OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

INVESTIGATIONAL FOOD-USE AUTHORIZATIONS: THE ROLE OF THE TARGET ANIMAL DIVISION REVIEWER

I. PURPOSE

This document describes the processes performed by the primary reviewer (PR) in the target animal divisions (TADs) in the Office of New Animal Drug Evaluation (ONADE) in response to requests for investigational food-use authorizations (IFUAs).[1] The processes include:

- defining the IFUA;
- assessing the submission and routing the consulting review request;
- handling IFUA requests included in a request to open an investigational file (A-0000 submission) and/or a claim of categorical exclusion (CE) or an environmental assessment (EA);
- performing actions needed when the consulting review is returned to the TAD reviewer;
- preparing an IFUA letter granting original or amended IFUAs;
- preparing an acknowledgement letter to transmit additional comments that cannot be communicated in the IFUA letter, when applicable;

[1] TADs with respect to IFUAs are the Division of Food Animals Drugs and the Division of Generic Animal Drugs. The principles in this document also apply to IFUA requests submitted to the Division of Animal Bioengineering and Cellular Therapies (DABCT), however, there are differences, and the reviewers assigned the request will evaluate requests on a case-by-case basis and make adjustments or changes to the process as needed. Review assignments are determined per division procedures and are not addressed in this document.

- preparing a letter incompleting or denying an IFUA request; and
- rescinding an IFUA.

This document DOES NOT explain the information the Division of Human Food Safety (DHFS) evaluates when responding to a request for an IFUA or the format and content of the IFUA table. For this information, see P&P 1243.4041.

II. WHAT IS AN IFUA?

An IFUA permits edible tissues from animal species treated with investigational new animal drugs to be used for food. An IFUA is issued after FDA has evaluated any potential public health hazards,[2] and determined appropriate mitigations of those hazards (e.g., explanation, withdrawal period requirement) to ensure the safety of the edible products (e.g., tissues, milk, eggs, honey) entering the human food chain. Sponsors of (generic) investigational new animal drug files [(J)INADs] may request permission to use clinical investigational animals or their edible products as human food. ONADE may grant these requests after an appropriate review under the provisions of 21 CFR 511.1(b). Sponsors must wait until they receive official concurrence from the Director of ONADE (i.e., via an IFUA letter), before they use investigational animals for human food purposes [21 CFR 511.1(b)(4)(v)(a)].

We code IFUA requests as O (original) or D (amended) submissions in the Submission Tracking and Reporting System (STARS). All IFUA requests are received by the TADs (assigned to the PR) and then consulted to the appropriate Environmental Team [Environmental Team 1 (HFV-161) or Environmental Team 2 (HFV-162)],[3] and if necessary, are consulted to the DHFS (see Section III – Steps 4 and 5).

CVM encourages drug sponsors to request an appropriate number of animals, commensurate for their anticipated investigational studies, when requesting the original IFUA. An IFUA is issued for a specific treatment regimen (i.e., route of administration, drug formulation, dose, dosing frequency, or class of animals to be treated) which may cover several indications under investigation. In some instances, however, the sponsor may need to amend an original authorization to provide for additional animals or to refine the treatment regimen. A request to amend the original authorization is not typically needed for a new indication, unless that indication falls outside of the authorized treatment regimen. A new CE may need to be submitted if the new clinical investigations are outside of the scope of previously accepted CE (see Step 4). Also, if the original authorization is limited by the amount of human food safety (HFS) information available at the time of the request, we may initially assign longer investigational withdrawal periods or milk discard times. These may be shortened via amended IFUA requests after the sponsor submits additional HFS information to their (J)INAD.

2 In most cases, the term "investigational animals" in our authorization letters refers to animals treated with the investigational new animal drug. However, in some cases, the IFUA may also include animals treated with the vehicle (i.e., excipient components of the formulation) or treated with a separate positive or negative control. The DHFS includes the appropriate information in the authorization table in the 'Other Restrictions or Conditions' section (or, if necessary, a separate table) if these animals are included in the authorization.

