OFFICE OF NEW ANIMAL PRODUCT EVALUATION AND OFFICE OF GENERIC ANIMAL DRUGS 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 Product Evaluation (ONAPE) and the Office of Generic Animal Drugs (OGAD) 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.[1] For an NF labeling supplement to qualify for 60-day review, it must meet the criteria in Section V.

B. ANADA NF Labeling Supplement 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 [2] (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. Branch Chiefs (BCs) 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 BC.

[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.

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 ONAPE or OGAD accepted a submission in paper and it was incorrectly coded in our Submission Tracking and Reporting System (STARS), send an email to the EDSR Mailbox to ask that the submission be recoded (per P&P 1243.3002).[3] The subject line should be STARS Correction Request. The ONAPE Business Informatics Branch manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

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 ONAPE or OGAD as a 180-day NF labeling supplement (see Appendix 1 for a process overview). ONAPE's or OGAD'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

[3] Internal information redacted.

ONAPE'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 for 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 BC 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 an 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 send an email with that information to the EDSR Mailbox requesting the submission be reassigned.[4] The subject line should be STARS Correction Request. The ONAPE Business Informatics Branch manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

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 eSubmitter Policy on the ONAPE 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 branch should be consulted on the application and if it should be formal or informal, then discuss with the consulting BC Request consults within five (5) days of receipt (per P&P 1243.3200; see the consulting review points of contact document on the ONAPE 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

[4] Internal information redacted.

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 Animal Drugs @ FDA 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. [5] 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 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 Branch 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

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

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 BC or DD.

Section 502(w)(3)[6] of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires the statement "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX" to be included on labeling (except representative (Blue Bird) labeling) of approved new animal drugs and generic new animal drugs, respectively, or else the drug will be considered misbranded. We encourage sponsors to add the statements to Blue Bird labeling, but this is voluntary on their part. Refer to the ONAPE Policy "Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs" (on the ONAPE Policy SharePoint) for additional information. If any labeling components in the NF supplement other than Blue Bird labeling (and exemptions identified in the ONAPE Policy) do not include the applicable labeling statement, the supplement must be amended with updated labeling including the statement before the supplement can be approved.

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),[7] 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 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

[6] 21 U.S.C. 352(w)(3)
[7] Examples include changes in feeding directions, approved species, etc.

(and the RLNAD for ANADAs). Record substantial differences in the MRA or review; and

- discuss questions about the labeling changes or differences with the BC/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 Staff (PRS) to request revisions using the 'CFR Batch Changes' email template. Attach the email as part of your MRA. NOTE: The Policy and Regulations Staff 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 PRS 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 Surveillance[8] (DPS) maintains the Drug Event Reporting (DER) database containing current OSC requests for labeling changes. Find the DER database through the CDP Portal. Instructions for accessing the DER are provided in ONAPE 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 there are concerns about the DER information, or if more information is needed, email DPS.[9]

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) Branch 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 Branch checks the MRA and if applicable, makes changes to the ADAFDA database.

[8] Internal information redacted.

[9] 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 all labeling components other than Blue Bird labeling (and exemptions identified in the ONAPE Policy on the Approved by FDA labeling statements), the supplement must be amended with updated labeling including the statement before the supplement can be approved.
- 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 addition, for medicated feeds only, determine whether any downstream applications or files exist (per P&P 1240.4023).

- In the MRA, discuss any additional significant differences between the proposed and currently approved labeling, other than those specifically requested by the sponsor.
- Discuss any additional future labeling changes with the BC 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 (DCGDA), and list the pertinent drug information and requested

changes. DPS will then send the sponsor a letter. Attach the email as an appendix in the MRA.

- For new animal drugs administered in or on animal feeds only, if the labeling is determined to have an impact on approved labeling in other applications or files (aka downstream labeling), identify the file number for each (A)NADA or veterinary master file (VMF) containing impacted labeling (aka downstream application or file).

- For new animal drugs administered in or on animal feeds only, if the labeling is determined to have an impact on approved labeling maintained in a veterinary master file (VMF), the applicable language from section V.B. of P&P 1240.4023 should be included in the approval letter.

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 all labeling components other than Blue Bird labeling (and exemptions identified in the ONAPE Policy on Approved by FDA labeling statements), state in the incomplete letter that the appropriate statement must be added to the labeling.

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 branch 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 BC 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 concurrence chain includes the PR, BC, and DD. NOTE: These submission types do not require a request for a Quality Control (QC) consulting review from the Quality Assurance (QA) Branch.

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 Branch is required, so the Appian

concurrence chain includes the PR, BC, DD, Division of Human Food Safety DD (for NFs intended for use in food animals), QA BC and OD.

