OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REVIEW OF ABBREVIATED AND NEW ANIMAL DRUG APPLICATION 60- AND 180-DAY NON-FEE PRIOR APPROVAL LABELING SUPPLEMENTS

I. PURPOSE

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

- Determine if a new animal drug application (NADA) Non-Fee (NF) Prior Approval Labeling Supplement should be subject to the standard review time (i.e., 180 days) or if it qualifies for a 60-day review
- Review a new animal drug application (NADA) 60-day NF Qualifying Labeling Supplement
- Review a NADA 180-day NF Labeling Supplement
- Review an abbreviated new animal drug application (ANADA or generic) 270-day NF Labeling Supplement
- Prepare an approval package for a NADA NF Labeling Supplement
- Process and finalize a NADA NF 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. See P&P 1243.6020 for additional information on NL labeling supplements.

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.

   One of the performance goals for the 2013 reauthorization of the Animal Drug User Fee Act (ADUFA III) defines the subset of prior approval labeling supplements as described in 21 CFR 514.8(c)(2)(i)(A) and (D) currently reviewed in 180 days, that qualifies for a shortened 60-day review time.[1] Therefore, there are two types of NADA NF supplements: those that have a review time of 180 days and other NFs that qualify for a 60-day review time. The standard review time for an NF Labeling Supplement is 180 days. For an NF Labeling Supplement to qualify for a 60-day review, it must meet the criteria as described in this document (see section V below).

III. ANADA NF LABELING SUPPLEMENTS

ANADA NF labeling supplements have a 270-day review clock and are not eligible for the shortened 60-day review time unless there is an approved B1 supplement (see Section VI.A, below for more details on the requirements for 60-day review). In addition, ANADA NF supplements (except for proprietary name change NFs), undergo a quality assurance (QA) review and are signed by the Office Director. The review of labeling changes for an ANADA NF labeling supplement follows the processes outlined in this P&P. Examples may include adding a species or indication approved for the reference listed new animal drug (RLNAD), but not included in the previous approval of the generic product because it was protected by marketing exclusivity or patent. For information on preparing, assembling, and routing the approval package for ANADA NF supplements, see P&P 1243.3800.

IV. WHO IS RESPONSIBLE FOR CREATING THE APPROVAL PACKAGE?

The primary reviewer (PR) is responsible for reviewing the NF 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 NF Labeling Supplement approval package and that applicable policies and procedures were followed and office templates utilized. The approval package may include: Memorandum Recommending Approval (MRA), supplemental approval letter, reviews prepared for the approval, Green Book and Animal Drugs (GBAAD) Form, and FEDERAL REGISTER (FR) update, see P&P 1243.3800.

V. CONFIRM THE SUBMISSION IS CORRECTLY IDENTFIED AS AN NF LABELING SUPPLEMENT

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

Examples of NF Labeling Supplements are:

[1] ADUFA III performance goals letter (page 9) https://www.fda.gov/media/85724/download

- Proprietary name change
- Minor revisions to warnings and indications not recommended by the Office of Surveillance and Compliance (OSC)
- A new piece of labeling (e.g., puppy pack, dispensing envelope)
- For medicated feeds, changing the feeding or mixing directions

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

If the submission came through eSubmitter and was coded incorrectly as an NF subclass, then the PR must void the submission. See P&P 1243.3011 for more detail (https://www.fda.gov/media/111974/download).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 by our Document Control Unit in paper and was coded incorrectly, the PR can submit a STARS Correction Request 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.

VI. DETERMINE IF AN NF LABELING SUPPLEMENT QUALIFIES FOR A 60-DAY REVIEW CLOCK

When a sponsor submits a labeling supplement in eSubmitter, they identify whether the supplement is an NL or NF and if it qualifies for a 60-day review time. When an (A)NADA 60-day NF Qualifying Labeling Supplement has been received in an ONADE division, the 60-day NF Triage Group will confirm that the supplement qualifies as an (A)NADA 60-day NF Labeling Supplement. Appendix 1 provides an overview of the processes. See also Appendix 2 for more information on the 60-day NF Triage Group and Triage Meeting. This is a recurring meeting and no consult request is necessary.

