OFFICE OF NEW ANIMAL PRODUCT EVALUATION AND OFFICE OF GENERIC ANIMAL DRUGS REVIEWER'S CHAPTER

MEMORANDUM RECOMMENDING APPROVAL (MRA) FOR ORIGINAL AND SUPPLEMENTAL (ABBREVIATED) NEW ANIMAL DRUG APPLICATIONS ((A)NADA)

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I. PURPOSE

This document provides instructions on how to use the Office of New Animal Product Evaluation (ONAPE) and the Office of Generic Animal Drugs (OGAD) template[1] to prepare a Memorandum Recommending Approval (MRA) for an original or B1 supplemental (abbreviated) new animal drug application [(A)NADA]. An MRA should always be part of the approval package for an (A)NADA (see P&P 1243.3800). This Policy and Procedure (P&P) does not apply to (A)NADAs for medicated feed combinations or to manufacturing supplements, minor labeling supplements (NFs and NLs) or conditional approvals (see P&Ps 1243.6020 and 1243.6030 for information on minor labeling supplements). See Standard Operating Procedure (SOP) 1243.000.007 for information on grammar standards.

II. PURPOSE OF AN MRA

An MRA briefs the individuals signing the approval (i.e., the center director, office director) on the basis for our recommendation to approve an (A)NADA. The MRA incorporates by reference the data, information, and reviews that support our recommendation. ONAPE or OGAD prepares an MRA as part of the final action package for the approval of an original (A)NADA. In addition, ONAPE prepares an MRA for supplemental NADA approvals that include safety and/or effectiveness data (B1 supplements).[2] For questions about which applications need an MRA, consult your branch chief (BC).

III. WHO PREPARES THE MRA USING THE OFFICE TEMPLATE?

The MRA is prepared by the reviewer, consumer safety officer, or other individual designated by the division to prepare the approval package for an application. If the reviewer has questions about who prepares the MRA, they should consult with their BC or division director (DD). BCs and DDs are responsible for ensuring that the correct version of the office template was used to create the (A)NADA MRA and confirming the accuracy of the dates and submission codes referenced in the MRA.

[1] Not applicable for Division of Biotechnology (DB). They have their own template.

[2] Supplemental ANADA approvals (outside of NF and NL labeling supplements) are very rare and not covered here.

IV. GENERAL INSTRUCTIONS FOR USING THE OFFICE TEMPLATE MRA

Use the appropriate ONAPE or OGAD MRA template located on the ONAPE or OGAD Template SharePoint. For questions about which MRA template to use, consult your BC. This section describes the contents of each section of the MRA in more detail than the template. Refer to this section as you use the MRA template.

A. General Instructions for Using the MRA Template:

1. Certain template boilerplate text is contained in content control fields or drop-down menus. Choose the appropriate information relating to your specific application. If none of the templated text is applicable, the fill-in or drop-down can be deleted and the text can be entered.

2. Words in brackets or italics may provide instruction, describe the information you are to provide, or give examples of the type of information that you are to include in a particular portion of the MRA.

3. Where you see brackets, italics, content control or text fields, provide information relating to your specific application.

4. Based on the type of application, select the appropriate boilerplate language for each section in the template.

5. Include all sections and subsections of the MRA (unless a comment bubble specifically allows for deletion of a (sub)section) identified in the template. For each section, include the boilerplate language or appropriate information described in the (A)NADA MRA template.

6. The header will appear on all pages (except the first page) of the MRA template. Double-click in the header to insert the Submission Tracking and Reporting System information (i.e., (A)NADA number and submission ID, and subclass code) in place of <A/N-000000-X-0000-XX>.

7. When writing the proprietary name, use the appropriate trademark symbols (i.e., ®, or ™). See P&P 1243.3015 for information on how to format the proprietary name.

8. Define acronyms and abbreviations (e.g., FDA, FD&C Act) the first time they appear in the document. Once defined, it is permissible for preparers to use the acronym or abbreviation in subsequent sections.

B. The “To” Line of the MRA

1. Original (A)NADA Approvals

   Address the MRA to the Center Director, through the Director of ONAPE or OGAD.

2. Supplemental NADA Approvals

   Address most MRAs for supplemental approvals to the Director of ONAPE, through the appropriate DD, except for supplements that would approve a new

species, significant new indications, or change in Rx/OTC status, which will be addressed to the Center Director, through the Director of ONAPE.[3]

C. General Information Table

The MRA's General Information table should be identical in all aspects to the General Information table in the FOI Summary, except the (J)INAD number will not appear in the FOI Summary.

