OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF NEW ANIMAL DRUG APPLICATION AND ABBREVIATED NEW ANIMAL DRUG APPLICATION SUPPLEMENTS (NL SUBCLASS)

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I. PURPOSE

This document establishes procedures for the Office of New Animal Drug Evaluation (ONADE) on how to:

- Determine if an abbreviated new animal drug application (ANADA) or new animal drug application (NADA) non-fee labeling supplement is correctly coded
- Review an (A)NADA NL Labeling Supplement
- Prepare an approval action package for an NL Labeling Supplement
- Process and finalize an (A)NADA NL Labeling Supplement

II. BACKGROUND AND SCOPE

There are two types of labeling supplements:

1. Changes being effected [(CBE) labeling supplements (CVM subclass code NL for Non-fee Labeling)], as defined in 21 CFR 514.8(c)(3), which can consist of style or design changes, and/or changes that increase safety that can be implemented immediately, prior to receipt of written notice of approval.

2. Prior approval labeling supplements (CVM subclass code NF for Non-fee Labeling), as defined in 21 CFR 514.8(c)(2), which consist of major changes that require approval prior to distribution of the drug made using the change. See P&P 1243.6040 for additional information on NF labeling supplements.

III. WHO IS RESPONSIBLE FOR CREATING THE APPROVAL PACKAGE?

The primary reviewer (PR) is responsible for reviewing the NL Labeling Supplement and preparing the approval package documents for the application. Team leaders (TLs) and division directors (DDs) are responsible for ensuring the accuracy of the NL Labeling Supplement approval package and that applicable policies and procedures were followed and office templates utilized. The approval package typically includes a Memorandum Recommending Approval (MRA), and supplemental approval letter. A Green Book and Animal Drugs (GBAAD) Form, Freedom of Information Summary, and a FEDERAL REGISTER (FR) update are not part of the approval package.

IV. CONFIRM THE SUBMISSION IS CORRECTLY IDENTIFIED AS AN NL LABELING SUPPLEMENT

The PR will confirm that the sponsor has correctly submitted the labeling supplement as an NL Labeling Supplement.

Examples of NL labeling supplements are:

- Formatting changes
- Trade dress (color, graphics, and font)
- Updating changes that do not affect safety and effectiveness
- Updating storage statement to current standards based on existing stability data
- Addition of the "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX" statement[1]
- Change in patent information
- Revisions to warnings that increase the assurance of drug safety (example: updating labeling to add a warning statement)
- Changes to text that that are identical to the documented, agreed-upon wording between the sponsor and the Office of Surveillance and Compliance (OSC).

Talk with your TL if there are questions about whether the submission should be an NL or NF Labeling Supplement.

If the submission was submitted electronically and was incorrectly coded as an NL subclass, the PR must void the submission. See P&P 1243.3011 for more detail. Then, notify the sponsor of the incorrect submission type and ask them to resubmit their submission with the correct submission type. If the submission was received via paper and is being accepted by ONADE in that format, the primary reviewer can submit a Submission Tracking and Reporting System (STARS) Correction Request

[1] Link to ONADE Policy on "Approved by FDA…" labeling statements
Internal information redacted.

Form to ask that the submission be recoded.[2] See P&P 1243.3002 for handling and rejecting paper applications and submissions received after October 1, 2018.)

V. PROCESSING THE NL SUBMISSION

A. Check for Completeness and Accuracy of the Submission[3]

Conduct an initial assessment of the submission (items 1 through 4, below) and determine whether it is sufficiently complete for review. If the submission is deficient on its face, issue a letter refusing to file the supplemental application within 30 days of receipt of the submission (see P&P 1243.2050).

1. Verify that the submission is assigned to the correct review division. If the submission needs to be re-assigned and you do not have STARS privileges to reassign submissions outside of your division, identify the correct division and submit a STARS Correction Request form to the EDSR mailbox (CVM.ONADE.EDSR.SUPPORT@FDA.HHS.GOV). If you have privileges, you don't need to submit the form and can just reassign the submission.

2. Verify that the eSubmitter Submission Report includes a request for a categorical exclusion under 21 CFR 25.33 or an Environmental Assessment (see P&P 1243.7220).

