OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

PROCESSING A REQUEST TO OPEN AN INVESTIGATIONAL (INAD) OR GENERIC INVESTIGATIONAL NEW ANIMAL DRUG (JINAD) FILE

I. PURPOSE

This document explains:

- what a (generic) new investigational animal drug ((J)INAD) file is,
- how to process and review the A-0000 submission, and
- how to process those A-0000 submissions containing multiple requests.

II. WHAT IS A (J)INAD FILE?

An INAD file contains correspondence and submissions that may be used to support a new animal drug application (NADA) (i.e., phased review submissions). Regulations governing unapproved new animal drugs intended for investigational use are in 21 CFR 511. When a sponsor plans to begin clinical studies, they will submit the information required to maintain their investigational exemption.[1] A JINAD file contains correspondence and submissions that may be used to support an abbreviated new animal drug application (ANADA).

For (J)INADs, the submission made by a sponsor to request an investigational file is an A-0000 submission.

III. WHEN DOES A SPONSOR REQUEST A (J)INAD FILE?

Sponsors of new animal drugs typically submit a request to open an INAD file when they have enough pilot data to start discussing the development process and/or they want to begin shipping drug for use in investigational studies. If the sponsor is pursuing a supplemental approval, we may request that the sponsor establish a new (J)INAD file so we can better administer review of the data.[2] Sponsors of generic products typically

[1] See P&P 1243.4065 Requirements for Investigational New Animal Drug Exemptions.
[2] See Guidance for Industry 191 Changes to Approved NADAs-New NADAs vs. Category II Supplemental NADAs.

submit a request to open a JINAD file after they have researched and identified a reference listed new animal drug (RLNAD) they intend to copy.

IV. INITIAL ROUTING AND PROCESSING OF A (J)INAD FILE REQUEST

A. Requests Made in Paper

When the Records and Information Management (RIM) Team receives a request to establish a (J)INAD file in paper, a team member follows the process described in P&P 1243.3002 for handling the paper request. If the intended recipient division identifies the paper submission as being an exception that can be accepted in paper, they instruct the RIM Team to accept the paper submission for filing.

The RIM Team date stamps the submission, records its receipt, cross-checks records to verify that it is an original submission, prepares a draft acknowledgement letter with a tentative (J)INAD file number, and enters pertinent information into the Submission Tracking and Reporting System (STARS). A copy of the draft acknowledgement letter is sent to the division for approval. Once approved, the RIM Team processes the submission. The RIM Team then mails the acknowledgement letter to the sponsor confirming receipt of the request and informing the sponsor of the (J)INAD file number. The submission is scanned and uploaded into our Corporate Document Management System (CDMS).

Note: If the division director does not believe it is appropriate to open a new (J)INAD file, they instruct the RIM Team to convert the file to a General Correspondence (GC). The respective target animal division (TAD) prepares the necessary documentation for this GC submission.

B. Requests Made Electronically

All requests to establish (J)INAD files that are received via eSubmitter result in an investigational file being automatically created. The sponsor is notified that their file has been created by an acknowledgement issued from the Electronic Submission Gateway. The acknowledgement contains the (J)INAD file number. If, once the TAD director receives the submission, they do not believe it is appropriate to open a new (J)INAD file, they request that the submission be voided and notify the sponsor of this action.[3]

C. The A-0000 and the User Fee Check

After the RIM Team creates the A-0000 submission for the request, they route the submission to the STARS Evaluation Queue for the Business Informatics (BI) Team to evaluate. If this is the first filing of a (J)INAD by the sponsor, they will be subject to a sponsor fee under either the Animal Drug User Fee Act (ADUFA) or the Animal Generic Drug User Fee Act (AGDUFA), whichever is applicable. Once the BI Team has confirmed the sponsor's user fee status is current, the submission is routed to the TAD for review.

[3] See P&P 1243.3011 Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications.

V. REVIEWING THE SUBMISSION

The primary reviewer (PR) reviews the submission and identifies any areas in which it is deficient. The PR may contact the sponsor to clarify the information submitted or request additional information through an amendment. The PR requests consulting reviews, if appropriate, within two working days of receipt of the submission.[4]

If the sponsor provides user safety information, the PR conducts an initial human user safety assessment following the process described in CVM ONADE Scientific Resource Document (SRD) 1243.130.001.[5] Typically, this is not done for generic new animal drugs.

If the product identified in the A-0000 submission contains nanomaterials or otherwise involves the application of nanotechnology, the PR should follow the early identification and information collection procedures described in P&P 1243.2600.