1. File Number

   Insert the (A)NADA application number and, if applicable, the (J)INAD number.

2. Sponsor, their Address, Drug Labeler Code, and U.S. Agent[4]

   If this is not the first approval for a sponsor, copy the sponsor's name, address, and drug labeler code exactly as it appears in 21 CFR 510.600(c). Do not copy the sponsor address provided in eSubmitter in this section. Use the listing in the electronic CFR to obtain the most recent information.[5] If this is a sponsor's first approval, consult your BC.

   If the sponsor does not reside or have a place of business within the U.S., insert the name and address of the authorized U.S. agent provided in "U.S. Agent/U.S. Employee Information" section in eSubmitter.[6] Delete the U.S. agent field if not applicable.

3. Proprietary Name(s)

   The proprietary name is the exclusive name the sponsor assigns to the approved drug product. It is commonly known as the tradename and may include trademarked and non-trademarked words. The proprietary name should match the product labeling. Use the proprietary name consistently throughout the MRA. Format the proprietary name per P&P 1243.3015.

4. Drug Product Established Name(s)[7]

   The drug product established name is the non-proprietary name of the drug product and may or may not include the route of administration and dosage form. To identify the drug product established name, refer to the product labeling.[8] The established name is typically presented within parenthesis under the proprietary name. Some examples include "(carprofen tablets)" and "(mebendazole oral suspension)". There may be exceptions, such as "(cyclosporine capsules) USP

[3] Note: If there is uncertainty about who the approver/signer of a supplemental approval should be, the DD or BC should always speak with the ONAPE Office Director.
[4] See P&P 1243.2020 on U.S agents.
[5] The electronic CFR (eCFR) provides the most up to date information. It is a different site than the online CFR, which is an electronic copy of the most recent printed CFR (issued in April of each year).
[6] 21 CFR §514.1(a).
[7] SOP 1243.130.003: Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs
[8] In some cases, the product established name as written on the labeling may be inconsistent. In these cases, refer to SOP 1243.130.003: Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs or discuss with your BC.

MODIFIED." Use the drug product established name consistently throughout the MRA.

5. Pharmacological Category

   This section describes the action of the drug product (e.g., anticoccidial, antimicrobial, or antiparasitic). Include the schedule if this is a controlled substance.

6. Dosage Form(s)

   Include the dosage form(s) even if it is part of the proprietary name or drug product established name. The dosage form refers to the physical description of the approved manufactured product. For appropriate dosage form terminology for new animal drugs, consult SOP 1243.130.003 (Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs) on the ONAPE SOP SharePoint site and the Dosage Form worksheet on the ONAPE template SharePoint site.

7. Amount of Active Ingredient(s)

   This section describes the amount of drug(s) per tablet, mL, percentage, or other measure of concentration. The amount should be expressed exactly as on product labeling, which may be on the basis of the active moiety, the active ingredient, or both.

8. How Supplied

   This section describes the size and description of the containers (e.g., 50- and 100-mL vials, 50-lb bag). This information should be expressed exactly as on product labeling.

9. Dispensing Status

   This section identifies whether the marketing status is by prescription (Rx), over the counter (OTC), or veterinary feed directive (VFD).

10. Dosage Regimen

    This section describes the approved dose, frequency, and duration of treatment as printed on the approved labeling. Detailed dosage and administration information from the product insert (e.g., dosing tables provided for the convenience of calculating dosage) should not reside here; however, wording included in this section should match the wording on the approved labeling. Tables that provide information on different doses by weight bands, clarifying the amount of new animal drug to give or apply when there are multiple concentrations or tablet sizes/strengths approved for the new animal drug, can be included here.

11. Route(s) of Administration

    This section describes how the product is administered.[9] For appropriate route of administration terminology for new animal drugs, consult SOP 1243.130.003 (Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs) on the ONAPE SOP SharePoint site and the Route of Administration worksheet on the ONAPE template SharePoint site.

12. Species/Class(es)

    This section identifies the target animal species to which the approval applies exactly as stated on product labeling in the "Indications" section. Some approvals apply to a specific class(es) within a species (e.g., lactating dairy cows). If there is a specific class(es) for the approval, include that information here. If there is no class limitation, enter the species in plain language (e.g., cattle rather than bovine, dogs rather than canine). For supplemental approvals, only list the species for which the supplement is approved. For additional examples of classes of major food animals, consult Guidance for Industry (GFI) #191, Appendix III.

