Section X of the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling.
  - b. Closes out the consulting review as described in P&P 1243.3029.

### C. CMC review

The DMT prepares a review documenting whether the CMC information, including any CMC information on the labeling, is acceptable. Once the TAD consulting reviewer returns the consult, DMT determines and documents the approval status of the supplement.

1. If the CMC information is acceptable and the labeling is acceptable, the DMT:
  - a. Prepares a supplemental application approval letter, including any language regarding submission of final printed labeling provided by the TAD.
  - b. Conveys to the TAD that the submission is acceptable and asks whether a GBAAD is required for this change. If so, at the time of this discussion, the

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<sup>12</sup> See P&P 1243.3026 for information related to requesting and processing submission amendments.

TAD reviewer completes a GBAAD form and emails it to the DMT reviewer to upload into Appian when closing out the submission.

- c. Prepares the final action package according to DMT procedures, consistent with ONADE procedures (P&P 1243.3030), including the GBAAD form, if necessary. The DMT reviewer will complete either the STARS "Review Summary" field or the Appian "Review Summary" field to indicate that the CMC supplement includes labeling.
  - d. Sends an email to the TAD indicating that the submission has been closed in Appian.
2. If the CMC information is not acceptable but there are no concerns with the labeling, the DMT:
    - a. Prepares a supplemental application incomplete letter listing the deficiencies in the CMC information. This letter should include the statement from the TAD consulting review that there are no concerns at this time with the labeling, but the labeling is not approved and the sponsor should re-submit the labeling with the reactivation.
    - b. Prepares the final action package according to DMT procedures, consistent with ONADE procedures (P&P 1243.3030).
    - c. Sends an email to the TAD reviewer indicating that the CMC supplement is incomplete.
  3. If the CMC information is acceptable but the labeling is not acceptable, DMT:
    - a. Prepares a supplemental application incomplete letter listing the deficiencies in the labeling using comments from the TAD consulting review.
    - b. Prepares the final action package according to DMT procedures, consistent with ONADE procedures (P&P 1243.3030).
  4. If the submitted CMC information is not acceptable and the labeling is not acceptable, DMT:
    - a. Prepares a supplemental application incomplete letter listing the deficiencies in the CMC information and the deficiencies in labeling using comments from the TAD consulting review.
    - b. Prepares the final action package according to DMT procedures, consistent with ONADE procedures (P&P 1243.3030).

#### **IV. REACTIVATIONS OF SUPPLEMENTS**

##### **A. Initial screening process**

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 as described for original supplements in section III.A above.

##### **B. Reactivation with labeling**

If the supplement contains labeling, or the original supplement contained labeling even if the reactivation does not, 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 final package is electronic, and generally consists of the review, letter, and GBAAD form, if appropriate. Build the sign-off in Appian according to the longest chain needed for your package. The primary reviewer and team leader sign both the review and letter. The division director signs the letter as appropriate, per division procedures.

When including documents in Appian, select "Yes" to answer the question "Should file be sent to the firm?" for only the letter.

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. These documents include:

- GBAAD, if present
- other pertinent information (memos to file, copies of sponsor communication emails, etc.)

The following documents, although they were reviewed as part of the package, are NOT uploaded in Appian:

- Appian consult return notification email(s)

#### **VI. FINALING OUT PACKAGES**

##### **A. Appian sign-off**

It is the responsibility of the 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 reviewer should initiate communication with the appropriate individuals when the package is stalled.

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

When the Document Control Unit (DCU) receives the completed and signed approval package that was submitted in paper, the Records and Information Management (RIM) Team:

- Mails the letter and enclosures to the applicant for packages received in paper, if applicable; and
- the BI Team updates STARS as appropriate when the approval is finalized, as part of the Green Book/AD@FDA monthly update process.

**VII. UPDATING VOLUME 0**

When new labeling is approved, the TAD updates the Volume 0.<sup>13,14</sup> When labeling is submitted in a CMC supplement, the labeling is not considered to be approved until the CMC supplement is approved.

**A. If the labeling is acceptable and the CMC supplement is approved:**

1. DMT notifies the TAD by email that the CMC supplement is approved (section III.C.1.d) after DMT closes the submission in Appian.
2. Within two weeks of receiving the email from DMT, 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 labeling is acceptable, but the CMC supplement is incomplete:**

1. The DMT notifies the TAD by email that the CMC supplement is incomplete (section III.C.2.c).
2. 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

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<sup>13</sup> See P&P 1243.3810 for updating the Volume 0.

<sup>14</sup> 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.



CVM Program Policy and Procedures Manual

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 STARS Submissions

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.



**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 finalling 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.

**APPENDIX 1**

Boilerplate language for TAD's consulting review to DMT for acceptable labels in CMC supplements:

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

Your final printed labeling must be identical to the facsimile labeling submitted <date and submission code>. 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 <Therapeutic Drugs for Non-Food Animals, Production Drugs, Therapeutic Drugs for Food Animals, Generic Animal Drugs (pick one)>. Any changes to this approved labeling will require a supplemental application.

*<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>*

OR

Your final printed labeling submitted <date and submission code for the FPL submitted> to the <A/NADA> is acceptable. Any changes to this approved labeling will require a supplemental application. The labeling should be provided in Portable Document Format (.pdf) files, which are an exact electronic representation of the final labeling.

*<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:**

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

*<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>*