OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

APPROVAL LETTERS

I. PURPOSE

This document describes the procedures you use to prepare and route the approval letter for:[1]

- original new animal drug applications (NADAs) and abbreviated new animal drug applications (ANADAs)
- (A)NADA supplements classified as B1 supplements,
- (A)NADA supplements classified as NF (non-fee supplements requiring prior approval),
- (A)NADA supplements classified as NL (non-fee labeling supplements), and
- manufacturing supplements.

II. SCOPE OF THE APPROVAL LETTER

The intent of our approval letter is to inform an applicant of the approval and the conditions of approval. It is not intended to provide the details of the basis for our decision to approve. Therefore, the approval letter does not specifically discuss findings relevant to particular technical sections (e.g., environmental impact, human food safety, effectiveness) of an application.

III. ELEMENTS OF APPROVAL LETTERS

When preparing an approval letter, use the office or division template for the type of approval letter you are writing.[2] Follow P&P 1243.3010 Format and Style Conventions for Letters. See standard operating procedure 1243.000.007 for information on grammar standards for final action packages that undergo a quality control review by the Quality Assurance Team. Further specific instructions for how to fill in certain fields of the approval letter template follow.

[1] For purposes of this document, "you" refers to a reviewer, consumer safety officer (CSO), or other individual from the team or division in the Office of New Animal Drug Evaluation (ONADE) responsible for preparing the approval letter for an application.
[2] Use the Division of Manufacturing Technologies template for manufacturing supplement approval letters. Use the Office templates for all other letters covered by this P&P.

A. Inside Address

Direct the letter to the attention of the responsible official (i.e., sponsor or other consultant or party making the submission on the sponsor's behalf)[3] named as the contact in the Responsible Official (or U.S. Agent) Information section of the eSubmitter form. Use the firm name and address provided for the responsible official in the Responsible Official (or U.S. Agent) Information section of the eSubmitter form. The responsible official's address in eSubmitter may be different from the sponsor's official address in 21 CFR 510.600, including but not limited to abbreviations (e.g., Vet vs Veterinary and/or punctation (e.g., Blvd. vs Blvd). In that case, the address of the approval letter will intentionally not match the address used for the sponsor in the other approval documentation (i.e., the memorandum recommending approval and the Freedom of Information Summary).

If the sponsor has a U.S. agent or a U.S.-based employee, use their firm name in the inside address and DO NOT include the foreign sponsor's name anywhere in the address block. However, if you find obvious typographical (i.e., spelling) errors in either the firm name, firm address, or responsible official information, you should use the correct information in the inside address instead of using the incorrect information from the form.[4]

Additionally, if the firm name in the Responsible Official (or U.S. Agent) Information section of the eSubmitter form appears to be incorrect or is unclear regarding the identity of the drug application sponsor (e.g., if the firm name is written in the eSubmitter form or cover letter as "Drug Company Animal Health" and the firm name listed in 21 CFR 510.600 is "Drug Company Animal Health, a Division of Drug Company Inc."), contact the responsible official to obtain the correct name. Likewise, if there is more than one responsible official involved in the submission (e.g., one responsible official made the initial submission and a different person is the responsible official for an amendment and you are not sure to whom to address the response, contact the sponsor to confirm the correct name to use. Note in your review documentation (i.e., MRA or primary (AA) review) that you contacted the sponsor to clarify the information, and if applicable, make note of the corrected name in your review documentation and in the Quality Control (QC) Review Request form (see P&P 1243.3210), and use the corrected name in the inside address.

You may also modify the stylistic presentation (capitalization, punctuation, and spacing) of the firm name and the official's name, titles, and degrees contained in the form to match the addressee's preference in the cover letter. However, do not add information (e.g., degrees) if it is not in the information provided in the eSubmitter form.