3. Check that all proposed labeling components mentioned in the eSubmitter Submission Report are included (or attached).

4. Verify the accuracy of information provided in the eSubmitter submission report. If there are inconsistencies in the information provided in the eSubmitter submission report, the cover letter, and/or attachments to the submission, refer to ONADE's eSubmitter Policy.[4]

If any of the items above are missing or incorrect, then discuss with your supervisor if you should Refuse to Review (RTR) the supplement (see P&P 1243.2050) or request an amendment (see P&P 1243.3026).

B. Determine If Consulting Reviews Are Needed

Consulting reviews are requested on a case-by-case basis (for examples, see Appendix 1). If you are uncertain whether a division or team should be consulted on the application and be assigned a consulting review, either formally or informally, ask the TL of the consulting team for their input and guidance. Request consults within 5 days of receipt per the procedures described in P&P 1243.3200 and see the consulting review points of contact document on the ONADE Template

[2] Link to STARS Correction Request Form
Internal information redacted.

[3] Note: if the supplemental application was made in paper and ONADE is accepting it, verify the signature and accuracy of the FDA Form 356v that is part of the application.

[4] Link to ONADE eSubmitter Policy
Internal information redacted.

SharePoint page. An informal consult may be sufficient, if a comprehensive review is not required. Typically, an informal consult request consists of a few specific questions for the consulting reviewer (CR) to which they can respond succinctly via email in lieu of a formal review. The PR's questions and the CR's responses should be documented as a memo to file or be included in the primary review, if applicable.

C. Access the Volume 0 to Obtain the Submission Location of the Currently Approved Labeling

The Volume 0 lists the submission(s) containing each of the components of the currently approved labeling.

1. Determine if an electronic Volume 0 exists by accessing the Volume 0 libraries in SharePoint.[5] If the application is listed, access the applicable (A)NADA file number to obtain the submission number for the currently approved labeling. Once the submission(s) containing the currently approved labeling has been identified, check STARS [Corporate Database Portal (CDP Web)] and/or the Corporate Document Management System (CDMS) to obtain copies of the labeling.

2. If an electronic copy does not exist, request the applicable paper Volume 0 from the Document Control Unit (DCU) using the Document Scanning Request Form.[6] NOTE: The Records and Information Management (RIM) Team turnaround is two business days.

If supplemental labeling has been submitted and approved multiple times in the history of this product [i.e., medicated feed (Blue Bird) labels)], then check all of the submissions in STARS to determine the currently approved labeling.

VI. LABELING

A. Compare Components of the Currently Approved Labeling Referenced in the Volume 0(s) (or the Administrative Record) to the Proposed Labeling in the Supplement

The PR compares the submitted labeling components (e.g., package insert, immediate container, carton, Type A medicated article bag, etc.) to the currently approved labeling referenced in Volume 0(s) or contained in the administrative file for the (A)NADA. This comparison is to determine if the sponsor made changes other than those proposed and specified in the cover letter or described in the eSubmitter Submission Report and to determine if the proposed labeling changes are acceptable. Acceptability of the changes is based on the type and scope of the proposed change and if the labeling reflects CVM's current thinking on the

[5] Link to Volume 0 library in SharePoint
Internal information redacted.

[6] Link to scanning request form
Internal information redacted.

contents of labeling components, such as expression of the active ingredient, listing of animal classes, location and font used for caution statements, etc. Compare the submitted labeling components to the components listed in the Volume 0. If the sponsor omitted certain components that require updates, notify the sponsor to submit the revised labeling components as an amendment to the submission. If there are questions about the acceptability of the changes, the PR should discuss these with the TL or DD.

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, 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. If the labeling included in the NL supplement does not include the applicable labeling statement, the PR 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.[7]

For NADA Animal Drug Availability Act (ADAA) feed combinations and for ANADA medicated feed combinations in which the effect of the supplement is related to changes in the Type A medicated article(s),[8] the PR should compare the submitted labeling to the approved labeling for the separately approved Type A medicated articles and to the approved labeling for the specific combination of drugs. For ANADA medicated feed combinations in which the changes are not related to changes in the Type A medicated article(s), only the comparison with the currently approved labeling for the RLNAD is needed.