The 60-day NF Triage Group makes the final determination if submissions qualify for a 60-day review. The decision to change the assigned review period from a 60-day to 180-day review period will be made on a case-by-case basis, taking into consideration the scope of the specific changes being made.

The standard review time for an NF Labeling Supplement is 180 days. For an NF Labeling Supplement to qualify for a 60-day review, it must meet the criteria as described below.

A. Requirements for 60-dy Review

- Prior approval labeling supplements must be consistent with 21 CFR 514.8(c)(2)(i) (A) or (D).

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

- NADAs and ANADAs that have a supplement approved using the 512(b)(1) process[3] (commonly called B1 Generic) are eligible for this 60-day NF process. ANADAs are not eligible for the 60-day NF process unless there is an approved B1 supplement.

- Labeling changes only (no manufacturing changes) may be considered for submission under the 60-day NF process, and

- The labeling supplement **must** be submitted using the eSubmitter electronic submission tool and the sponsor must have requested a 60-day review clock, and

- The sponsor's submission includes a complete list of labeling changes and certify that the list is complete, and no other changes have been made to the currently approved labeling, **and**

- CVM can determine upon initial review that the changes will not decrease the safety of drug use.

B. Examples of Changes That May Qualify the NF Labeling Supplement for a 60-day Review

- Changes or deletions to existing text or addition of new text which can be adequately verified, validated, and evaluated within the 60-day timeframe and does not require review of safety or effectiveness information. (Any changes to text that have been previously negotiated and agreed upon, in writing, between the sponsor and the Office of Surveillance and Compliance (OSC) should continue to be submitted as an NL labeling supplement CBE 21 CFR 514.8(c)(3) (see P&P 1243.6020).

- Change in existing graphics or addition of new graphics.

- Change in trade dress not otherwise covered under 21 CFR 514.8(c)(3)(i) and (ii), which addresses NL labeling supplements.

- Change in proprietary name.

- Addition of a new presentation that is similar to the approved labeling (e.g., a single-dose carton).

- Minor changes to feeding and mixing directions that can be evaluated adequately within 60 days.

VII. NADA LABELING SUPPLEMENTS THAT DO NOT QUALIFY FOR 60-DAY REVIEW

If the 60-day NF Triage Group determines that the submission identified as a 60 day60-day NF by the sponsor does not qualify for a 60-day review, the Triage Group division representative responsible for the submission will notify the PR.

[3] A B1 generic supplement is a supplemental application made to an approved ANADA for which submission and evaluation of safety and/or effectiveness data was required. For example, when the sponsor of an ANADA adds an indication or species to the approval that is not approved for the RLNAD.

The PR will complete the Change Review Time workflow in Appian. This action may issue correspondence to the sponsor informing them that the labeling supplement was converted to a 180-day NF Labeling Supplement and updates the review time and due date in the Submission Tracking and Reporting System (STARS). Refer to the Appian user guide for instructions on completing the Review Time Change.[4] **Note** the PR must select "Yes" for Firm Notification to have correspondence issued.

A. Check for Completeness and Accuracy of the Submission

Conduct an initial assessment of the submission 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, identify the correct division and submit a STARS Correction Request form to the EDSR mailbox (Internal information redacted.).

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 accuracy of information provided in eSubmitter Submission Report. If there are inconsistencies in the information provided in eSubmitter, the cover letter, and/or attachments to the submission, refer to ONADE's eSubmitter Policy.[5]

5. For paper submission, verify signature and accuracy of the FDA Form 356v.

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

B. Determine If Consulting Reviews Are Needed

Consults are requested on a case-by-case basis (for examples, see Appendix 4). If you are uncertain whether a division or team should be consulted on the application and be assigned a consulting review and if it should be formal or informal, 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

[4] Link to Appian User Guide
Internal information redacted.

[5] Link to 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 asked of 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 one is prepared.

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. See P&P 1243.3810 for more information.

1. Determine if an electronic Volume 0 exists by accessing the Volume 0 libraries in SharePoint.[6] 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 (via 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.[7] NOTE: The 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 the submissions in STARS to determine the currently approved labeling.