13. Indication(s)

    In this section, include any new indication(s) we are approving. If no new indication is being approved, include only the indication(s) impacted by the supplemental approval or indication(s) necessary to provide context for the supplemental approval. (Examples: for an approval with multiple species, if the approval is for a reduced withdrawal period for swine, include only the swine indication(s). For an approval adding a new pathogen to an approved indication, include the complete indication with all previously approved pathogens and the added pathogen.) Indication(s) should always be provided, even for supplemental approvals that do not change any existing indications, so readers will know what indication(s) the approval applies to.

    Copy the indication(s) verbatim from the indication(s) 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. If the proprietary name appears in the indication, format the name the same way the proprietary name is formatted elsewhere in the approval package; i.e., if the indications section of the package insert does not use the trademark symbol for the drug (®, ™), still include it here for consistency across documents.

14. Effect(s) of Supplement (NADA only)

    If this is a supplemental approval, this section should briefly describe the changes we are approving. For original approvals, delete this row from the General Information section.

[9] For an original approval, list all information. For supplemental NADAs, abbreviate the information to include only that to which the supplement applies, unless the currently approved information is needed to provide context. If you include all of the previously approved information with the new or modified information, then highlight (by bolding) the new or modified information so that the new or modified information is readily distinguishable.

15. Reference Listed New Animal Drug (RLNAD) (ANADA only)

    Provide the RLNAD proprietary name, drug product established name, (A)NADA number and sponsor name as indicated in the template.

D. Suitability Petition (ANADA only)

Suitability petitions (SP) allow sponsors of generic new animal drugs to request permission to submit an ANADA for a generic that differs from the RLNAD in specific ways, as defined under section 512(n)(3) of the Federal Food, Drug, and Cosmetic Act. The permissible differences include:

- route of administration,
- dosage form, strength (concentration),
- a change in one active ingredient in a combination drug, and
- a change in one Type A medicated article in a feed-use combination.

To approve a SP, the proposed change should not require the petitioner to conduct investigations to demonstrate the safety or effectiveness of the generic new animal drug for its intended uses. If the generic drug product is the subject of an approved SP, provide the information requested in the template for this section.

E. Effectiveness (NADA only)

This section identifies the submission/review document(s) and technical section complete (TSC) letters (if applicable) that contain the effectiveness data pertinent to this approval. If necessary, include additional effectiveness information unique to the application. For supplemental NADAs that do not contain new effectiveness studies, use the boilerplate language in the template.

F. Target Animal Safety (NADA only)

This section identifies the submission/review document(s) and TSC letters (if applicable) that contain the safety data pertinent to this approval. If necessary, include additional target animal safety information unique to the application. For supplemental NADAs that do not contain new target animal safety studies, use the boilerplate language in the template.

G. Bioequivalence (ANADA only)

This section identifies the submission/review document(s) and TSC letter (if applicable) that contain the bioequivalence data pertinent to this approval. If a waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) was granted, provide that information using the first paragraph in the MRA template. If an *in vivo* bioequivalence study was performed, provide the appropriate information as outlined in the second paragraph of the MRA template.

H. Human Food Safety (HFS)

This section identifies the submission/review document(s) and TSC letters (if applicable) that contain the safety data pertinent to this approval. If necessary, include additional HFS information unique to the application.

If the product is for use in non-food producing animal species, then include the standard language in the template explaining that we did not require HFS data. For approvals that result in a tolerance change for an approved drug, the preparer should document in the MRA that an email was sent to the Office of Surveillance and Compliance (OS&C). See P&P 1243.3760 for drug tolerance notification process.

I. Chemistry, Manufacturing Methods, and Controls

This section identifies the submission/review document(s) and TSC letters (if applicable) that contain the chemistry and manufacturing data pertinent to the approval and also documents the current GMP compliance status of the drug manufacturing facility. For all the original applications, the expiration date of the approved drug should also be documented. If a supplemental approval did not include a change in expiration dating, it should be documented as “Not applicable”. See P&P 1243.3800 for information on how to perform cGMP status checks for approvals.

