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 (NF SUBCLASS)

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 an NADA 60-day NF Qualifying Labeling Supplement
- Review an 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 an (A)NADA NF Labeling Supplement
- Process and finalize an (A)NADA NF Labeling Supplement

II. BACKGROUND AND SCOPE

A. 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), consist of revised information pertaining to effects, dosages, adverse reactions, and contraindications, the addition of an intended use, and any other labeling changes except those described in 21 CFR 514.8(c)(2). NF supplements require approval prior to distribution of the drug made using the change.

B. NF Supplement Review Times

1. NADA NF Labeling Supplements

   One of the performance goals for the 2013 reauthorization of the Animal Drug User Fee Act (ADUFA III) defines a 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).

2. 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 512(b)(1) supplement[2] (see section V.A, below for more details on the requirements for 60-day review). ANADA NF supplements which provide for the addition of a species, class, subclass, or indication (usually as a result of expiration of patent or marketing exclusivity provisions) or which provide for a change in withdrawal period(s) and/or residue warning(s), undergo a quality assurance (QA) review and are signed by the Office Director. The review of an ANADA NF labeling supplement that is signed by the Office Director follows the processes outlined in this P&P. For information on preparing, assembling, and routing the approval package for ANADA NF supplements, see P&P 1243.3800.

III. 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

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

[2] As defined under Section 512(b)(1) of the Federal Food, Drug, and Cosmetic Act, a generic sponsor may provide safety and effectiveness data to support addition of a new indication or species (not approved for the reference listed new animal drug) to an approved ANADA.

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.

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

As the PR, you will confirm that the sponsor has correctly submitted the labeling supplement as an NF Labeling Supplement. Examples of NADA and ANADA NF labeling supplements are in Appendix 4. Please note that these examples are not a comprehensive list of all possible NF labeling supplement changes. For example, an NF labeling supplement may have labeling changes that fall under both the NF and the NL labeling supplement categories. Discuss with your TL if there are questions about whether the submission should be an NF or NL Labeling Supplement. If the submission was created using eSubmitter and was coded incorrectly as an NF subclass code, then you must void the submission. See P&P 1243.3011 for more details. Then, notify the sponsor of the incorrect subclass code and ask them to resubmit their submission with the correct subclass code. If the submission was received by our Document Control Unit (DCU) in paper and was coded incorrectly, you can submit a Submission Tracking and Reporting System (STARS) Correction Request Form to ask that the submission be recoded.[3] See P&P 1243.3002 for handling and rejecting paper applications and submissions.

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

When a sponsor creates a labeling supplement using eSubmitter, they identify whether the supplement is an NL or NF and if it qualifies for a 60-day review time. Appendix 1 provides an overview of the processes.

The decision to change the assigned review period from a 60-day to 180-day review period should 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. Depending on the extent of labeling changes, a submission coded as a 60-day NF by the sponsor may not qualify for, or may require more than, 60 days for review. See section VI for information on converting a 60-day NF to a 180-day NF, and Appendix 4 for examples of NF labeling supplements.

[3] Link to STARS Correction Form
Internal information redacted

A. Requirements for 60-day Review

- Prior approval labeling supplements must be consistent with 21 CFR 514.8(c)(2)(i) (A) or (D).
- NADAs and ANADAs that have a supplement approved using the 512(b)(1) process 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 should include a complete list of labeling changes and the sponsor should 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.

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

If it is determined that the submission identified as a 60-day NF by the sponsor does not qualify for a 60-day review, you will prepare a letter to inform the sponsor of the review time change using the office's Review Time Change letter template and 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 STARS. Refer to the Appian user guide for instructions on completing the Review Time Change.[4] **Note** you 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

[4] Link to Appian User Guide
Internal information redacted

STARS Correction Request form to the EDSR mailbox
Internal information redacted

2. Verify that the eSubmitter Submission Report includes a claim of 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 the eSubmitter Submission Report, 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 request 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 3). If you are uncertain whether a division or team should be consulted on the application 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 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 for the CR 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

[5] Link to eSubmitter Policy
Internal information redacted

[6] Internal information redacted

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 DCU using the Document Scanning Request Form.[7] NOTE: The Records and Information Management 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.