VIII. LABELING COMPARISON

For qualifying 60-day NF Labeling Supplements, please see Appendix 3 for information on the Triage Meeting and Review timeline before proceeding with the labeling review and additional review steps. For 180-day NF Labeling Supplements, follow the procedures below.

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

[6] Internal information redacted.

[7] 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 (or with the 60-day NF Triage Group, if applicable).

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 NF 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.[8]

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),[9] 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 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 Appendix 3, item 8 for more detail on requesting an amendment for a 60-day NF Labeling Supplement.

For NF Labeling Supplements to an ANADA, the PR compares the proposed new generic labeling to the currently approved RLNAD labeling, as well as to the

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

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

currently approved generic labeling. Each of these is referenced in their respective Volume 0 or in the (A)NADA administrative file.

Steps for comparison of the labeling:

- Review the eSubmitter Submission Report and cover letter, if applicable, 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 (and the RLNAD for ANADAs). 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 Outlook Template called Request CFR Batch Changes. The template is on the ONADE Template Page in SharePoint.[10] 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. See ONADE Standard Operating Procedure 1243.120.001 entitled ONADE Process For Accessing The Drug Experience Reporting (DER) Database To Perform Status Checks for instructions on how to access the DER database. Use the DER database to determine whether any outstanding labeling change requests identified in the DER database are incorporated in the labeling for the pending submission. If necessary, contact OSC (Post-Approval Review Team, HFV-216) to get more information.

[10] Internal information redacted.

D. Comparing Supplemental Application Information to Animal Drugs @ FDA

Compare the information in the submission to the information in Animal Drugs @ FDA. If information in the submission related to the Animal Drugs @ FDA has changed, note the changes in the Animal Drugs @ FDA section of the MRA. Also, fill out a GBAAD form and include it in the final approval package to request changes to Animal Drugs @ FDA. When the submission is finalized, the Business Informatics Team will check the GBAAD and, if applicable, make changes to the Animal Drugs @ FDA database. See P&Ps 1243.5741, P&P 1243.3801, P&P 1243.3900.

NF supplements with a 60-day review time do not require the GBAAD form, as they generally do not result in changes to Animal Drugs @ FDA. Rather, for these supplements, it should be noted in the Memorandum Recommending Approval (MRA) whether or not there are changes needed to Animal Drugs @ FDA. When the submission is finalized, the Business Informatics Team will check the MRA and if applicable, make changes to the Animal Drugs @ FDA database.

E. Determine the Outcome of the NF Supplement

1. If the NF Labeling Supplement can be amended, proceed to Section VIII.F.
2. If the NF Labeling Supplement can be approved without an amendment, proceed to Section IX.A.
3. If the NF Labeling Supplement cannot be approved, proceed to Section IX.B.

F. If the Supplement Can Be Amended

If the observed deficiencies in the NF 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 to document correspondence with the sponsor. Include the email correspondence with the sponsor in the Memo to File or as an appendix to the review document.

See Appendix 5 for more information on what changes require an amendment.

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

IX. FINALIZING THE SUBMISSION

A. When We Are Approving the Labeling Supplement

If the labeling is found to be acceptable and we are approving the supplement, the Volume 0 should be updated accordingly (P&P 1243.3810) and the PR should prepare the MRA (P&P 1243.5741) and an (A)NADA Supplemental Approval Letter using the office templates. Templates are located on the ONADE Template Page in SharePoint.[11]

- 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 labeling changes with the TL and determine if the sponsor should be contacted to make them aware of the changes we want them to make or if the changes 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 the DCU2 mailbox, 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 5.

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 labeling 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.

[11] Internal information redacted.

We may decide we cannot approve an (A)NADA 60-day NF Qualifying Labeling Supplement at any time during the review process, including during the Submission Review Team Meeting (for 60-day NF Qualifying Labeling Supplements; see Appendix 3) or following receipt of amended labeling.

For both 60- and 180-day NF submissions, 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 will work with the TL and DD to complete review of the package so that the package is signed-off in Appian by day 60 or day 180, as appropriate for the submission type. The Appian concurrence chain includes the PR, TL, and DD. NOTE: These submissions types 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 NF submission. Speak to your TL if you are unsure which code is correct. (See P&P 1243.3030.)

