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

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I. PURPOSE

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

- determine whether 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 NADA 180-day labeling supplements and 60-day NF qualifying labeling supplements;
- review abbreviated NADA (ANADA) 270-day NF labeling supplements; and
- prepare, process, and finalize the approval package for an (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), these consist of changes to style or design and/or that increase safety and that can be implemented immediately, prior to receipt of written notice of approval (see P&P 1243.6020 for information on NL supplements); and
2. prior-approval labeling supplements (CVM subclass code NF; for non-fee labeling): as defined in 21 CFR 514.8(c)(2), these 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.
A. NADA NF Labeling Supplement Review Times

The standard review time for an NF labeling supplement is 180 days. One of the performance goals for the 2013 Animal Drug User Fee Act (ADUFA III) reauthorization 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. As such, there are two types of NADA NF supplements: 1) NFs with a 180-day review, and 2) NFs that qualify for a 60-day review. For an NF labeling supplement to qualify for 60-day review, it must meet the criteria in Section V.

B. ANADA NF Labeling Supplements Review Times

ANADA NF labeling supplements have a 270-day review clock and are not eligible for a shortened 60-day review unless there is an approved 512(b)(1) supplement (see Section V.A for details on the 60-day review requirements). ANADA NF supplements that provide for the addition of a species, class, subclass, or indication (e.g., as a result of expiration of patent or marketing exclusivity provisions) or that 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 (OD). The review of an ANADA NF labeling supplement signed by the OD follows the processes outlined in this P&P. For information on preparing and routing an ANADA NF supplement approval package, see P&P 1243.3800.

III. RESPONSIBILITY 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).

IV. CORRECT IDENTIFICATION AS AN NF LABELING SUPPLEMENT

The PR confirms that the sponsor has correctly submitted the labeling supplement as an NF labeling supplement. See Appendix 4 for examples of NADA and ANADA NF labeling supplements. This is not a comprehensive list of all possible NF labeling supplement changes; e.g., an NF labeling supplement may have changes that fall into both NF and NL labeling supplement categories. If there are questions about whether the submission is an NF or NL labeling supplement, consult with your TL.

If the submission was submitted electronically and incorrectly coded as an NF, void the submission per P&P 1243.3011 and contact the sponsor to ask them to resubmit it with the correct subclass code. If ONADE accepted a submission in paper and it was incorrectly coded, submit a Submission Tracking and Reporting System (STARS) Correction Request Form to ask that the submission be recoded (per P&P 1243.3002).

1 ADUFA III performance goals letter (page 9) https://www.fda.gov/media/85724/download
2 Per Federal Food, Drug, and Cosmetic Act, Section 512(b)(1), 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.
V. DETERMINATION WHETHER AN NF LABELING SUPPLEMENT QUALIFIES FOR A 60-DAY REVIEW CLOCK

The standard review time for an NF labeling supplement is 180 days; to qualify for 60-day review, it must meet the criteria in Section A below.

The sponsor creates a labeling supplement using eSubmitter, identifies it as an NL or NF, and selects whether it qualifies for 60-day review (see Appendix 4 for examples of NF labeling supplements). Depending on the extent of labeling changes, a submission coded by the sponsor as a 60-day NF may not qualify for, or may require more than, 60 days for review and may be recoded by ONADE as a 180-day NF labeling supplement (see Appendix 1 for a process overview). ONADE’s decision to change the assigned review time from 60 days to 180 days is made on a case-by-case basis, taking into consideration the scope of the specific changes being made. See Section VI for information on converting a 60-day NF to a 180-day NF.

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.
- Only labeling changes (no manufacturing changes) may be considered for submission under the 60-day NF process.
- The labeling supplement must be submitted using the eSubmitter electronic submission tool and the sponsor must have requested a 60-day review clock.
- 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.
- 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 the submission identified by the sponsor as a 60-day NF does not qualify for 60-day review, then prepare a letter to inform the sponsor of the review time change using ONADE’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 submission 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. 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 (items 1-5 below) and determine whether it is sufficiently complete for review. If any of the items are missing or incorrect, discuss with your TL whether you should request an amendment (per P&P 1243.3026) or refuse to file (RTF) the supplement (per P&P 1243.2050). If
the submission is deficient on its face, then issue a RTF letter within 30 days of submission receipt (see P&P 1243.2050).