J. Environmental Impact

This section identifies the reviews, TSC letters (if applicable), environmental information in the end-game meeting memo (if applicable), and any other environmental review documents (e.g., finding of no significant impact (FONSI)) (if applicable). Also include the appropriate boilerplate language for accepting a claim of categorical exclusion, preparation of an environmental assessment and FONSI, or preparation of an environmental impact statement and record of decision.

K. Freedom of Information Summary

Include the boilerplate language provided in the MRA template. If applicable, reference the reviews and letters that are relevant to the application.

L. Labeling

This section identifies the submission/reviews and TSC letters (if applicable) that contain the approved labeling information. If the labeling needs to be updated due to typographical errors, that information should be included in this section.

If applicable, this section also identifies that the labeling application includes changes initiated by OS&C.

For a supplemental approval to a drug product intended for use in or on animal feed, this section also identifies the file numbers for (A)NADAs and veterinary master files that contain labeling components impacted by the supplemental approval (aka

downstream applications or files).[10]

This section also confirms that all non-Blue Bird labeling components include the "Approved by FDA under NADA # XXX-XXX" or "Approved by FDA under ANADA # XXX-XXX" statement, as required by Section 502(w)(3)[11] of the FD&C Act. List any non-Blue Bird labeling components that do not include the statement and provide a justification per exemptions permitted in the ONAPE Policy Addition of Approved by FDA Statements to Labeling of Approved New Animal Drugs and Abbreviated (Generic) New Animal Drugs.

M. All Other Information (AOI) (NADA only)

This section identifies the submission/reviews and TSC letters (if applicable) that contain the sponsor's affirmative statement that there is no AOI that are applicable to this submission. If the sponsor provides an affirmative statement via email, the preparer should reference the email in this section and include a copy of the email in the approval package.

N. Special Concurrence

For most approvals include the boilerplate language "None" from the template. If the approval required communication between the ONAPE and OGAD Regulatory Counsel and Office of Chief Council on legal issues, consult with the ONAPE and OGAD Regulatory Counsel for the verbiage to be included in this section.

O. Bioresearch Monitoring Status

Document the BIMO status check in this section. If there are issues associated with the status check consult with your BC. See P&P 1243.3800 for information on how to perform status checks for approvals.

P. Drug Experience Report (DER) Status

This section is where we include information provided by the individual who reviewed the adverse drug experience/event history for the approved drug product report. If the DER is reviewed by the Division of Pharmacovigilance and Surveillance reference the email confirmation in this section. If necessary, add any additional information for further clarification of the DER report. See P&P 1243.3800 for information on how to perform status check approvals.

Q. Supplemental Applications (NADA only)

For supplemental approvals, include the boilerplate language in the MRA to state whether there was a need for the reevaluation of the safety and effectiveness data in the original NADA. For original approvals, delete the boilerplate language and insert "Not applicable".

[10] 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

[11] 21 U.S.C. 352(w)(3)

R. Patent Term (NADA only) or Patent Certification (ANADA only)

NADA: This section identifies any relevant patents and the expiration date for each patent that was provided by the sponsor in the application or in the labeling technical section. If the sponsor provides an affirmative statement in the application stating that there is no patent information, include the boilerplate language in the template. If the sponsor provides an affirmative statement via email, the preparer should reference the email in this section and include a copy of the email in the approval package.

ANADA: This section identifies any relevant RLNAD patents and the expiration date for each patent. Choose the appropriate patent certification information in the MRA template. The template contains boilerplate language documenting that the reviewer confirmed the patent information provided by the sponsor with what is listed in the Green Book on Animal Drugs @ FDA.

S. Exclusivity (NADA only) or Marketing Exclusivity (ANADA only)

NADA: This section contains information on whether marketing exclusivity was granted or not to the sponsor. Include the appropriate boilerplate language provided in the MRA template. The boilerplate language explains why we have or have not granted exclusivity. In some cases, the boilerplate language in the MRA template may not be appropriate; in such a case, see P&P 1243.5780 for additional language or if necessary, contact the ONAPE Regulatory Counsel.

ANADA: This section contains information on whether there are any unexpired marketing exclusivity periods listed for the RLNAD. Include the appropriate boilerplate language provided in the MRA template. The template includes boilerplate language to describe any RLNAD indications protected by marketing exclusivity (if applicable).

T. Regulation

This section contains information on the draft regulation amending the animal drug regulations (Title 21 of the Code of Federal Regulations) to reflect the supplemental or original approval. Use the appropriate boilerplate language provided in the MRA template.