B. Body of Letter

1. Opening Paragraph

   Format the proprietary name in the approval letter using the exact format from the product labeling. The proprietary name is formatted as it is on the label (i.e., use

[3] Examples of when it is acceptable for a submission to be sent to us by another party on the sponsor's behalf: 1) the company is not a United States company, they will have U.S. Agent; 2) correspondence may come from consultants; 3) a parent company submits information on a subsidiary's behalf.

[4] Note: If the application was submitted in paper, the person who signed the 356v is the Responsible Official.

the same capitalization as on the immediate container or Type A medicated article label and include any trademark/registered symbol).[5] Use that format throughout all approval documents in all locations where the proprietary name is used, including any trademark symbol associated with the proprietary name (e.g., ®, ©, ™).[6]

In situations where the application was submitted by another party on the sponsor's behalf, identify the sponsor by name in the opening paragraph of the letter.

For original (A)NADA approvals, include the full indication(s), and if appropriate, any additional conditions of use. An adequate description of what we are approving is critical to ensure that the applicant knows exactly what drug and uses we are approving. This also ensures we have a clear record on which to base an enforcement action if the applicant is marketing the drug for unapproved uses. Copy the indication(s) verbatim from the indication section of the package insert. If there isn't a package insert, copy it from the immediate container's carton labeling or the immediate container label. For supplemental approvals, include only the changes (indications, species, or other conditions of use) that are being approved in the supplement. If the proprietary name appears in the indication, format the name the same way the proprietary name is formatted elsewhere in the approval package.

In cases where the expiration dating changes as part of a supplemental (A)NADA approval, include the expiration dating sentence in the letter.

2. Market Exclusivity

   The approval letter templates include boilerplate for marketing exclusivity information. Where appropriate, you will select the boilerplate that applies.[7]

3. Standard Language for Antimicrobials of Medical Importance if No Microbial Food Safety (MFS) Assessment Was Conducted

   Include the standard language as the second paragraph for all supplemental applications (and certain original applications)[8] for antimicrobials of medical importance intended for use in food-producing animals in which no MFS assessment (under Guidance for Industry (GFI) # 152) was conducted for the pending application. This language applies to antimicrobials of medical importance regardless of indication or proposed use, including single ingredient and combination applications. Antimicrobials of medical importance are listed in Appendix A of GFI #152. If the antimicrobial in the application is not in this list but it is in a *class* that is on the list, then it is of medical importance (e.g., tilmicosin is not on the list in GFI #152 but the class it belongs to (macrolides) is on the list).

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[5] Note: This is not the process for products reviewed by the Division of Animal Bioengineering and Cellular Therapies (DABCT). Consult your team leader if you are in the DABCT.

[6] For information on proprietary names, see P&P 1243.3015 Proprietary Names.

[7] See P&P 1243.5780 for information on marketing exclusivity.

[8] Standard language is included in the approval letter templates for supplemental (A)NADAs (B1, NF, or NL subclass codes), Animal Drug Availability Act (ADAA) combinations, and ANADAs involving combinations of Type A medicated articles used to manufacture Type C medicated feeds. It should also be included in (A)NADA manufacturing supplement approval letters (use the language in the (A)NADA NL letters). For applications other than those listed above that meet the criteria, contact the ONADE Policy Team to obtain the appropriate language.

Contact the Microbial Food Safety Team (HFV-157) in the Division of Human Food Safety (DHFS) if you are unsure whether an MFS assessment was conducted for the pending application or if you are unsure whether the antimicrobial is of medical importance. Note: Most currently approved antimicrobials for use in food-producing animals are of medical importance.

4. Labeling and Veterinary Feed Directive (VFD) Paragraph

   Choose the paragraph below that pertains to the type of labeling submitted with the application.

   a. Dosage Form Products

      If the submission includes only facsimile labeling,[9] use the paragraph that requests submission of FPL prior to marketing and references the date of the facsimile labeling submission and submission code. This paragraph explains that FPL must be identical to the facsimile labeling approved as part of the application, except when FPL replaces "XXX-XXX" in the "Approved by FDA…" statement with the actual A/NADA number.[10] This paragraph also instructs the applicant when to submit FPL to the Center for Veterinary Medicine (CVM).[11]

      If acceptable FPL for all components was provided with the application, use the paragraph acknowledging acceptability of the FPL.