The initial assessment includes the following steps.

1. Verify that the submission is assigned to the correct review division. If the submission needs to be reassigned, identify the correct division and complete the STARS Correction Request form.

2. Verify that the eSubmitter submission report includes a claim of categorical exclusion under 21 CFR 25.33 or an environmental assessment (per 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 the ONADE’s “eSubmitter Policy” on the ONADE Policy SharePoint.

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

B. Determine Whether Consulting Reviews are Needed

Consults are requested on a case-by-case basis (see Appendix 3 for examples). If you are uncertain whether a division or team should be consulted on the application and if it should be formal or informal, then discuss with the TL of the consulting team. Request consults within five (5) days of receipt (per P&P 1243.3200; see the consulting review points of contact document on the ONADE Template SharePoint). 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. Your questions for the CR and the CR’s responses should be documented as a memo to file (MTF) or be included in the primary review, if applicable.

Note that in the rare instance where the product is approved in both food and non-food animal species under two (A)NADAs [i.e., the labeling includes more than one (A)NADA number], the Division of Companion Animal Drugs and Division of Food Animal Drugs coordinate (via a consult or informally) to update Volume 0s, CFR citations, and the Internal information redacted listings for both (A)NADAs.

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).

1. Determine whether an electronic Volume 0 exists by accessing the Volume 0 SharePoint libraries.³ If the application is listed, access the applicable file number to obtain the submission number for the currently approved labeling. Once the submission(s) containing the currently approved labeling has been

³ Link to Volume 0 SharePoint Internal information redacted
identified, obtain copies of the labeling from STARS [Corporate Database Portal (CDP Web)] or the Corporate Document Management System (CDMS).

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. NOTE: The Records and Information Management Team turnaround is two (2) 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, see Appendix 2 for information on the review timeline before proceeding with the labeling review and additional 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

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 the Volume 0 or contained in the (A)NADA file. This comparison is to determine whether: 1) the sponsor made changes other than those proposed and specified in the cover letter or described in the eSubmitter Submission Report; and 2) if the proposed labeling changes are acceptable. Acceptability is based on the type and scope of the proposed change(s) and whether the labeling reflects CVM’s current thinking on the contents of labeling components (e.g., expression of the active ingredient, listing of animal classes, location and font used for caution statements). 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. Discuss any questions about the acceptability of the changes with your 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 in the NF supplement does not include the applicable labeling statement, refer to the ONADE Policy “Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs” (on the ONADE Policy SharePoint) for information on when and how to ask the sponsor to add the statement to the labeling.

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),\(^4\) compare the submitted labeling to

\(^4\) Examples include changes in feeding directions, approved species, etc.
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 compare with the currently approved labeling for the reference listed new animal drug (RLNAD).

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, request these changes be made by the sponsor and instruct them to submit revised labeling by amendment. See Appendix 2, item 8 for details on requesting an amendment for a 60-day NF labeling supplement.

For ANADA NF labeling supplements, compare 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 file. Steps for the labeling comparison include:

- review the eSubmitter Submission Report and cover letter, if applicable, for a summary of the proposed labeling changes. If discrepancies exist between the two, contact the sponsor for clarification;
- note the differences between the currently approved labeling (in the 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; and
- discuss questions about the labeling changes or differences with the TL/DD.

B. Compare Changes to the Regulations

Compare the electronic CFR (eCFR) citation (http://ecfr.gov) under Title 21 CFR Section 520-558) 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 (A)NADA history in the administrative record. Use the MRA to document any substantive discrepancies. If the eCFR is incorrect, email the CVM Policy and Regulations Team (HFV-6) to request revisions using the ‘CFR Batch Changes’ email template. 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 Pharmacovigilance and Surveillance5 (DPS) maintains the Drug Event Reporting (DER) database containing current OSC requests for labeling.

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5 Internal information redacted
changes. Find the DER database through the CDP Portal. Instructions for accessing the DER are provided in ONADE SOP 1243.130.002. Determine whether the outstanding labeling change requests identified in the DER database are incorporated in the labeling for the pending supplement. If more information is needed, email DPS at Internal information redacted.

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

Compare the submission information to that in ADAFDA. If the ADAFDA information in the submission has changed, then 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 checks the GBAAD and, if applicable, makes changes to the ADAFDA database. See P&Ps 1243.3801, 1243.3900, and 1243.5741.