3 Environmental Team 1 is primarily responsible for the review of therapeutic drugs (including antiparasitics, antimicrobials, and non-heritable gene therapies) and import tolerances. Environmental Team 2 is primarily responsible for the review of reproductive and production drugs, DABCT products, and food additive petitions.

III. INITIAL ASSESSMENT OF THE SUBMISSION BY TAD (AA) REVIEWER

The PR should conduct an initial assessment of the submission within the first five days using the checklist below. The TAD reviewer performing the AA review (i.e., PR or you) assesses the completeness and accuracy of the submission but does not perform the scientific review of the toxicology, residue chemistry, and/or antimicrobial resistance information in the submission. The latter is performed by the DHFS consulting reviewer (CR) (see P&P 1243.4041).

A. Step 1: Does the Request Contain Sufficient Information?

Review the information in Items 1 through 9 below to ensure it is complete and consistent with your understanding of the sponsor's proposed project(s) under their (J)INAD. Before requesting a consulting review from DHFS, conduct an initial assessment of the submission and determine whether the information is sufficiently complete for review. In general, the minimum information necessary for an original or amended IFUA review is as follows:

1. chemical composition of the experimental drug product(s), including at least the full chemical name of the active ingredient(s) and not just the active moiety (when applicable), and percentages and/or concentrations of the active ingredient(s) and all excipient(s). If the sponsor is proposing to investigate new uses of an already approved new animal drug or approved human drug, they should identify the proprietary and established names of the drug product, the (abbreviated) new animal drug application ((A)NADA) or new drug application (NDA) number under which it is approved, and the reference listed new animal drug (RLNAD) for generic animal drugs;

2. maximum dose (or dose range) per animal (i.e., mg/kg or mg/lb) or maximum drug concentration or concentration range per unit of feed or water (i.e., g/ton, ppm, or mg/mL); for salts, whether the expression of concentration/ strength of the drug(s) is based on the active moiety or the active ingredient (e.g., 10 mg "drug hydrochloride", equivalent to 8.5 mg "drug", per kg body weight). Remember to consider whether the maximum dose or dose range requested will be adequate to cover the protocol of all of the studies to be conducted on animals that would likely enter the food chain, not just for the proposed dose or dose range of the product (e.g., proof-of-concept studies, pharmacokinetics (payout) studies, effectiveness studies). However, the dose (or dose range) should be reasonably consistent with the projected conditions of use. Inform the sponsor to request additional treatment regimens in an amended IFUA, if needed;

3. for combination, sequential, or similar uses, the composition of other drugs that will be used with the experimental product in investigational studies;

4. dosage form(s);

5. route(s) of administration;

6. frequency and duration of dosing. Remember to consider if the maximum duration will be adequate to cover the protocol for all studies to be conducted on animals that would likely enter the food chain, not just for the proposed duration of the product (e.g., if they are conducting studies at longer duration for evaluation of reproductive safety or to determine payout kinetics);

However, frequency and duration of dosing should be reasonably consistent with the projected conditions of use. Inform the sponsor to request additional treatment regimens in an amended IFUA, if needed].

7. target animal species and classes;

8. number(s) of animals requested. Verify that the number of animals requested for their proposed studies or the requirements for approval is adequate. If the sponsor requests authorization for a number of animals that seems excessive, or if the requested number would raise public health concerns based on the information provided, we may grant fewer animals than the sponsor requested. In addition, if the sponsor has requested too few animals, the TAD PR should contact the sponsor to discuss the appropriate number of animals to use. If the sponsor agrees that increasing the number of animals is warranted, they should be instructed to submit an amendment to the submission.

9. any approved new animal drugs that may be used either in conjunction or separately with the investigational animal drug, and the specific conditions of use for the approved new animal drugs in the investigational studies.

If the IFUA request does not contain the information listed in 1 through 9 above, or if you consider the sponsor's request to be deficient for another reason, discuss the submission with your team leader (TL), and if appropriate, the DHFS TL(s). CVM will not attempt to remedy incomplete or poor-quality submissions. If it is agreed that the IFUA request does not contain sufficient information for review, reviewers follow the procedures in P&P 1243.2050. If the deficiencies are minor, request an amendment (see P&P 1243.3026).