VII. LABELING COMPARISON

For qualifying 60-day NF Labeling Supplements, please see Appendix 2 for information on the review timeline before proceeding with the labeling review and additional review steps. For 180-day and 270-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

As the PR, you compare 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 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, you should discuss these with the TL or DD.

We are 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, refer to the ONADE Policy 'Initial Recommendations for the Addition of

[7] Document Scanning Request Form
Internal information redacted

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] you 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 reference listed new animal drug (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, you should request these changes be made by the sponsor and instruct the sponsor to submit revised labeling in an amendment. See Appendix 2, 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 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 Internal information redacted under Title 21 CFR Section 520-558) to the proposed labeling. If

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

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

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 the Office of Surveillance and Compliance (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.

D. Comparing Supplemental Application Information to Animal Drugs @ FDA (ADAFDA)

Compare the information in the submission to the information in Animal Drugs @ FDA. If the information in the submission related to ADAFDA has changed, note the changes in the ADAFDA section of the MRA. Also, fill out a GBAAD form and include it in the final approval package to request changes to ADAFDA. When the submission is finalized, the Business Informatics (BI) 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 typically 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 MRA whether there are changes needed to Animal Drugs @ FDA. When the submission is finalized, the BI Team will check the MRA and if applicable, make changes to the ADAFDA database. If the NF supplement includes OSC-initiated labeling changes, a GBAAD form should be prepared as described in P&P 1243.3801.

[10] Link to ONADE Template Page in SharePoint
Internal information redacted

E. Determine the Outcome of the NF Supplement

1. If the NF Labeling Supplement can be amended, proceed to section VII.F.
2. If the NF Labeling Supplement can be approved without an amendment, proceed to section VIII.A.
3. If the NF Labeling Supplement cannot be approved, proceed to section VIII.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 IX, recommending the addition of the statement.
- You can include correspondence with the sponsor as an attachment to the MRA or prepare a Memo to File or Review to document correspondence with the sponsor, if necessary. If you prepare a Memo to File or Review, include the email correspondence with the sponsor as an appendix to your review document.

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

VIII. 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 you should prepare the MRA (P&P 1243.5741) and a supplemental approval letter using the office templates. Templates are located on the ONADE Template Page in SharePoint.

- 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 the 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 prospective changes to the labeling that the sponsor should make in a future supplement. Send an email to the Internal information redacted , 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.

After completing the above items, proceed to section VIII.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 VII.A, to ask that the appropriate statement be added to the labeling by September 30, 2023.

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 2) 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, you will work with the TL and DD to complete the review of the package so that the package is signed-off in Appian by day 60, day 180, or day 270, as appropriate for the submission type.

For NADAs the Appian concurrence chain includes you (the PR), TL, and DD. NOTE: These submissions types do not require a request for a Quality Control consulting review from the Quality Assurance (QA) Team.

For ANADA NF supplements which provide for the addition of a species, class, subclass, or indication (usually as a result of expiration of patent or marketing exclusivity provisions), or which provide for a change in withdrawal period(s) and/or residue warning(s), a request for a Quality Control consulting review from the QA Team is required. Therefore, the Appian concurrence chain for these supplements include you (the PR), TL, DD, Division of Human Food Safety DD (for NF's intended for use in food animals), QA TL and OD.

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 SIG LD – Significant supplement approved date of letter; letter sent

SUP MIN LD – Minor supplement approved date of letter; letter sent (use for all ANADA NF non-B1 supplements)

You 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.

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

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

IX. REFERENCES

Code of Federal Regulations (Title 21)

Part 514 – New Animal Drug Applications

Part 514.8 – Supplements and other changes to an approved application

Guidance for Industry (GFI)

GFI #191, Changed to Approved NADAs – New NADAs vs. Category II Supplemental NADAs

GFI #240, Proprietary Names for New Animal Drugs

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

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 – Assessing Submission Quality and Amending and Resetting the Clock on 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

1243.3800 – 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 – Updating the Animal Drugs @ FDA Website and Green Book

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

1243.6020 – Review of Abbreviated and New Animal Drug Application 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

X. 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.

April 2, 2020 – Updated to fix a typo in section IX. C. Assembling and Routing the Final Action Package for the Submission in Appian. In the list of the most common final action codes, "SUP SID LD" was incorrect and was changed to "SUP SIG LD".