NF supplements with a 60-day review typically do not require the GBAAD form, as they generally do not result in changes to ADAFDA. For these supplements, it should be noted in the MRA whether there are changes needed to ADAFDA. When the submission is finalized, the BI Team checks the MRA and if applicable, makes changes to the ADAFDA database. If the NF supplement includes OSC-initiated labeling changes, then a GBAAD form should be prepared.

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.

• Prepare a MTF or review or attach the email as an appendix to the MRA to document correspondence with the sponsor, if necessary. If you prepare a MTF 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 for approval, update the Volume 0 accordingly (per P&P 1243.3810), and prepare the MRA (per P&P 1243.5741) and supplemental approval letter.

- 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 whether there are prospective labeling changes that the sponsor should make in a future supplement. Send an email to [Internal information redacted] with the subject line “Prospective Changes”, copy the DD of OSC DPS (HFV-240), and list the pertinent drug information and requested changes. HFV-240 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, do 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, 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, 180, or 270, as appropriate for the submission type.

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

For ANADA NF supplements that provide for either the addition of a species, class, subclass, or indication (usually as a result of expiration of patent or marketing exclusivity provisions) or a change in withdrawal period(s) and/or residue warning(s), a request for a QC consulting review from the QA Team is required, so the Appian concurrency chain includes the PR, TL, DD, Division of Human Food Safety DD (for NFs intended for use in food animals), QA TL and OD.

In the final action package, choose the appropriate final action code. Speak to your TL if you are unsure which code is correct (see P&P 1243.3030). Below are the most common final action codes for NF submission.

- 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)

In the STARS Review Summary field (i.e., the effect of the supplement), note 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&Ps 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 generates 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 (per P&P 1243.3810).
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


1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

ONADE Standard Operating Procedures and Scientific References

1243.130.002– 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

Appian User Guide

Internal information redacted

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.

February 10, 2022 – Updated page 8 Section IV.C to change the SOP number from 1243.120.001 to 1243.130.002. The number of the SOP has changed from 1243.120.001 to 1243.130.002 because there is no longer a Division of Production
Drugs and the new owner of the SOP is the Division of Food Animal Drugs (HFV-130). Reference section updated too.

July 5, 2022 - Updated SharePoint links and references to OSC due reorganization.

August 12, 2022 – Updated Appendix 4 to clarify the types of ANADA labeling supplements that were included in the example list. Corrections of minor typos and formatting issues.
APPENDIX 1: (A)NADA NF PROCESS FLOW CHART

6 Only NADAs (per ADUFA III) and ANADAs with approved B1 supplements are eligible for the 60-day NF process. See Section V.A. for 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, schedule the submission review team meeting to be held by day 28 to discuss the review. Meeting attendees should include the PR, CRs from OSC DPS and/or OSC Division of Animal Food Ingredients (DAFI), the TL from each vested team, and any other CRs, as necessary.

2. In preparation for the submission review team meeting, all meeting attendees should review the submission following procedures in Section VII and prepare comments accordingly.

3. At the submission review team meeting, meeting attendees 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, then the discussion may be conducted using other suitable methodology (e.g., email exchange); in which case, you may cancel the official meeting. If the changes are more complex, a reviewer’s comments are extensive, or discussion among the reviewers is needed, the meeting attendees may use the scheduled meeting.

4. The PR leads the submission review team meeting and takes note of all substantive comments. 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. 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 drafts a MTF or review to document sponsor correspondence to be included in the final action package. The labeling mockup should be included as an appendix to a MTF or review document.

   • Alternatively, the PR may capture comments as text for 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) is 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 notes 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.7

7. The OSC or other CR 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 CRs should return their official consult to the PR in Appian by day 33. The PR will document the CR’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 CR indicates agreement or includes any comments regarding unresolvable disagreements in the MRA, as noted in Item #6. Minor additional comments for future reference may also be included in Appian.

8. If the submission requires an amendment, the PR emails 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 seven days (or five business days).

If the sponsor informs CVM that they are unable to amend the labeling within seven business days but would still like to amend the labeling the submission, then 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 recoding the supplement rather than incompleting it, 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 the MTF 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, then no additional review by the CRs or meeting of the submission review team group is warranted. If the sponsor made additional, undiscovered or unrequested changes, then the PR and CRs should consider the extent 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, then the PR and CRs should discuss if the submission should be converted to a 180-day NF labeling supplement or be incompleting.