The submission codes (e.g., C-xxxx) of approved labeling for the Type A medicated articles can be found in the Volume 0 under the (A)NADA numbers. The Volume 0 for the (A)NADA for ADAA feed combinations lists the submission ID of the most recently approved Blue Bird labeling. The PR determines if changes made to the Type A medicated article labeling occurring after the most recently approved combination Blue Bird labeling are relevant to the combination. If so, the PR should request these changes be made by the sponsor and instruct the sponsor to submit revised labeling in an amendment (see P&P 1243.3026 for more information on requesting amendments).

For NL Labeling Supplements to an ANADA, the PR compares the proposed new generic labeling to the currently approved RLNAD labeling, as well as to the currently approved generic labeling. Each of these is referenced in their respective Volume 0 or in the (A)NADA administrative file.

[7] Link to ONADE Policy on approved by FDA statements
Internal information redacted.

[8] Examples include changes in feeding directions, approved species, etc.

Steps for comparison of the labeling:

- Review the eSubmitter Submission Report and/or cover letter for a summary of the proposed labeling changes. If discrepancies exist between the two, the PR should contact the sponsor for clarification.
- Note the differences between the currently approved labeling (in Volume 0 or administrative record) and the proposed labeling with a side-by-side comparison. Record substantial differences in the MRA or review.
- Discuss any questions about the changes to or differences in the labeling with the TL or DD.

B. Compare Changes to the Regulations

Compare the electronic Code of Federal Regulations (eCFR) citation (http://ecfr.gov) under Title 21 CFR Section 500 599) to the proposed labeling. If there is a substantive discrepancy with the eCFR, determine whether the proposed labeling or the eCFR is correct by checking the history of the (A)NADA in the administrative record. Document any substantive discrepancies in the MRA. If the eCFR is incorrect, email the CVM Policy and Regulations Team (HFV-6) to request revisions using the CFR Batch Changes Outlook template.[9] Attach the email as part of your MRA. NOTE: The Policy and Regulations Team has six months to update the CFR, so request only minor changes this way. If major or significant changes to the CFR are required, email HFV-6 directly (not using the template) to request the changes be implemented more rapidly. If significant research was required to verify correctness of labeling and the CFR, add a note to the Volume 0 that references the appropriate files to check or cite a review that documents the details of your comparison.

C. Determine if the Sponsor Has Addressed Any Outstanding Labeling Changes Requested by OSC

OSC's Division of Surveillance (DS) maintains the Drug Event Reporting (DER) database containing current OSC requests for labeling changes. Find the DER database through the CDP Portal. The PR determines whether the outstanding labeling change requests identified in the DER database are incorporated in the labeling for the pending supplement. The instructions for accessing the DER are provided in the document found in the ONADE SOP on the process for accessing the Drug Experience Reporting database.[10] If necessary, contact OSC (Post-Approval Review Team, HFV-216) to get more information.

D. Comparing Supplemental Application Information to Animal Drugs @ FDA

Compare the information in the submission to the information on Animal Drugs @ FDA. If information in the submission related to the Animal Drugs @ FDA has

[9] Link to ONADE Template Page in SharePoint. Scroll down to Outlook Template section
Internal information redacted.

[10] See ONADE SOP 1243.120.001 ONADE Process for Accessing the Drug Experience Reporting (DER) Database to Perform Status Checks

changed, note the changes in the Animal Drugs @ FDA section of the MRA. When the submission is finalized, the Business Informatics Team will check the MRA and, if applicable, make changes to the Animal Drugs @ FDA database. See P&P 1243.3801, 1243.3900, and P&P 1243.5741.

E. Determine If We Can Approve the NL Supplement

1. If the NL Labeling Supplement can be amended, proceed to Section VI.F.
2. If the NL Labeling Supplement can be approved without amendment, proceed to Section VII.A.
3. If the NL Labeling Supplement cannot be approved, proceed to Section VII.B.

F. If the Supplement Can Be Amended

If the observed deficiencies in the NL Labeling Supplement can be corrected in an amendment:

- Email the sponsor and provide the requested labeling changes and a due date for their amendment, see P&P 1243.3026.
- If the applicable "Approved by FDA…" statement is not already included on the labeling and the submission needs to be amended for any other reason, include in the amendment request applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, recommending the addition of the statement.
- Prepare a Memo to File or Review or attach the email as an appendix to the MRA to document correspondence with the sponsor.