REFUSE SUP – Refuse to file supplemental application; letter sent

INC APP – Incomplete application; letter sent

INC APP 30 – Incomplete application; CBE-30 offered upon resubmission; letter sent

SUP SID LD – Significant supplement approved date of letter; letter sent

The PR should note in the STARS Review Summary field (i.e., the effect of the supplement) that the submission was reviewed under the 60-day NF Qualifying Labeling Supplement process, if applicable. This will make it easier for future tracking of the number of such submissions received by CVM and provide an identifiable link to the types of information provided in these submissions.

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 supplement is being approved and contained 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.

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

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. [12]

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)."

3. Final Printed Labeling

   If the submission contained 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.

X. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

Part 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

1243.3026 – Amending and Resetting the Clock on Submission Tracking and Reporting System (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

[12] Internal information redacted.

1243.3210 – Requesting a Quality Control Review from the Quality Assurance Team for Final Action Packages Signed by the Office or Center Director

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 Green Book

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

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

1243.6020 – Review of New Animal Drug Application (NADA) and Abbreviated New Animal Drug Application (ANADA) Labeling Supplements (NL Subclass)

1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

ONADE Standard Operating Procedures and Scientific References

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

ONADE Overarching Principles of Review

XI. VERSION HISTORY

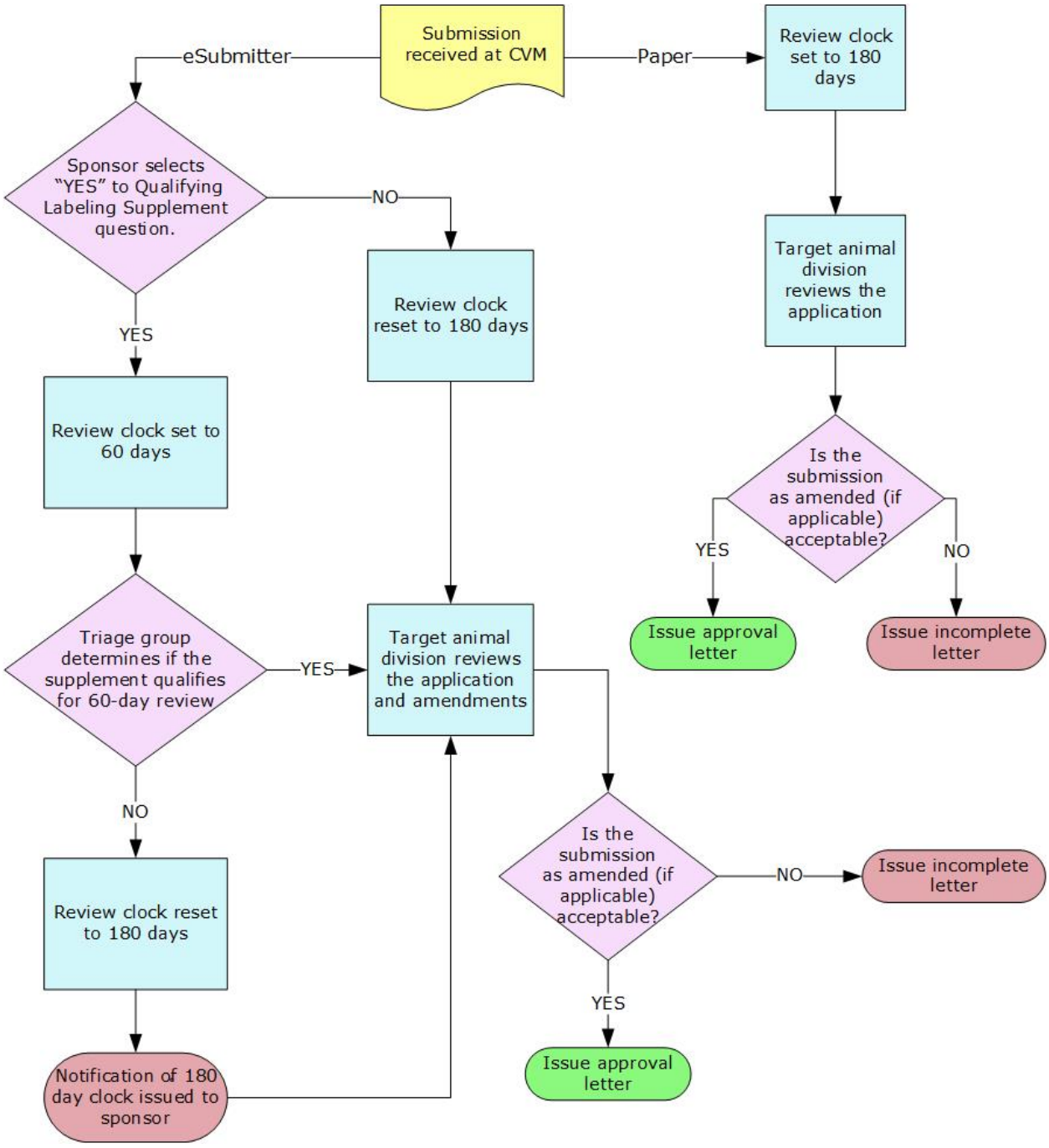
October 1, 2014 – original version of 1243.6040