If the product identified in the A-0000 submission is protein-based, the sponsor may need to address immunogenicity concerns. See the ONADE SRD 1243.135.001 and ProTech/Immunomodulators Focus Group (PI FG) SharePoint for current procedures, including boilerplate language for the A-0000 letter and adding the proposed product to the PI FG spreadsheet.[6]

If the product identified in the A-0000 submission is an oncology drug, the sponsor may need to address human user safety concerns. See the Oncology Standard Operating Procedure (SOP) on the Division of Companion Animal Drugs SharePoint for current procedures, including boilerplate language for the A-0000 letter.[7]

If the product identified in the A-0000 submission is a combination anthelmintic for grazing species with highly or completely overlapping indications, the sponsor may need to address specific attributes of an ideal (appropriate) anthelmintic combination early in the development process, if appropriate. See Appendix 2 of the ONADE Internal Policy titled “ONADE Internal Policy on Effectiveness Requirements for Anthelmintic Combinations in Grazing Species (ruminants/equines) with Highly or Completely Overlapping Indications” on the ONADE Office Policies SharePoint for boilerplate language for the A-0000 letter.[8]

If the sponsor identifies the submission as providing early information (EI), follow the procedures described in P&P 1243.2200 including boilerplate language for the A-0000 letter.

If the submission is for a cannabidiol (CBD) product, include the following boilerplate in the additional comments section of the acknowledgement letter.

> The Drug Enforcement Agency (DEA) is the lead federal agency for regulating controlled substances. FDA does not enforce the Controlled Substances Act (CSA) or other laws within DEA’s jurisdiction. Activities related to growing and

[4] See P&P 1243.3200 for information on how to request a consulting review.
[5] Internal information redacted.
[6] Internal information redacted.
[7] Internal information redacted.
[8] Internal information redacted.

manufacturing cannabis for use as an investigational new animal drug for research must comply with CSA and DEA requirements if the cannabis or cannabis-derived compound exceeds the threshold of 0.3 percent delta-9 THC by dry weight. We encourage you to contact DEA with questions regarding Schedule I cannabis or the CSA.

If applicable, the PR should send a consulting review request to the Clinical Pharmacology Team as described in ONADE SOP 1243.166.001.

A. Information That We Generally Receive in an A-0000 Submission

1. Sponsor information including the sponsor's name, address, telephone number(s), email address, and contact person or, if they are a foreign sponsor, US agent information. The US agent should include a signed letter from the foreign sponsor stating that they are appointing <name of person or company> as their US agent.[9]

2. Drug identification information. This may include the drug/chemical name or other unique identifier, the pharmacological category, and the dosage form.

3. Species and if applicable, class of animals

4. Dosage regimen, if this information is known (e.g., the route of administration, dose, frequency, and duration of treatment administration).

5. Indication, if this information is known. Often, only a high-level description of the indication (e.g., "respiratory disease") is provided in the A-0000 for an INAD. It is understood that the final indication wording (e.g., "treatment of bovine respiratory disease associated with [specific pathogens]) will be developed (and often revised) as the project moves forward and the data supporting the indication are evaluated.

For products with novel indications, use the evaluation described in the ONADE SOP 1243.100.001.[10] For products that are proteins, modified proteins, and peptide new animal drugs (referred to in this document collectively as protein products), see SRD 1243.135.003.

If the sponsor requested that information in the INAD be publicly available, the submission should detail the scope of the disclosure.

Request an amendment or ask the sponsor to clarify if you determine that the submission does not address or include the above information.

B. Labeling

The sponsor is not required to submit investigational labeling along with their request to open an (J)INAD file. The acknowledgement letter informs the sponsor of their obligations regarding investigational labeling and "Notices of Claimed Investigational Exemption for a New Animal Drug," in accordance with 21 CFR 511.1.

[9] See P&P 1243.2020 - United States (U.S.)-Based Employee and U.S. Agent Representation of Foreign Sponsors.
[10] Internal information redacted.

VI. ADDITIONAL INFORMATION FOR SUBMISSIONS REQUESTING A JINAD FILE

1. Requests to establish a JINAD file should include the information in Section V and also contain the following information:

2. Reference listed new animal drug (RLNAD) information: Sponsors are required to identify the RLNAD for their proposed generic drug, including trade name (and/or established name), dosage form, strength(s), sponsor name, and (A)NADA number;

3. Patent information: Sponsors should list any patents applicable to the RLNAD, and their expiration dates. Verify the patent information submitted by using the FDA Green Book. Note: If the time to patent expiration is greater than 5 years, consult your team leader for guidance on how to proceed;

4. Marketing exclusivity information: Sponsors should indicate if there are any marketing exclusivities applicable to the RLNAD, and their expiration dates. Verify the accuracy of the marketing exclusivity information submitted by the sponsor using the FDA Green Book. Note: If the period for marketing exclusivity is 5 years, consult your team leader for guidance on how to proceed; and

5. If the sponsor indicates that a suitability petition was previously submitted for the proposed generic product, and their request was granted, a copy of the letter approving the petition should be included with their JINAD request. If the proposed generic drug product has a different dosage form, strength, route of administration, and/or active ingredient (in a combination drug product), and a suitability petition has not been submitted, document this in the primary (AA) review and notify the sponsor they must have an approved suitability petition for the proposed differences from the RLNAD before proceeding with their application.

