OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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

I. PURPOSE

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

- determine whether an abbreviated new animal drug application (ANADA) or new animal drug application (NADA) non-fee labeling supplement (NL) is correctly coded in the Submission Tracking and Reporting System (STARS);
- review an (A)NADA NL labeling supplement;
- prepare an approval action package for an NL labeling supplement; and
- process and finalize an (A)NADA NL labeling supplement.

II. BACKGROUND AND SCOPE

There are two types of labeling supplements.

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

2. Prior approval labeling supplements (CVM subclass code NF for Non-fee Labeling), as defined in 21 CFR 514.8(c)(2), 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)(3). NF supplements require approval prior to distribution of the drug made using the change (see P&P 1243.6040).

III. WHO IS RESPONSIBLE FOR CREATING THE APPROVAL PACKAGE?

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

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

As the PR, you confirm that the sponsor has correctly submitted the labeling supplement as an NL labeling supplement. See Appendix 3 for examples of NL labeling supplements. Discuss with your TL if there are questions about whether the submission should be an NL or NF labeling supplement.

If the submission was submitted electronically and incorrectly coded as an NL, then void the submission (see P&P 1243.3011), notify the sponsor of the incorrect subclass code, and ask them to resubmit the submission with the correct subclass code. If ONADE accepted the submission in paper and it was coded incorrectly, send an email to the EDSR Mailbox to get the submission recoded (see P&P 1243.3002 for handling and rejecting paper applications and submissions).[1] The subject line should be STARS Correction Request. The ONADE Business Informatics Team manages the mailbox. When the change in STARS has been made, the requestor will get a notification email from the EDSR Mailbox.

V. PROCESSING THE NL SUBMISSION

A. Check for Completeness and Accuracy of the Submission[2]

Conduct an initial assessment of the submission (items 1-5 below) and determine whether it is sufficiently complete for review.

1. Verify that the submission is assigned to the correct review division. If you have STARS assignment privileges, reassign the submission to the correct division. If you do not have STARS assignment privileges, send an email to the EDSR Mailbox to get the submission reassigned appropriately. The subject line should be STARS Correction Request. The ONADE Business Informatics Team 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 (see P&P 1243.7220).

[1] Internal information redacted.

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

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

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

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

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

B. Determine Whether Consulting Reviews are Needed

If the submission is in response to Office of Surveillance and Compliance (OSC)-initiated labeling revisions, then send an informal consult (i.e., email) to OSC Division of Pharmacovigilance and Surveillance (DPS; HFV-240)[3] so they can confirm that all requested changes have been made.

Additional consults are requested on a case-by-case basis (see Appendix 1 for examples). If you are uncertain whether a division, branch, or team should be consulted on the application, either formally or informally, then discuss with the branch chief or TL of the consulting branch or 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 for 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 or be included in the primary review, if applicable.

Note that in the rare instance where the product is approved in both food-animal species 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 should coordinate (via a consult or informally) to update Volume 0s, CFR citations, and the Animal Drugs @ FDA listings for both (A)NADAs.

[3] Internal information redacted.

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.[4] If the application is listed, then 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 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 of the submissions in STARS to determine the currently approved labeling.

VI. LABELING COMPARISON

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.

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

Section 502(w)(3)[5] 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 ONADE Policy "Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs" (on the ONADE Policy SharePoint) for additional information. If any labeling components in the NL supplement other than Blue Bird labeling (and exemptions identified in the ONADE 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),[6] 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 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 NADA ADAA and ANADA medicated feed combinations lists the submission ID of the most recently approved Blue Bird labeling. Determine whether the 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 the sponsor to submit revised labeling in an amendment (see P&P 1243.3026 for more information on requesting amendments).

For NL labeling supplements to an ANADA, 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 administrative file. Steps for comparison of the labeling:

- Review the eSubmitter Submission Report and cover letter for a summary of the proposed labeling changes. If discrepancies exist between the two, then contact the sponsor for clarification.

[5] 21 U.S.C. 352(w)(3)
[6] Examples include changes in feeding directions, approved species, etc.

- Note the differences between the currently approved labeling (in Volume 0 or administrative record) and the proposed labeling with a side-by-side comparison. Record substantial differences in the MRA or review.

- Discuss any questions about the changes to or differences in the labeling with the TL or DD.

B. Compare Changes to the Regulations

Compare the electronic 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, then determine whether the proposed labeling or the eCFR is correct by checking the (A)NADA history in the administrative record. Document any substantive discrepancies in the MRA. If the eCFR is incorrect, email the CVM Policy and Regulations Team (HFV-6) to request revisions using the 'CFR Batch Changes' 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 OSC

OSC DPS[7] 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 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 there are concerns about the DER information, or if more information is needed, then email DPS.[8]

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

Compare the information in the submission to the information in ADAFDA. If the ADAFDA information in the submission has changed, then note the changes in the ADAFDA section of the MRA. When the submission is finalized, the Business Informatics Team will check the MRA and, if applicable, make changes to the ADAFDA database. See P&Ps 1243.3801, 1243.3900, and 1243.5741.

[7] Internal information redacted.
[8] Internal information redacted.