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

7 Internal information redacted

Responsible Office: Office of New Animal Drug Evaluation
Date: August 12, 2022
### APPENDIX 3: EXAMPLE OF WHEN TO REQUEST A CONSULT (FORMAL OR INFORMAL)

<table>
<thead>
<tr>
<th>Type of Question</th>
<th>Who to Consult</th>
</tr>
</thead>
</table>
| New or significant changes to approved trade dress                               | OSC HFV-216 (for formal consults in Appian)\(^8\)  
OSC HFV-240 (for informal email consults)\(^9\)                                                  |
| Verification of USP monograph or established name, changes to the storage conditions, in-use statements, immediate containers, or product sizes | Division of Manufacturing Technologies (DMT)                                                         |
| CMC-related changes to the labeling (e.g., formulation, storage statements, manufacturer) | DMT                                                                                                 |
| Medicated feed labeling change                                                    | OSC HFV-216 (for formal consults in Appian)\(^8\)  
OSC HFV-240 (for informal email consults)\(^9\)                                                  |
| All ANADA NF signed by OD                                                         | ENV                                                                                                |
| Changes to residue warnings or withdrawal statements                             | HFS                                                                                                |
| Labeling that includes both food animal and non-food animal species               | Division of Food Animal Drugs (DFAD, HFV-130)  
or  
Division of Companion Animal Drugs (DCAD, HFV-110)                                             |

For new products, the DMT contact is the CMC reviewer for the submission. For older products, the PR sends an email to the DMT mailbox requesting additional information.\(^{10}\) If the labeling supplement requires revision and a formal consulting request is required, then the WG informs the PR which team to consult at that time.

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8 Due to the reorganization of OSC, the Division of Pharmacovigilance and Surveillance (DPS) is the correct division to handle labeling consults. However, STARS and Appian have not yet been updated with the correct HFV codes, so continue to use HFV-216 for formal consults.

9 Email consults should be directed to Internal information redacted

10 Internal information redacted
APPENDIX 4: EXAMPLES OF NF AND NL LABELING SUPPLEMENTS

Table 1: Examples of 60-and 180-Day Pioneer NFs and 270-Day Generic NFs

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

Table 2: NADA NL Labeling Supplement Examples

<table>
<thead>
<tr>
<th>NL Examples (NADA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correction of spelling errors</td>
</tr>
<tr>
<td>Revised drug product name (e.g., due to USP monograph or per GFI #240&lt;sup&gt;11&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Changed artwork codes or artwork revisions</td>
</tr>
<tr>
<td>Minor color/graphic changes (e.g., changed border or text color, logo, font size, animal picture, worm or parasite icons)</td>
</tr>
<tr>
<td>Minor formatting changes (e.g., relocation of text or changing presentation of text from a horizontal box to a vertical box)</td>
</tr>
<tr>
<td>Changed (or added) warning statements requested by OSC</td>
</tr>
<tr>
<td>Updated website for reporting adverse events</td>
</tr>
<tr>
<td>Updated sponsor name, address, trademark or copyright statements, drug label codes, or country of origin</td>
</tr>
<tr>
<td>Updated storage information statements</td>
</tr>
<tr>
<td>Revisions to align with CVM’s current thinking on labeling components</td>
</tr>
<tr>
<td>Revised target animal classes to fit current nomenclature (Appendix III, GFI #191&lt;sup&gt;12&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Updated revision date</td>
</tr>
<tr>
<td>Updated patent information</td>
</tr>
<tr>
<td>Revised target bacteria name</td>
</tr>
<tr>
<td>New labeling component (e.g., shipping label)</td>
</tr>
<tr>
<td>Added the “Approved by FDA” statement</td>
</tr>
<tr>
<td>Deletion of false, misleading, or unsupported intended uses or claims for effectiveness (typically an OSC recommendation)</td>
</tr>
</tbody>
</table>

<sup>11</sup> GFI #240 “Proprietary Names for New Animal Drugs”
<sup>12</sup> GFI #191 “Changes to Approved NADAs- New NADAs vs. Category II Supplemental NADAs”