December 1, 2015 – minor text revisions of 1243.6040

April 3, 2019 –Expanded the information in this current P&P to include processing information on both 60 and 180-day NF labeling supplemental applications and to add instructions on when and how to ask for addition of "Approved by FDA…" statements to labeling.

August 5, 2019 – Updated FDA.gov URL links to new directed links due to migration of new FDA.gov Website. No other updates needed. Minor formatting of some information also updated.

APPENDIX 1: (A)NADA NF PROCESS FLOW CHART[13]



[13] Only NADAs (per ADUFA III) and ANADAs with approved B1 supplements are eligible for the 60-day NF process. See Section VI.A. for more details on requirements for 60-day review.

APPENDIX 2: THE 60-DAY NF TRIAGE GROUP AND TRIAGE MEETING

A. Composition of the 60-day NF Triage Group

The 60-day NF Triage Group consists of one member (PR/consumer safety officer (CSO)) from each ONADE and OSC division that reviews labeling supplements. The 60-day NF Triage Group also consists of one TL from each ONADE and OSC division that reviews these types of supplemental applications. The TLs will only be involved if in any discussion or follow up meetings are held to resolve issues of disagreement.

Members of the 60-day NF Triage Group attend as-needed weekly meetings to confirm that any (A)NADA 60-day NF Qualifying Labeling Supplements received during the previous week qualify for the 60-day process. Representation on the 60-day NF Triage Group with a member of each division in ONADE that receives (A)NADA 60-day NF Qualifying Labeling Supplements ensures consistency in interpretation of what types of labeling changes are permitted for the 60-day NF review process.

The 60-day NF Triage Group will have a rotating Group Manager. The Group Manager role is a rotating responsibility between ONADE members of the 60-day NF Triage Group that review labeling supplements (Division of Therapeutic Drugs for Non-Food Animals/HFV-110, Division of Production Drugs/HFV-120, and Division of Therapeutic Drugs for Food Animals/HFV-130). The rotation will take place every six months, or as necessary.

The Triage Group Manager's responsibilities include:

- Schedule a recurring weekly meeting for the 60-day NF Triage Group

  NOTE: To ensure that the current Group Manager maintains control of the meeting invitation, each new Group Manager will schedule the recurring meeting. When a new Group Manager steps in, it is their responsibility to send a new meeting invitation to the group occurring at the same day and time. The previous Group Manager will then cancel their invitation/recurrence. This will ensure that the meeting time and weekday remain consistent.

- Search STARS for any new (A)NADA 60-day NF Qualifying Labeling Supplements that have been submitted within the previous seven calendar days; this should occur two days prior to each scheduled weekly meeting.

- If the review of STARS indicates a new (A)NADA 60-day NF Qualifying Labeling Supplement has been received, the Group Manager should notify the 60-day NF Triage Group representatives that the weekly triage meeting will be held; if no new submissions were received, the Group Manager will cancel the weekly meeting.