      If the application contains a mix of facsimile and FPL, you will use the paragraph that requests submission of FPL prior to marketing and the paragraph that acknowledges the acceptability of the FPL. It will be important to be clear in the letter as to which components are facsimile and which are FPL.

   b. Type A Medicated Articles and Combination Medicated Feeds

      In most cases, for single ingredient Type A medicated articles, we approve labeling for the Type A medicated article, representative labeling for Type B and Type C medicated feeds manufactured from the Type A medicated article, and if applicable, a representative VFD(s). If we are approving the application based upon facsimile labeling, the applicant needs to submit FPL via eSubmitter for the Type A medicated article identical to the approved facsimile labeling for their product. Because Type B and Type C medicated feed labeling is representative labeling (i.e., it includes general information about the feed but varies depending on mixing), the applicant does not need to submit FPL for Type B and Type C medicated feeds or for the VFD(s).[12]

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[9] See the Facsimile Labeling Policy on the ONADE Policy SharePoint Page
Internal information redacted.

[10] In the rare occurrence that you find typographical errors in the labeling submitted with an (A)NADA, check with your supervisor to determine whether to 1) request revised labeling as an amendment or 2) describe the changes in the approval letter and allow the sponsor to make the changes when they submit FPL. For feeds, this would also include submission of updated Type B and Type C medicated feed labeling. Requesting corrections in the approval letter is strongly discouraged.

[11] 21 CFR 514(b)(3)(vi) requires sponsors to submit three copies of their final printed labeling. ONADE is currently accepting a single copy because submissions are received electronically.

[12] Type B and C medicated feed labeling generally includes the name of the drug, the indications, the active ingredients, a guaranteed nutrient analysis that must meet the Association of American Feed Control Officials (AAFCO) standards, a list of the ingredients mixed, mixing or feeding directions, warnings, and cautions.

For single ingredient medicated article approvals, if a facsimile Type A medicated article label was submitted, use the paragraph in the letter requesting the submission of FPL for the Type A medicated article as described above. If acceptable FPL for the Type A medicated article was submitted, use the paragraph acknowledging acceptability of the FPL of the Type A medicated article.

For combination medicated feeds (ADAA or non-ADAA) with no Type A medicated article labeling (i.e., because the combination approval is only for the combining of the Type A medicated articles into a Type B and/or Type C medicated feed), the boilerplate paragraph states that the Type B and Type C medicated feed labels (and VFD(s), if applicable) are acceptable.

If the application contains a mix of facsimile and FPL, you will use the paragraph that requests submission of FPL prior to marketing and the paragraph that acknowledges the acceptability of the FPL. It will be important to be clear in the letter as to which components are facsimile and which are FPL.

5. Manufacturing Paragraph

For supplements or ADAA combination approvals that do not involve a change in the Chemistry, Manufacturing, and Controls (CMC) information, do not put a manufacturing paragraph in the approval letter.

For all other (A)NADA approval letters, use the manufacturing paragraph provided in the letter.

Type C free-choice medicated feeds. In those instances, in which we are approving an original or supplemental application for a Type C free-choice medicated feed that does not require a feed mill license (i.e., manufactured from a Category I Type A medicated article using a formulation that will be published in the CFR), do not put a manufacturing paragraph in the approval letter. If we are approving an original or supplemental application for a Type C free-choice medicated feed that does require a feed mill license (i.e., manufactured from a Category II Type A medicated article or using a proprietary feed formulation), use the following alternative manufacturing paragraph:

The manufacture of full-scale commercial batches using manufacturing instructions that have been determined to yield a properly mixed medicated feed product of the specified formulation is not a requirement for approval. However, medicated feed manufacturers must be able to assure that following the manufacturing instructions will result in a properly mixed feed under good manufacturing practices (GMPs) for medicated feeds (21 CFR 225.102(b)(1)(iv)).[13] Therefore, the feed mill should document the successful evaluation of multiple full-scale batches (usually a minimum of three (3)) of the specific free-choice formulation prior to shipment of the medicated feed product. In addition, adequate cleanout procedures for all equipment used in the manufacture and distribution of medicated feeds are essential to assure proper drug levels and avoid contamination (21 CFR 225.65).

[13] For medicated pet foods, contact the Division of Manufacturing Technologies for the appropriate GMP citation.

C. Complimentary Closing and Signature Block[14]

In the closing paragraph, provide the contact information for the division director and/or team leader according to your division procedures.

The center director signs the approval letter for original applications and supplements that would approve new animal species, significant new indications, and changes in Rx/OTC status.[15] The ONADE director signs the approval letter for other B1 supplemental applications (that approve changes other than those delegated to the center director). The division director signs the approval letter for NF supplements,[16] NL supplements, and manufacturing supplements. If there is any uncertainty about whether a new indication is significant and who should sign the approval, the division director or team leader should always speak with the ONADE director.

D. Enclosure Notation

Include a notation of any other documents that should be sent to the sponsor with the approval letter (e.g., FOI Summary).

IV. FINAL ROUTING FOR APPROVAL LETTERS

A. Approval Letter for an Original or Supplemental (A)NADA

The approval letter for original or B1 supplemental (A)NADAs will be routed as part of the (A)NADA approval package. Routing for (A)NADA approval packages is described in P&P 1243.3800. When uploading files into Appian, select the radio button beside “Yes, send to firm” to send the sponsor a copy of the approval letter and a copy of the enclosures (e.g., FOI Summary).

Routing of NF supplements is described in P&P 1243.6040.

Routing of NL supplements is described in P&P 1243.6020.

B. Approval Letter for a Manufacturing Supplement

The director of the Division of Manufacturing Technologies, HFV-140, has signature authority for approval of manufacturing supplements described in 21 CFR 514.8. The approval letter for manufacturing supplemental (A)NADAs will be routed as part of the final action package. See P&P 1243.6030.

V. REFERENCES

CVM Policies and Procedures Manual – ONADE Reviewer’s Chapter

1243.3010 - Format and Style Conventions for Letters

1243.3015 – Proprietary Names

[14] You can find the delegations of authority for approval of new animal drug applications, medicated feed mill license applications and their supplements in the Staff Manual Guide, Delegations of Authority (Volume II), Section 1410.502.

[15] For generic products, the ONADE Director signs the letter for new indications, species, etc. that are a result of the RLNAD exclusivity expiring in an NF supplement.

[16] For generic products, the ONADE Director signs the letter for new indications, species, etc. that are a result of the RLNAD exclusivity expiring in an NF supplement.

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

1243.3800 - Reviewing, Preparing, and Routing Approval Packages for Certain Abbreviated and New Animal Drug Applications

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

1243.5780 - Exclusivity and Exclusivity Marketing Rights Boilerplate Language for Use in the Following Documents: Memorandum Recommending Approval, Letter to Applicant, and Freedom of Information Summary

1243.6020 - Review of New Animal Drug Application and Abbreviated New Animal Drug Application Labeling Supplements (NL Subclass)

1243.6030 - Review of Labeling Changes in Manufacturing Supplements

1243.6040 - Review of Abbreviated and New Animal Drug Application 60- and 180-day Non-Fee Prior Approval Labeling Supplements

ONADE Standard Operating Procedures

1243.000.007 – Grammar Standards for Final Action Packages that Undergo a Quality Control Review by the Quality Assurance Team

ONADE Office Policy Page

Facsimile Labeling

Guidance for Industry (GFI)

GFI #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

VI. VERSION HISTORY

November 16, 2001 – original version

August 15, 2003 – Revised

December 10, 2007 - Revised to incorporate format and style conventions, changes and boilerplate language agreed upon by ONADE Management, incorporating active voice where possible, sample letters, and revised overall format.