E. Determine Whether We Can Approve the NL Supplement

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

F. If the Supplement Can Be Amended

If the observed deficiencies in the NL Labeling Supplement can be corrected in an amendment, then take the steps below. See Appendix 2 for more information on what changes may require 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 ONADE Policy "Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs"), the supplement must be amended with updated labeling including the statement before the supplement can be approved.
- Prepare a Memo to File or review or attach the email as an appendix to the MRA to document correspondence with the sponsor.

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

VII. FINALIZING THE SUBMISSION

A. When We Are Approving the Labeling Supplement

If the labeling is found to be acceptable for approval, then update the Volume 0 (per P&P 1243.3810) and prepare the MRA (per P&P 1243.5741) and supplemental approval letter (see templates on the ONADE Templates SharePoint). In addition, for new animal drugs administered in or on animal feeds, also determine whether any existing applications or files are impacted by this approval (aka downstream applications or files).[9]

[9] See P&P 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

- 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 changes with the TL. Determine whether the sponsor should be contacted to make them aware of the changes or if the changes we want them to make should only be included as comments in the approval letter.

- In the MRA, state whether there are prospective labeling changes that the sponsor should make in a future supplement. Send an email to the DCU Mailbox[10] 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 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 VMF, the applicable language from section V.B. of P&P 1240.4023 should be included in the approval letter.

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

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

B. When We Are Not Approving the Labeling Supplement

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

If the applicable "Approved by FDA…" statement is not already included on all labeling components other than Blue Bird labeling (and exemptions identified in the ONADE Policy "Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs"), state in the incomplete letter that the appropriate statement must be added to the labeling.

[10] Internal information redacted.

When you have determined we cannot approve the labeling, 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. The Appian concurrence chain includes you (the PR), TL, and DD. NOTE: These types of submissions do not require a request for a Quality Control consulting review from the Quality Assurance Team.

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

REFUSE SUP – Refuse to file supplemental application; letter sent

INC APP – Incomplete application; letter sent

SUP MIN LD – Minor supplement approved date of letter; letter sent

In the STARS Review Summary, note the effect of the supplement. 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 labeling 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 ONADE 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 Team 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 ONADE 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 ONADE division(s) 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 ONADE 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 ONADE 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 (see P&P 1243.3810).

VIII. REFERENCES

Statutes

Rehabilitation Act

29 U.S.C. 794d

§508

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 #240 - Proprietary Names for New Animal Drugs

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

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- 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

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

1243.3801 – Completing the Green Book and Animal Drugs @ 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

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

1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

ONADE Standard Operating Procedures and Scientific Reference Documents

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

ONADE Office Policy Page

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

IX. VERSION HISTORY

August 23, 2007 – Original version

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

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

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

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

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

April 10, 2019 – Updated to conform with changes to the newly prepared NF Labeling Supplement P&P (1243.6040), to reflect current functionality of the Appian Additional Action Screen, and to add instructions on when and how to ask for addition of "Approved by FDA…" statements to labeling.

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

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

September 17, 2020 – Revised to include instructions related to applications containing OSC-initiated labeling 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. Section V. B. was updated to note that if the labeling changes were requested by OSC, there should be an informal consult sent to OSC's HFV-216 to confirm all changes requested have been made. Updated to fix some punctuation errors.

February 10, 2022 – Revised reference to the DER SOP. 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).

July 5, 2022 –The title in Appendix 3 Table 2 was updated to remove 60-day ANADA NF supplements as this is not an existing submission type. Section xx was updated to clarify the responsibilities of the consulting reviewer for labeling changes that impact both food producing and non-food producing animals. Updated SharePoint links and references to OSC due reorganization, including a new email address for informal consults.

March 22, 2023 – Updated Section II to fix the wrong CFR number used for NF supplements. The paragraph with "… and any other labeling changes except those described in 21 CFR 514.8(c)(2)". It should be 21 CFR 514.8(c)(3).

April 24, 2023 – Section VI.C. was updated to remove the paragraph about emailing OSC to provide labeling language for the Green Book monthly update was removed. Safety-related labeling changes are no longer published on the Green Book Monthly Update webpage. These safety related labeling changes are now published on the Animal Drug Safety-Related Labeling Changes | FDA web page, which is managed by OSC. 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.

May 30, 2023 – Section V.B and VI.C were updated to include the mailbox for contacting the Division of Pharmacovigilance and Surveillance in OSC. Section VII.A and Appendix 1 were updated to reflect the OSC reorganization and remove all uses of mail code HFV-216 and replace that with the OSC code HFV-240. Section VI.C. and VII.A. were updated to reflect the reorganization of OSC as well. Minor formatting errors in the TOC.

September 30, 2023 -- Sections III.A and F, VII.A and B, and Appendix 2 updated for changes associated with the law requiring the "Approved by FDA" labeling statement taking effect.

December 7, 2023 – Updated sections IV. And V. 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 submissions recoded or reassigned in STARS.

March 29, 2024 – Revised section VII 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. Updated section IV and V to remove the mention of the retired Stars Correction Form and to email the EDSR Mailbox instead.

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

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

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

   If the applicable “Approved by FDA…” statement is not included on the labeling, the labeling must be amended to add the statement.

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

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

   Examples: Expression of the active ingredient for products where the labeling does not match the drug product monograph, listing of animal classes

APPENDIX 3. EXAMPLES OF NL AND NF LABELING SUPPLEMENTS

Table 1: 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[13])
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[14])
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)

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

Table 2: 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)	