B. 60-day NF Triage Meeting

The 60-day NF Triage Group has a weekly meeting to review (A)NADA 60-day NF Qualifying Labeling Supplements submitted in the previous week. The Group Manager notifies the group as to whether there are supplemental applications to discuss or if the meeting will be cancelled. If the group is notified that an (A)NADA 60-day NF

Qualifying Labeling Supplement has been received, they should plan to discuss the submission during the next scheduled meeting. In-person meetings and/or other electronic methods (i.e., teleconference, WebEx, by email, etc.) for conducting this discussion can be considered for the formal triage meeting.

The 60-day NF Triage Group will assess the changes discussed within the cover letter or eSubmitter Submission Report. The group evaluates the proposed labeling changes identified in the submission to determine if the submission qualifies for a 60-day review.

Examples of instances when the 60-day NF Triage Group may recommend changing from a 60-day to 180-day review period:

1. Submitted labeling appears to include significant changes to the labeling, including the addition or deletion of sections, major changes to the text or font size, and/or with extensive changes to the mixing directions of Type A medicated article labeling, such that CVM has determined that the changes will decrease the safety of the drug use.

2. Submitted labeling change is to a Type A medicated article label and it impacts Type B and/or Type C Blue Bird labels that are not included in the submission or have not been reviewed previously by CVM.

3. Submission of promotional or advertising information. Exceptions may include promotional statements or rebate coupons.

A determination of the impact of the proposed changes on safety will be made on an individual submission basis during the Triage Meeting.

Once the 60-day NF Triage Group determines the acceptability of the supplement as an (A)NADA 60-day NF Qualifying Labeling Supplement, the ONADE division representative on the 60-day NF Triage Group for the division assigned that submission should immediately (i.e., at the conclusion of the meeting) notify the PR for the NF Labeling Supplement of the decision.

1. If the submission is acceptable for a 60-day review period, the PR should follow process the submission as described in Section VII above and follow the timeline for the 60-day review described in Appendix 3.

2. If the submission review period needs to be changed to 180 days, the PR should complete the Change Review Time workflow in Appian (refer to Section VI) and then proceed with the labeling review.

3. In instances where there is disagreement on whether the NF Labeling Supplement qualifies for the 60-day review process, which cannot be resolved during the Triage Meeting, a follow-up meeting should be held as soon as possible. This meeting should include the designated team leaders from each division on the 60-day NF Triage Group, who will aid in prompt resolution of the issue. If the dispute cannot be resolved quickly, the division director from each division should be promptly involved in the discussion.

APPENDIX 3: (A)NADA 60-DAY NF QUALIFYING LABELING SUPPLEMENT TIMELINE AND PROCEDURES

If the 60-day NF Triage Group determines that the submission qualifies as an (A)NADA 60-day NF Labeling Supplement, then the (A)NADA 60-day NF Qualifying Labeling Supplement timeline will be followed.

1. By day 10, the PR should schedule a meeting to be held by day 28 to discuss the review (Submission Review Team Meeting). Attendees of this meeting should include the PR, consulting reviewers from the Division of Surveillance (DS) and/or Division of Animal Feeds (DAF), the TL from each vested team/division, and any other consulting reviewers (CR), as necessary.

2. In preparation for the Submission Review Team Meeting, all meeting attendees should review the submission following procedures in Section V, above and prepare comments accordingly.

3. At the Submission Review Team Meeting, meeting attendees will discuss their review of the submission. The scope of the review should be limited to the changes identified in the letter. That is, the (A)NADA 60-day NF Qualifying Labeling Supplement is not the forum in which to update outdated labeling or modify other wording or graphics that has remained unchanged. The meeting format itself may vary, depending on the complexity of the submission. If the relevant parties of the group believe they can come to a decision without holding a meeting, the discussion may be conducted using other suitable methodology, such as an email exchange, in which case, the PR may cancel the official meeting. Alternatively, if changes are more complex, a reviewer's comments are extensive, or if discussion is needed among the group of reviewers, the meeting attendees may use the scheduled meeting.

4. The PR leads the formal Submission Review Team Meeting and takes note of all substantive comments made. It is recommended that the proposed labeling be shared electronically during the meeting, so that all attendees can see and comment on each piece of the labeling at the same time. The PR should add the appropriate changes and/or comments directly to the labeling.