U. Communication Staff Notification

This section provides information on whether the division has or has not sent advance notification of the upcoming approval to the communication staff (FDA's Office of External Affairs and the External Communications Staff). See P&P 1243.3800 to follow the instructions for the notification process.

V. Citizen's Petition Status

The preparer should reference the confirmatory email from the Policy and Regulations Staff in this section and include it in the approval package. In cases where the approval has an impact on an existing citizen's petition, the preparer should consult with their BC or DD to determine the appropriate boilerplate language to include in this section.

W. Recommendation

Include the boilerplate language provided in the MRA template to confirm that all the technical sections are complete and support the approval of the application.

V. REFERENCES

Code of Federal Regulations (Title 21)

§ 510.600, Names, addresses, and drug labeler codes of sponsors of approved applications

§ 514.1, Applications

Guidance for Industry (GFI)

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

CVM Program Policies and Procedure Manual

1240.2325 – CVM Guidance on Media Inquiries

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 – Office of New Animal Product Evaluation (ONAPE) and Office of Generic Animal Drugs (OGAD) Reviewer's Chapter

1243.3015 – Proprietary Names

1243.3760 – Drug Tolerance Notification Process

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

1243.5761 – Freedom of Information Summary (FOI) for Original and Supplemental New Animal Drug Applications (NADA)

1243.5780 - Exclusivity and Exclusive 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 Supplements (NL Subclass)

1243.6030 – Review of Labeling Changes in Manufacturing Supplements

1243.8220 – Requesting a Bioresearch Monitoring (BIMO) Status Check

ONAPE and OGAD Template Page

Dosage Form Worksheet

Route of Administration Worksheet

ONAPE and OGAD Office Policy Page

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

ONAPE and OGAD Standard Operating Procedure (SOP)

1243.000.007 – Grammar Standards

1243.130.003 – Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs

VI. VERSION HISTORY

August 31, 2016 – Original version.

August 28, 2019 – Removed section on distribution copies of the MRA and filing paper copies of the MRA as this is no longer current practice. Revised also to include reference to the proprietary names P&P and information about speaking the ONADE director if there is any uncertainty about who should sign the approval package for the addition of a new indication. Updated the format to the current format for ONADE P&Ps.

November 2, 2020- Updated to add information on all the sections in the MRA template for NADA and ANADA approvals.

January 26, 2021 – Minor edits to fix typographical errors and errors in the titles of some references.

February 17, 2021 – Updated to remove the line that says to send an email to the Environmental Team in the Environmental Impact section J.

July 12, 2021 – Quality systems review for minor formatting updates.

March 14, 2023 – Updated footnote 8 on page 3 to remove the mention the established name P&P, which is still in draft, and direct them to the ONADE policy on the established name.

September 30, 2023 - 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. Sections IV.L updated for changes associated with the law requiring the “Approved by FDA” labeling statement taking effect.

March 29, 2024 – Revised Section IV. L. Labeling to include a reference to the downstream labeling P&P and to include information on OSC initiated labeling changes would be included in the MRA. It also now states that the labeling section of the MRA for supplemental approvals for products used in or on animal feed, if applicable, will identify the file numbers for any new animal drugs and veterinary master files that contain

labeling components that are impacted by the supplemental approval (aka downstream applications). The new P&P was added to the references of this document. In the Purpose Section, included a reference to the SOP on grammar standards for final action packages that undergo a quality control review by the Quality Assurance Team.

August 5, 2024 – Revised to clarify grammar and formatting rules. Revised the title for SOP 1243.000.007 to reflect its new title.

July 9, 2026 – Revised Sections IV.C.6 (Dosage Form(s)) and IV.C.11 (Route(s) of Administration) to include a reference to SOP 1243.130.003 (Determining the Active Ingredient, Dosage Form, Route of Administration, and Product Established Name for New Animal Drugs) and the associated Dosage Form and Route of Administration worksheets. Revised to reflect the reorganization of the Office of New Animal Drug Evaluation (ONADE) into the Office of New Animal Product Evaluation (ONAPE) and the Office of Generic Animal Drugs (OGAD). Changed all references from team leaders to branch chief. Updated to reflect the current division names and other organizational and title changes. Changed references from shaded fill-in text or shaded areas to content control fields for templates. Expanded acronyms and abbreviations. Revised to INAD to (J)INAD.