VII. COMBINED REQUESTS OR THE SUBMISSION OF OTHER INFORMATION WITH THE A-0000

Sponsors sometimes include other requests in their A-0000. Examples include requests for an investigational food-use authorization (IFUA), protocol review, meeting, bioequivalence waiver, environmental claims (e.g., categorical exclusion), and expedited review.[11] If additional requests are made within the A-0000 submission:

1. contact the sponsor informally (e.g., by phone or email) and inform them that the request to open the (J)INAD will be reviewed but the additional requests will not be reviewed under the A-0000 submission. Also instruct them to resubmit each additional request separately under the appropriate submission code(s);

2. document in your A-0000 review that the additional requests were not reviewed under the A-0000 submission and that the sponsor was contacted; and

3. include the template language regarding additional requests in the A-0000 acknowledgement letter.

[11] Submission of early information or other background materials to facilitate CVM's understanding of the project is acceptable. See P&P 1243.2200.

VIII. PREPARING THE FINAL ACTION PACKAGE

Prepare a review and an acknowledgement letter using the specific office templates according to the procedures in P&Ps 1243.3009 and 1243.3010. Follow the procedures described in P&Ps 1243.3005 and 1243.3030 to prepare clean electronic documents and assemble the final action package.

IX. REFERENCES

Code of Federal Regulations

Part 511 – New Animal Drugs for Investigational Use

CVM Guidance for Industry

191 - Changes to Approved NADAs-New NADAs vs. Category II Supplemental NADAs

CVM Program Policies and Procedure Manual – ONADE Reviewer's Chapter

1243.2020 - United States (U.S.)-Based Employee and U.S. Agent Representation of Foreign Sponsors

1243.2200 - Submission and Review of Early Information (EI) to Presubmission Conferences and Protocol Review

1243.2600 - Review of ONADE-regulated Products that Contain Nanomaterials or Otherwise Involve the Use of Nanotechnology

1243.3002 - Handling and Rejecting Paper Applications and Submissions

1243.3005 - Creating Clean Electronic Files

1243.3009 - Format and Style Conventions for Reviews and Submission Summaries

1243.3010 - Format and Style Conventions for Letters

1243.3011 - Voiding Submissions and Discontinuing the Review of Pending Submissions and Applications

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)

1243.4065 - Requirements for Investigational New Animal Drug Exemptions

ONADE Standard Operating Procedures and Scientific Reference Documents

CVM SOP 1243.100.001 - ONADE Process for Determining Whether a Proposed Indication (Claim) is Valid

CVM SOP 1243.166.001 - Clinical Pharmacology Team (HFV-166) Involvement and Communications During the Project Lifecycle

CVM SRD 1243.130.001 - Human User Safety Assessment

CVM SRD 1243.135.001 – Immunogenicity Evaluation and Testing of New Animal Drugs for Target Animal Safety and Effectiveness

CVM SRD 1243.135.003 - Points to Consider When Evaluating Proteins, Modified Proteins, and Peptide Products

FDA Green Book

X. VERSION HISTORY

March 31, 2009 – Beta test version

June 30, 2009 – Revised Beta test version

March 15, 2010 – Final Version

December 5, 2011 – Revised version to address bundled submissions

August 30, 2017 - Revised to incorporate electronic review processes, expand discussion of bundled submission procedures, and reference the SOP on valid indications.

March 9, 2018 – Revised to provide instructions regarding user safety assessments, clinical pharmacology assessment, and process for products that may contain nanomaterials.

January 17, 2019 – Updated references to reflect the P&P 1243.4090 for human user safety assessment is now a CVM ONADE Scientific Resource Document and is found on the ONADE Standard Operating Procedures and Resource Documents SharePoint page.

May 8, 2019 – Revised section V to include information about investigational files being opened for protein-based and oncology new animal drug products and links to resources for them.

April 20, 2020 – Revised to include reference to P&P 1243.2200 for early information; reference to P&P 1243.3002, P&P 1243.3009, P&P 1243.3010, and P&P 1243.3011.

June 26, 2020 - Updated all internal links for SharePoint sites because FDA has migrated this information to a new version of SharePoint.

July 6, 2020 – Updated references

February 20, 2021 – Updated section V to include updated information about combination anthelmintic products and to point to the ONADE Policy on effectiveness requirements for anthelmintic combinations in grazing species (ruminants/equines) with highly or completely overlapping indications.

December 23, 2021 –Updated section V to include standard language for cannabidiol (CBD) products and V.A.1. with language that states if there is a U.S. agent, the agent should include a signed letter from the foreign sponsor that identifies them as the U.S. agent. In that section, there is now a reference to the P&P 1243.2020, and it was added to the reference section as well.

August 31, 2023 – Cyclical quality systems review completed, and minor formatting updated. 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.