B. Step 2: Ensure Consistency in the Submission

Look through the entire submission, to determine the purpose(s) of submission and the information included. If there are inconsistencies in the information provided in the eSubmitter report, cover letter, and/or attachments to the submission, refer to ONADE's "eSubmitter Policy" on the Office Policy Page for the appropriate action.

C. Step 3: Does the Submission Contain More Than One Request?

If the IFUA request is included within an A-0000 submission, follow the instructions in P&P 1243.4000. If the IFUA request includes a claim of CE or an EA, inform the sponsor that the information should be resubmitted, using the appropriate submission code, to the appropriate Environmental Team. Document in your review and letter that the additional request was not reviewed under the IFUA request and the sponsor was notified to resubmit the information. If the sponsor indicates that they intend to render the investigational animals for use as animal feed ingredients, the TAD PR should be aware that CVM no longer provides authorization for rendering of investigational animals. The TAD PR should inform the sponsor that rendered animals are not used for human food.

D. Step 4: Request a Consult from Environmental Team 1 (HFV-161) or Environmental Team 2 (HFV-162)

The TAD PR requests a consult to the appropriate Environmental Team when an FUA request is received. The Environmental Team reviewer: 1) determines

whether there are any discrepancies between the IFUA request and a previously accepted CE; 2) determines if a new CE, EA, or EIS is necessary; and 3) informs the TAD reviewer of the decision (see P&P 1243.7220 for further information on environmental review considerations).

NOTE to the TAD reviewer: The IFUA may be granted if a CE or EA has been submitted, but not yet reviewed by the Environmental Team. Requests for amended IFUAs that ONLY ask for additional animals do not require a consulting review by the Environmental Team. Similarly, requests for amended IFUAs that ONLY ask for a waiver of the requirement for notification of the date and place of slaughter do not require a consulting review by the Environmental Team. Contact the appropriate Environmental Team if you are unsure whether a consulting review request is appropriate.

E. Step 5: Request a DHFS Consulting Review

If the information is sufficiently complete for review, request a consulting review from the DHFS (see P&P 1243.3200). The DHFS determines which team has the "lead" and requests second-level consults as needed. If it is not clear whether you or the DHFS reviewer should review specific information included in the submission, provide clarification in the instructions for the CR when completing the request in Appian. If the sponsor submits minor amendments, including increases in number of animals requested, be sure to consult them to DHFS.

NOTE to the TAD reviewer: Requests for amended IFUAs that ONLY ask for additional animals do not require review by DHFS. Similarly, requests for amended IFUAs that ONLY ask for a waiver of the requirement for notification of the date and place of slaughter do not require review by the DHFS. In these cases, the TAD PR generates a table to be included in the amended IFUA letter based on the most recent applicable authorization. Note that original or amended IFUAs that include discard of liver or kidney, injection site or implant removal, or other nonstandard slaughter practices cannot have the notification of the date and place of slaughter requirement waived. Contact the DHFS to determine if a consulting review request is appropriate.

IV. OVERVIEW OF REVIEWER RESPONSIBILITIES

The DHFS CR reviews the information in the submission and determines whether to recommend granting, incompleting, or denying an IFUA. See P&P 1243.4041 for a description of the type of information the DHFS will review for an IFUA. The TAD PR may also determine that the request should be denied or incompleted (see Section X). The TAD PR and DHFS CR should coordinate all amendment requests to minimize the number of amendments needed from the sponsor (see P&P 1243.3026). Note to the TAD PR: be sure to consult minor amendments to the DHFS CR.