April 28, 2020 – Updated section VII to make it clear the reviewer is to use the ONADE Review Time Change letter template to inform the sponsor of the change in review time.

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

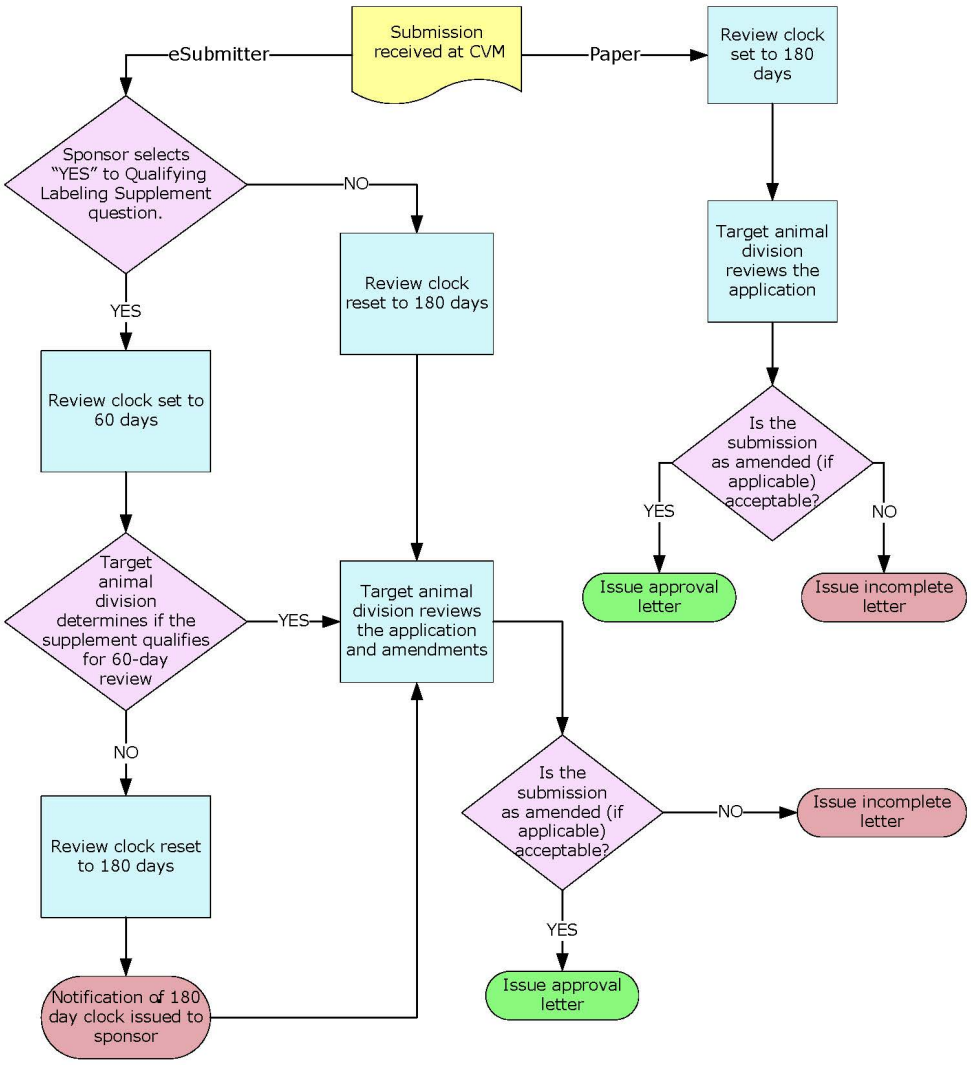
August 25, 2020 – Updated to replace the link to the ONADE template page and the link to the Document Scanning Request form that now have new locations.