In the final action package, choose the appropriate final action code. Speak to your BC 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, check “yes” to the question “does the submission contain acceptable labeling?” on the Appian Additional Actions screen. This action will prompt additional options for selection (select all that apply):

- Selecting “This submission contains FPL.” will generate an automatic email to notify OSC that ONAPE or OGAD has received FPL to aid in OSC’s maintenance of the DER database.

- Selecting “This submission contains approved veterinary NSAID labeling for posting on Animal Drugs at FDA.” will generate an automatic email to notify the Business Informatics Branch that approved veterinary NSAID labeling may need to be updated in ADAFDA.

- Selecting “This submission contains Blue Bird labeling.” will generate an automatic email to notify OSC that ONAPE or OGAD has approved Blue Bird labeling that will need to be updated or otherwise included in the Blue Bird label repository.

- Selecting “This submission includes labeling for a pioneer product.” will generate two additional prompts to notify the appropriate ONAPE or OGAD branch(es) that the labeling supplement approval may directly impact approved labeling in other applications.

  Selecting the first prompt, “This submission includes the approval of changes to

Type A medicated article labeling, medicated feed Blue Bird labeling, and/or VFD(s).", will generate an automatic email to notify both the Division of Food Animal Drugs and the Division of Generic Animal Drugs that ONAPE has approved medicated feed labeling components that may impact labeling maintained in one or more NADAs or ANADAs. This prompt should only be selected if the reviewer has identified the labeling change will impact a downstream (A)NADA for a drug product intended for use in or on medicated feed.

Selecting the second prompt, "This submission includes the approval of changes to the labeling of a non-medicated feed dosage form.", will generate an automatic email to notify the Division of Generic Animal Drugs that ONAPE has approved labeling components that may impact labeling maintained in one or more ANADAs.

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)

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

#240, Proprietary Names for New Animal Drugs

CVM Policies and Procedures Manual

1240.4023 – Notifying Sponsors When Approved Supplemental Labeling Changes in an Upstream New Animal Drug Application Approved for Use In or On Animal Feed Will Require Revisions to Approved Downstream Labeling Components

CVM Policies and Procedures Manual – ONAPE and OGAD 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

ONAPE and OGAD Standard Operating Procedures

1243.130.002 - Process for Accessing the Drug Experience Reporting (DER) Database to Perform Status Checks

ONAPE and OGAD Policy Page

Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs

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.

May 30, 2023 – Updated VII.C., VIII.A. Appendix 2 and 3 to reflect changes resulting from the OSC reorganization (i.e., removed any mention of HFV-216 and replaced it with HFV-240) and included the use of the organizational term of branch and team to reflect that OSC has branches and ONADE has teams. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font. The flowchart in Appendix 1 was updated to the Arial font.

September 30, 2023 - Sections VII.A and F, and VIII.A and B updated for changes associated with the law requiring the “Approved by FDA” labeling statement taking effect.