March 12, 2008 – Revised to clarify what address to use for the inside address and to make grammatical changes.

July 1, 2008 – Revised to correct grammar in exclusivity paragraph of sample letter.

November 17, 2008 – Division of Manufacturing Technologies revised the document to add clarifying information regarding the manufacturing paragraph (paragraph 4) of the approval letter and free-choice feeds.

December 4, 2008 – Revised to properly format footnotes 8 and 9.

February 4, 2009 – Revised to correct citation in manufacturing paragraph in sample letters in Appendices 1 and 2. Paragraph now correctly cites Section 501(a). Added a citation to P&Ps 1243.3010 and 1243.5741 for information on how to format the proprietary name.

June 10, 2009 – Revised to reflect policy on facsimile labeling for a Type A medicated article that is reduced in scale and instructions in sample letters for NADA and ANADA and their supplements were added.

August 31, 2010 – Revised to replace sample letters with templates, and update boilerplate language to currently used wording.

October 31, 2017 - Revised to incorporate updated procedures. Internet version has been redacted to remove internal information.

March 9, 2018 – Revised to clarify procedures regarding the inside address of the letter.

August 6, 2018 – Revised to include specific information regarding formatting of the proprietary name and where to get the indications for the new animal drug product for the approval letter in section III. B. 1. and reference the P&P for proprietary names (i.e., 1243.3015).

December 14, 2018 – Revised to correct a typographical error.

April 4, 2019 – Revised to add instructions on when and how to ask for addition of "Approved by FDA…" statements to labeling. Revised to remove information about send the FONSI with the approval letter to the sponsor. This is no longer done. Added a section on marketing exclusivity to let the reader know there is boilerplate in the approval letter template to handle exclusivity and reference the P&P on exclusivity.

August 20, 2019 – Revised to change ABCT Team to a division. Updated referenced P&P titles and added information about if there is any uncertainty about who should sign a supplemental approval for a new indication to have the team leader or division director speak with the ONADE office director.

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

January 26, 2021 – Minor typographical errors corrected, and titles of some references corrected.

August 3, 2021 - revised section III to address what boilerplate should be included in the approval letter when the application contained a mix of facsimile and final printed labeling.

October 22, 2021 – revised to clarify that the responsible official's address in eSubmitter may be different from the sponsor's official address in 21 CFR 510.600 and if that is the case the approval letter will have a different address then the memorandum recommending approval and Freedom of Information Summary.

September 20, 2022- Section II. B. 1 was revised to specify the product labeling to be used to identify the format of the proprietary name.

December 8, 2022 – Section III. A. was updated to include information on what to do when more than one responsible official is involved in a sponsor's submission.

March 24, 2023 – Updated Section II. A Inside address to add the option of submitting on behalf of U.S. based employee to the section that has U.S. agent/U.S. based employee. Also updated to bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, the font of this document was changed from Verdana 10-point font to Arial 11-point font.

June 9, 2023 – Updated Section III. B to incorporate information from the ONADE policy "Approval of Antimicrobials for Food Animals". The information in this policy is being incorporated into our existing process documentation and the policy itself will be retired from the policy page in SharePoint.

September 30, 2023 - Section III. B. updated for changes associated with the law requiring the "Approved by FDA" labeling statement taking effect on 9/30/2023.

April 5, 2024 – Updated section III. A. to clarify that a U.S. firm may have consultants who submit applications on the firm's behalf. In that case, we will send our response letter to that consultant as they are the responsible official for the firm. Also, included a reference to the SOP on grammar standards for final action packages that undergo a quality control review by the QA Team in the first paragraph of section III.