The TAD PR:

- prepares the AA review and the letter to the sponsor (i.e., either an authorization granted, incomplete, or denied letter); and
- determines the target animal "Species" and "Class" information and ensures that the sponsor's proposed terminology is as accurate and complete as possible at this stage of the investigation (e.g., the sponsor may use multiple animal classes during non-pivotal studies and then refine their target class based on

results). The terminology (e.g., dosage form, route of administration, species, class) should be consistent with the TAD AA reviewer's understanding of the investigations proposed under the (J)INAD, and with CVM's current standard terminology.[4]

Once determined, inform the DHFS and Environmental Team CRs of the "Species" and "Class" terminology as soon as possible, and no later than one month after creating the consulting review. If the sponsor's proposed "Species" and "Class" terminology is not appropriate, is unclear, deficient, and/or if there are inconsistences within the submission, discuss with your TL and then email the sponsor to propose more appropriate terminology or get clarification. Confirm that CVM's proposed revised terms adequately cover the animals the sponsor intends to use in the investigational studies. Attach the email communications with the sponsor to the TAD AA review (see Section V.A) and inform the CR(s). Also, be sure to inform the CRs if there should be a change in terminology and/or number of animals authorized from what the sponsor requested, as described above in Section III, Step 1, item 8.

Based on the information provided in the submission, the DHFS recommends one of the following actions:

- Grant authorization - The request for an IFUA is appropriate and conditions for the safe use of the investigational new animal drug in the requested target animal species and class are provided;
- Authorization incomplete - The request for an IFUA is incomplete because additional information is needed in order for ONADE to make determination to grant or deny the request that cannot be remedied in an amendment; or
- Deny authorization – Deny the request for the IFUA until the sponsor provides requested information and ONADE determines that the information is acceptable.

If the DHFS recommends that authorization be granted:

- At least seven (7) business days before the consulting due date, the DHFS reviewer emails a proposed IFUA table to the TAD PR and the TAD TL. In the email, the DHFS reviewer indicates when they would like to have a reply from the PR and gives ample time for review of the table (at least 3 business days). The TAD PR discusses the proposed table with their TL. The reviewer, their TL, and the DHFS reviewer ensure that the proposed table accurately describes the investigational drug(s), investigational animals, intended dosing regimen, investigational withdrawal period and/or milk discard time, and any other restrictions or conditions. As appropriate, they consider other information in the (J)INAD when reviewing the proposed table (see Appendix 1 for additional considerations for specific new animal drug products regarding cattle ear implants).
- The TAD PR prepares an AA review (see Section V.A), ensuring that all requests and information in the submission and amendments are addressed in the IFUA table or letter; e.g., investigational labeling, request for a waiver from the

4 Consider Appendix III in CVM's GFI #191 for recommended terminology for classes of major food animals. Note that in some cases, broader terms that include multiple classes may be appropriate to cover the investigational studies under the (J)INAD before the final target animal is determined for the intended product.

requirements for notification of the date and place of slaughter, etc. (see Section V.A.4).

- The TAD PR prepares the appropriate IFUA letter, (e.g., terrestrial, aquaculture, original or amended) (see Sections VI and VII, respectively). The TAD PR may request a copy of the authorization table in Word from the DHFS reviewer to facilitate preparation and formatting of the letter.
- If applicable, the TAD PR prepares a separate Acknowledgement Letter to transmit additional comments (see Section VIII).

If the DHFS recommends that authorization be denied, see Sections V.B. and IX.

V. CONTENTS OF THE TAD (AA) REVIEW

Prepare a review document using the Office template as instructed in P&P 1243.3009.

A. If the IFUA Request is Being Granted.

The AA review document should do the following.

1. Indicate the type of letter(s) to issue (i.e., auth grnt or ack/auth).

2. The relevant email(s) from the DHFS reviewer to the TAD and subsequent emails regarding authorization table concurrence prior to returning the consulting review should be included.

3. If additional revisions to the authorization table are required after the DHFS consult is returned, the TAD PR describes in their review any minor changes that they made to the authorization table. Generally, the TAD PR transmits the authorization conditions as provided in the table from the DHFS consulting review. If changes to the authorization table are needed that were not previously identified, contact the DHFS reviewer and discuss what changes to make. Summarize these discussions and the agreed upon changes to the authorization table in the AA review. The review should include DHFS concurrence on any changes made to the table (i.e., attached email from the DHFS reviewer).