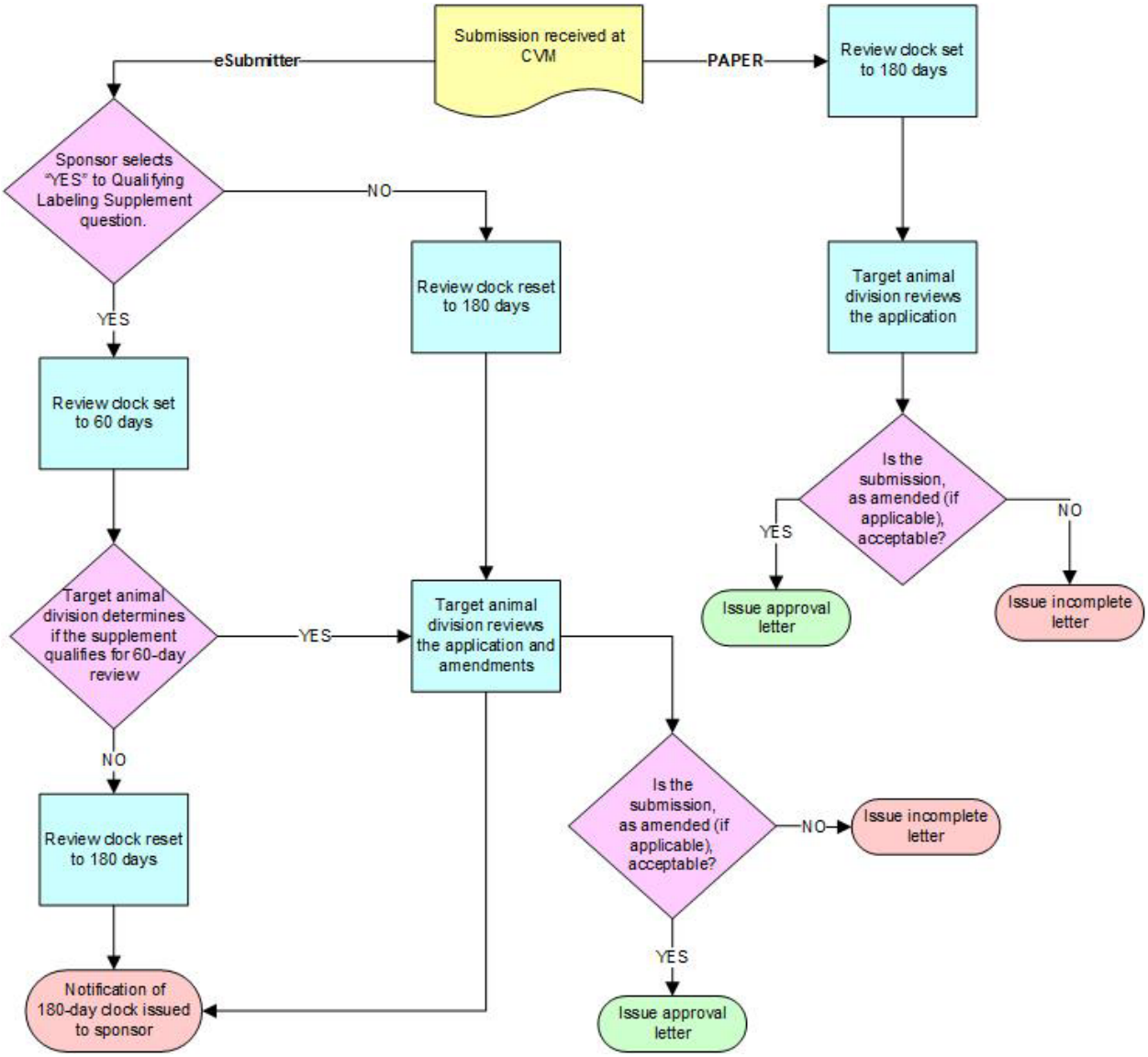
December 7, 2023 – Updated sections IV. And VI. A. to remove the STARS Change Request Form information. That form has been retired. The instructions are to now send an email request to the EDSR Mailbox to get all the appropriate files cross-referenced in STARS.

March 29, 2024 – Revised section VIII to include information relevant to the process for notifying sponsors of other applications and files (aka downstream applications and files) about the recent approved labeling changes that impact their labeling (per P&P 1240.4023). Added the new P&P to the references.

January 21, 2025 – The Office of New Animal Drug Evaluation (ONADE) has reorganized into the Office of New Animal Product Evaluation (ONAPE) and the Office of Generic Animal Drugs (OGAD). Updated all reference of ONADE to ONAPE or OGAD. Updated all HFV codes to the new abbreviation.

July 30, 2025 – Updated to add Office of Generic Animal Drugs (OGAD) to the header and footer.

APPENDIX 1. (A)NADA NF PROCESS FLOW CHART[10]



[10] 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 branch 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 BC from each vested branch and any other CRs, as necessary.

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

3. At the submission review branch 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 branch 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 Branch Meeting. In instances where there is disagreement that cannot be resolved during the Submission Review Branch 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 ONAPE or OGAD 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 ONAPE Overarching Principles of Review on the ONAPE and OGAD Policy Page in SharePoint.[11]

7. The OSC or other CR may email the ONAPE or OGAD 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 Branch 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 Branch 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 it 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 branch group is warranted. If the sponsor made additional, undiscussed, 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 incompleted.

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

[11] Internal information redacted.

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 DCGDA (for formal consults in Appian)[12] OSC DCGDA (for informal email consults)[13]
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 DCGDA2 (for formal consults in Appian) OSC DCGDA2 (for informal email consults)
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) or Division of Companion Animal Drugs (DCAD)

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.[14] If the labeling supplement requires revision and a formal consulting request is required, then the WG informs the PR which branch to consult at that time.

[12] Due to the reorganization of OSC, the Division of Pharmacovigilance and Surveillance (DPS) is the correct division to handle labeling consults.
[13] Email consults should be directed to Internal information redacted.
[14] 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

NF Examples (NADA)	NF Examples (ANADA)
New labeling component (e.g., new carton, new puppy pack presentation) that may require an OSC labeling consultation	Addition of a species, class, subclass, or indication (usually due to 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 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: NADA NL Labeling Supplement Examples

NL Examples (NADA)
Correction of spelling errors
Revised drug product name (e.g., due to USP monograph or per GFI #240[15])
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[16])
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)

[15] GFI #240 "Proprietary Names for New Animal Drugs"
[16] GFI #191 "Changes to Approved NADAs- New NADAs vs. Category II Supplemental NADAs"