See Appendix 2 for more information on what changes may require an amendment.

If we can approve the application as amended, proceed to Section VII.A; otherwise proceed to Section VII.B.

VII. FINALIZING THE SUBMISSION

A. When We Are Approving the Labeling Supplement

If the labeling is found to be acceptable for approval, the Volume 0 should be updated accordingly (P&P 1243.3810) and the PR should prepare the MRA (P&P 243.5741) and an (A)NADA Supplemental Approval Letter. Templates are located on the ONADE Template Page in SharePoint:[11]

[11] Link to ONADE Template SharePoint page
Internal information redacted.

- In the MRA, discuss any additional significant differences between the proposed and currently approved labeling, other than those specifically requested by the sponsor.

- If the applicable "Approved by FDA…" statement is not already included on the labeling, include applicable language from the approval letter template to request addition of the statement in final printed labeling, a general correspondence submission for Blue Bird labeling, or future supplemental applications.

- Discuss any additional future changes with the TL and determine if the sponsor should be contacted to make them aware of the changes or if the changes we want them to make should only be included as comments in the approval letter.

- In the MRA, state if there are changes to the labeling the sponsor should make in a future supplement. Send an email to DCU2mailbox@fda.hhs.gov, copying the TL of the Post-Approval Review Team (HFV 216) with the subject line "Prospective Changes" and list the pertinent drug information and the requested changes. HFV-216 will then send the sponsor a letter. Attach the email as an appendix in the MRA.

For more information on approval letter comments and prospective changes, see Appendix 2.

After completing the above items, proceed to Section XI.C.

B. When We Are Not Approving the Labeling Supplement

If we are not approving the supplement, prepare an incomplete letter and a review to document and describe the unacceptable labeling changes found in the current labeling and/or changes required to make the labeling acceptable.

If the applicable "Approved by FDA…" statement is not already included on the labeling, include in the incomplete letter applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, to ask that the appropriate statement be added to the labeling by September 30, 2023.

When the labeling is determined to be not approvable, the PR does NOT update the Volume 0 for that application.

C. Assembling and Routing the Final Action Package for the Submission in Appian

Once the draft final action package has been prepared, regardless of whether we are approving the supplement or not, the PR should work with the TL and DD to complete review of the package so that the package is signed-off in Appian by day 60. The Appian concurrence chain includes the PR, TL, and DD. NOTE: These types of submissions do not require a request for a Quality Control consulting review from the Quality Assurance Team.

In the final action package, choose the appropriate final action code. Below are the most common final action codes for NL submissions. Speak to your TL if you are unsure which code is correct. (See P&P 1243.5741.)

REFUSE SUP – Refuse to file supplemental application; letter sent
INC APP – Incomplete application; letter sent
SUP MIN LD – Minor supplement approved date of letter; letter sent

The PR should note in the STARS Review Summary the effect of the supplement. Finalize and load the submission and all accompanying documentation into Appian based on division policies. Refer to P&P 1243.3005 and 1243.3030 for creating clean electronic files and preparation of the final action package.

If the labeling supplement is being approved and contained final printed labeling (FPL), notify OSC by checking the appropriate box on the Appian Additional Actions screen. This will generate an automatic email to notify OSC that ONADE has received FPL to aid in OSC's maintenance of the DER database.

D. Other Administrative Tasks to Complete After the Final Action Package Closes When the Supplement is Approved

1. Medicated Feeds

   After the approval letter is issued, use the "Notice of Medicated Feed Approval" Outlook template on the ONADE Template Page in SharePoint to notify OSC of a new supplemental approval and the availability of the Type B and/or Type C medicated feed labeling in CDMS for the OSC Blue Bird labeling project.

2. Updating Volume 0

   Update the Volume 0. See P&P 1243.3810 for "Creating and Maintaining a Reference Copy of the Currently Approved Labeling for an Application (Volume 0)."