4. If there was a need to communicate with the sponsor or DHFS about the proposed Species and/or Class, the record of these communications and their outcome should be summarized in the AA review. Pertinent emails should be attached to the review.

5. Address any other allowable requests (i.e., requests that do not require separate submissions) made by the sponsor in the submission and amendments. Examples of additional requests include, but are not limited to:

    - Inclusion of investigational labeling

      If the sponsor includes investigational labeling (or labeling language) in the submission, state whether it is acceptable (i.e., does the investigational caution statement match the statement provided in 21 CFR 511.1?). If the sponsor does not submit investigational labeling to the (J)INAD file, note that in the AA review and use the boilerplate language provided in the template for the letter.

- Request for a waiver from the notification of slaughter requirement

  For eSubmitter submissions, check whether this request is marked in the eSubmitter form. If the sponsor requests, we may waive the requirement for notification [21 CFR 511.1(b)(5)(iii)] of the date and place of slaughter only if the sponsor states that investigational animals will remain under investigational conditions and under their supervision for the established drug investigational withdrawal period. Use the boilerplate language provided in the letter template. Remember that IFUAs that include discard of liver or kidney, injection site or implant removal, or other nonstandard slaughter practices cannot have the notification of date and place of slaughter waived. If a waiver is not granted, notification of the intent to slaughter investigational animals for human food are submitted to CVM as an S (slaughter notification) submission in STARS. Typically, a reply to the sponsor is not necessary and the reviewer will close out the submission with a final action of FNR or FNR w/Memo.

  A waiver from the requirement for notification of slaughter is not applicable to animals that are not subject to United States Department of Agriculture/Food Safety and Inspection Service (USDA/FSIS) inspection. As of March 1, 2016, USDA/FSIS has jurisdiction over all terrestrial animals and *Siluriformes* fish that are harvested and sold for human food in the United States (9 CFR Parts §§ 530–561.2). We refer to *Siluriformes* fish as catfish in the document for simplicity because this is the most commonly marketed in the United States of the *Siluriformes* order. Use the boilerplate language provided in the applicable aquaculture IFUA letter template when a sponsor requests a waiver for animals that are not applicable (e.g., salmonids).

- Simultaneous use of specific approved new animal drugs

  The sponsor may ask to simultaneously administer specific approved new animal drugs to investigational animals. If this is determined by the DHFS reviewer to be acceptable, it is addressed in the IFUA letter, e.g., in the "Additional Comments" section below the IFUA table, including the names of all drugs the sponsor intends to use and the conditions of use. If simultaneous administration of any specific approved new animal drugs to investigational animals is determined by the DHFS reviewer to require a different investigational withdrawal period and/or milk discard time, these are addressed in the IFUA table.

NOTE to the reviewer: such requests may be intended only for pilot studies; acceptability of simultaneous use of other drugs for an IFUA does not necessarily mean that this use will be acceptable in protocols and studies intended to provide safety data or substantial evidence of effectiveness.

6. If the submission is an amended IFUA request, summarize the status of previous authorizations granted under the (J)INAD. Amended IFUAs may replace (i.e., supersede) previous authorizations, or be granted in addition (i.e., concurrent) to previous authorizations. For example, we may replace a previous authorization if only the number of animals changes and all other conditions of a previous authorization remain the same, or when the administrative record is not clear about the conditions of the previous authorization. When we replace a previous authorization, the number of

animals authorized previously is also replaced (i.e., the animal count starts over with the replacement authorization, regardless of how many animals were remaining in the previous authorization).

Concurrent authorizations are appropriate when the sponsor wishes to continue to investigate the drug under the conditions of the previous IFUA(s), but also under conditions where one or more of the conditions of a previous authorization are different. These differences might be in the class of a species, dose or dose range, formulation, delivery system (e.g., different implant; when applicable), and/or new variation within a major route of administration (i.e., intramuscular (IM) vs. subcutaneous (SC) injection).

The AA review and letter should clearly indicate the status of each previous authorization granted. For each authorization, note whether it is still valid, or whether it was replaced by a subsequent authorization.