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

October 28, 2020 – Revised to remove references to 60-Day NF Triage Group and other conforming changes.

July 9, 2021 – As a result of an audit of NF and NL supplements, it was determined more clarity with regard to what is an NF or NL supplement was needed in the associated P&Ps on the subject (i.e., 1243.6020 and 6040). This document was therefore revised to include an appendix with NL and NF labeling supplement examples. Updated to fix a couple broken links and some punctuation errors.

APPENDIX 1: (A)NADA NF PROCESS FLOW CHART[11]



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

APPENDIX 2: (A)NADA 60-DAY NF QUALIFYING LABELING SUPPLEMENT TIMELINE AND PROCEDURES

If the target animal division 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, you 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 VII, 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, you 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. You, as the PR, lead 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. You 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.[12]

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 of the changes and determine their acceptability for completing the submission in

[12] Internal information redacted

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 VII and VIII above, respectively.

APPENDIX 3: EXAMPLE OF WHEN TO REQUEST A CONSULT (FORMAL OR INFORMAL)

Type of Question	**Who to Consult**
New or significant changes to approved trade dress	OSC (HFV-216)
Verification of USP monograph or established name, changes to the storage conditions, in-use statements, immediate containers, or product sizes	DMT
Medicated feed formulation change and/or labeling change	DMT (HFV-141) OSC (HFV-226)
All ANADA NF signed by OD	ENV
Changes to residue warnings or withdrawal statements	HFS

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.[13] 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.

[13] Internal information redacted

APPENDIX 4: EXAMPLES OF NF AND NL LABELING SUPPLEMENTS

Table 1: NF Labeling Supplement Examples (60-Day and 180-Day Pioneer NFs and 60-Day and 270-Day Generic NFs)

NF Examples (NADA)	NF Examples (ANADA)
New labeling component (e.g., new carton or a new puppy pack presentation) that may require an OSC labeling consultation	Addition of a species, class, subclass, or indication (usually as a result of expiration of patent or marketing exclusivity provisions)
Font size revisions that are potential safety issues (e.g., drug product strength size changed from 12 pt font to 6 pt font)	Change in withdrawal period(s) and/or residue warning(s)
Drug product return to market	Change in proprietary name
Change in mixing and/or feeding directions for a medicated feed	Minor changes to feeding and mixing directions for a medicated feed
Creation of combination blue bird labeling	Changes in trade dress (including addition of a labeling presentation)
Changes that reflect a transfer of ownership and/or sponsor information (that may require right of reference information)	Correction of errors in species, class, subclass, or indication (due to RLNAD error)
Change in the active drug ingredient concentration (e.g., medicated feeds)	
Added adverse event and/or safety information (sponsor initiated)	

Table 2: NL Labeling Supplement Examples (NADA)

NL Examples (NADA)
Correction of spelling errors
Revised drug product name (e.g., due to USP monograph or per GFI #240[14])
Changed artwork codes or artwork revisions
Minor color/graphic changes (e.g., changed border or text color, logo, font size, animal picture, worm or parasite icons)
Minor formatting changes (e.g., relocation of text or changing presentation of text from a horizontal box to a vertical box)
Changed (or added) warning statements requested by OSC
Updated website for reporting adverse events
Updated sponsor name, address, trademark or copyright statements, drug label codes, or country of origin
Updated storage information statements
Revisions to align with CVM's current thinking on labeling components
Revised target animal classes to fit current nomenclature (Appendix III, GFI #191[15])
Updated revision date
Updated patent information
Revised target bacteria name
New labeling component (e.g., shipping label)
Added the "Approved by FDA" statement
Deletion of false, misleading, or unsupported intended uses or claims for effectiveness (typically an OSC recommendation)

[14] Guidance For Industry #240, Proprietary Names for New Animal Drugs https://www.fda.gov/media/111947/download

[15] Guidance for Industry #191, Changes to Approved NADAs- New NADAs vs. Category II Supplemental NADAs https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-191-changes-approved-nadas-new-nadas-vs-category-ii-supplemental-nadas