    - If there are numerous changes to the proposed labeling, it may be appropriate to prepare a mockup of the labeling component(s) with comment bubbles (and use of other Adobe PDF editing tools, as needed) to capture the changes requested. If it is necessary to edit mock labeling, it can be utilized to request an amendment from the sponsor or to provide comment(s) to the sponsor in an incomplete letter. The PR should draft a Memo to File or Review to document correspondence with the sponsor to be included in the final action package. The labeling mockup should be included as an appendix to a Memo to File or review document.

    - Alternatively, the PR may capture comments as text for direct inclusion in the MRA.

5. Do not document interim discussions, deliberative debates, or individual reviewer positions. The MRA should only capture the agreed upon decisions and any

language to be sent to the sponsor in an amendment request, if necessary. A copy of any associated materials (e.g., mockup labeling with comment bubbles) may also be included in the MRA.

6. In most cases, the final action of the submission (i.e., approvable as is, requires an amendment, unacceptable/incomplete) will be determined during the Submission Review Team Meeting. In instances where there is disagreement that cannot be resolved during the Submission Review Team Meeting, relevant persons from the review group should have a follow-up discussion by day 30. During this time, reviewers may seek additional involvement from their respective DD or other parties, as needed. In instances where no agreement between ONADE and OSC is reached and it is decided we will approve the supplement despite there being no agreement, the PR should note the disagreement in the MRA, including the reason for the disagreement. The basis for granting approval despite lack of consensus is documented in Item II.6 of the ONADE Overarching Principles of Review on the ONADE Policy Page in SharePoint.[14]

7. The OSC or other consulting reviewer may email the ONADE PR to acknowledge their agreement (with the proposed labeling, comments to be sent to the sponsor, etc.) prior to returning the consult. However, the consulting reviewers should return their official consult to the PR in Appian by day 33. The PR will document the consulting reviewer's comments in the MRA during the Submission Review Team Meeting, thus consulting reviews are typically returned in Appian without a formal review. In the "comments section" of Appian, each consulting reviewer should indicate his/her agreement, or should include any comments regarding unresolvable disagreements in the MRA, as noted above in #6. Minor additional comments for future reference may also be included in Appian.

8. If the submission requires an amendment, the PR prepares an email to the sponsor outlining the changes required and/or recommended, as discussed during the Submission Review Team Meeting. Send amendment requests to the sponsor by day 31 and request the sponsor submit the amended labeling within 7 days (or 5 business days). If the sponsor informs CVM that they are unable to amend the labeling within 7 business days but would still like to amend the labeling the submission, inform the sponsor that is possible, but the supplement will be converted to a 180-day NF Labeling Supplement. If the sponsor is okay with the recoding of the supplement rather than our incompleting the submission, convert the supplement to a 180-day NF Labeling Supplement. Inform the sponsor that if there are additional, minor changes (e.g., updating address or copyright information) they wish to make, these changes should be discussed with the PR before submitting the amendment. Attach any email correspondence with the sponsor as an appendix to a Memo to File or Review to document the requested labeling changes. Once the sponsor submits the amended labeling, the PR ensures only the requested changes were made. If the PR finds no additional changes in the labeling, no additional review by the consulting reviewers or meeting of the Submission Review Team Group is warranted. If the sponsor made additional, undiscussed or unrequested changes, the PR and CRs should consider the extent

[14] Internal information redacted.

of the changes and determine their acceptability for completing the submission in 60 days. If the changes are not acceptable for completing the review in 60 days, the PR and CRs should discuss if the submission should be converted to a 180-day NF Labeling Supplement or be incompleted.

For details on performing the labeling comparison and finalizing the submission, see Sections VIII and IX above, respectively.

APPENDIX 4: EXAMPLE 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)

For new products, the DMT contact is the CMC reviewer for the submission. For older products, the PR can send an email to the DMT mailbox requesting additional information.[15] If the labeling supplement requires revision and a formal consulting request is required, the WG will inform the PR which team to consult at that time.

[15] Internal information redacted.