VIII. REFERENCES

Statutes

Rehabilitation Act

29 U.S.C. 794d

§508

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

514.8 – Supplements and other changes to an approved application

CVM Program Policy and Procedures Manual

1243.2050 – Refuse to File and Refuse to Review

1243.3002 – Handling and Rejecting Paper Applications and Submissions

1243.3005 – Creating Clean Electronic Files

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

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

1243.3800 – Reviewing, Preparing, and Routing Approval Packages for Certain Abbreviated and New Animal Drug Applications

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)

1243.3900 – Maintaining the Animal Drugs @ FDA Website and the Green Book

1243.5741 – Memorandum Recommending Approval (MRA) for Original and Supplemental New Animal Drug Applications

1243.5761 – Freedom of Information (FOI) Summary for Original and Supplemental New Animal Drug Applications (NADA)

1243.6040 – Review of Abbreviated and New Animal Drug Applications 60- and 180-day Non-fee (NF) Prior Approval Labeling Supplements

1243.7220 – Processing Environmental Impact Submissions for NADAs

ONADE Standard Operating Procedures and Scientific Reference Documents

1243.120.001 - ONADE Process for Accessing the Drug Experience Reporting (DER) Database to Perform Status Checks

ONADE Office Policy Page

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

IX. VERSION HISTORY

August 23, 2007 – Original version

March 12, 2008 – Revised to remove hotlinks that did not work.

June 16, 2009 – Revised to reflect that OSC maintains a DER database and that if ONADE wants future labeling changes alert OSC using the DCU2 Outlook mailbox. Copies of emails to DCU2 should be included in the approval package.

November 10, 2009 – Revised the section regarding supplements that can be approved to remove redundancy.

October 22, 2012 – Revised to include electronic review procedures and limit to NL labeling supplements.

June 22, 2016 – Updated to current format, added background information, slight reorganization of information, and redaction of internal information.

April 10, 2019 – Updated to conform with changes to the newly prepared NF Labeling Supplement P&P (1243.6040), to reflect current functionality of the Appian Additional Action Screen, and 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.

APPENDIX 1. EXAMPLES OF WHEN TO REQUEST A CONSULT (FORMAL OR INFORMAL)

Type of Question	Who to Consult
New or modified trade dress	OSC (HFV-216)
Verification of USP monograph or established name	DMT
Medicated feed formulation change and/or labeling change	DMT (HFV-141) OSC (HFV-226)
Potential promotional statements in the labeling	OSC (HFV-216)
Tradename change	OSC (HFV-216)
All label change supplements initiated by the Division of Surveillance	Contact the requesting team in the Division of Surveillance

Note: For medicated feeds ONADE will schedule a meeting with OSC to discuss proposed labeling changes. If the labeling is acceptable, OSC will not prepare a review. If there are changes that must be made or should be made to conform to the CVM guidance on Blue Bird labeling, Division of Animal Feeds will provide comments in a written review. They commit to a 30-day turnaround on a written consult.

APPENDIX 2. DESCRIPTION OF AMENDMENTS VS. APPROVAL LETTER COMMENTS VS. PROPSECTIVE CHANGES

1. Amendment (Required) Changes: Request a required amendment to the submission for any change that would pose a public health risk if not immediately implemented. If the sponsor does not make these changes, the supplement is incomplete.

   Examples: Errors in dosing instructions or mixing/feeding directions, lack of warning or caution statements, location and font used for caution statements

   If the applicable "Approved by FDA…" statement is not already included on the labeling and the submission needs to be amended for any other reason, include in the amendment request applicable language from the ONADE Policy Initial Recommendations for the Addition of Approved by FDA Statements to Labeling, Section X, recommending the addition of the statement.

2. Approval Letter Comments: Include in the approval letter only comments related to minor typographical or style-type changes that: 1) do not call into question the approval, 2) are easily fixed with minimal chance for the sponsor to introduce errors, and 3) would not pose a public health risk if they were never implemented.

   If the applicable "Approved by FDA…" statement is not already included on the labeling, include applicable language from the approval letter template to request addition of the statement in final printed labeling, a general correspondence letter for Blue Bird labeling, or future supplemental applications.

3. Prospective Changes: Major changes that are required but cannot be addressed during the timeframe of the submission review AND do not pose an immediate health risk.

   Examples: Expression of the active ingredient, listing of animal classes