When determining the total number of animals granted for an amended IFUA, refer to Appendix 2 for examples.

To keep track of all previous IFUAs granted under the (J)INAD, the following table is recommended for inclusion in the AA review for all amended IFUAs. Whenever a new amended IFUA is requested, copy the table from the previous amended authorization granted, insert it in the AA review for the new amended IFUA, and update it appropriately. If this is the first amended IFUA request or no table was included in the previous review, create one for this review.

Table 1. Example of a table in the TAD AA review to summarize the status of previous IFUAs

Submission identification	**Authorization letter date**	**Summary of authorization terms**	**Status**
I-123456 O-0001	January 11, 2007	200 lactating dairy cows treated with drugimycin at up to 10 mg/kg once by SC injection; 24-hour milk discard and 5-day withdrawal period assigned; waiver of notification of slaughter granted.	replaced by D-0011
I-123456 D-0011	May 17, 2007	request for 1,000 additional animals treated as described in O-0001	currently valid; replaced O-0001
I-123456 D-0019		600 lactating dairy cows treated with drugimycin up to 10 mg/kg once by IM injection (new route); 24-hour milk discard and 5-day withdrawal period assigned; waiver of notification of slaughter granted.	current submission; valid upon issue of current amended authorization; does not replace D-0011

7. Provide any additional comments from the TAD AA reviewer and CRs to transmit in the letter(s). These comments vary depending on the type of information submitted, and/or division procedures.

B. If the IFUA Request is Being Denied or Incomplete.

The TAD PR summarizes the basis for denial or incompletion and any decisions or discussions beyond the information in the DHFS review in their review. In the review, the reviewer indicates that an auth deny letter or incomplete letter will be issued.

VI. PREPARING AN ORIGINAL IFUA LETTER

Use the applicable original IFUA letter template. The Office Director (OD) is the signature authority for IFUA letters. In addition to the authorization table, the original IFUA letter includes:

- boilerplate language regarding the Notice of Claimed Investigational Exemption (NCIE) forms and other important information from the regulations. Do not change or delete these paragraphs;
- for products used in terrestrial species or catfish, a paragraph regarding the requirement for notification to CVM and USDA/FSIS of the date and place of slaughter. We may waive notification if requested by the sponsor (and there are no nonstandard slaughter practices, such as discard of liver or kidney, injection site or implant removal included in the IFUA). Choose the correct notification paragraph based on the information submitted and whether the sponsor requested to waive notification of slaughter;
- additional boilerplate paragraphs regarding investigational labeling, if needed;
- an "Additional Comments" section. Include the boilerplate comments and add any other comments determined to be appropriate from the DHFS review or your review; and
- if authorization is granted for a terrestrial species or catfish, include a cc: block with "USDA/FSIS" indicated below the enclosure line. The RIM Team/Document Control Unit (DCU) will issue a copy of the letter and any other corresponding documents to USDA/FSIS.

NOTE: For aquaculture IFUA letters, only those authorizations that include catfish should have a copy sent to USDA/FSIS. Because USDA/FSIS only inspects catfish and terrestrial animals, all other aquaculture IFUA letters are not sent to USDA/FSIS.

VII. PREPARING AN AMENDED IFUA LETTER

Use the applicable amended IFUA letter template. The ONADE Director is the signature authority for amended IFUA letters. In addition to the authorization table, the amended IFUA letter includes:

- language clarifying the status of previous authorization(s). Use the appropriate paragraph(s). See Appendix 3 for examples of how to use the boilerplate language;
- boilerplate language regarding the NCIE forms and other important information from the regulations. Do not change or delete these paragraphs;

- for products used in terrestrial species or catfish, a paragraph regarding the requirement for notification to CVM and USDA/FSIS of the date and place of slaughter. We may waive notification if requested by the sponsor (and there are no nonstandard slaughter practices, such as discard of liver or kidney, injection site or implant removal included in the IFUA). Choose the correct notification paragraph based on the information submitted and whether the sponsor requested to waive notification of slaughter;
- additional boilerplate paragraphs regarding investigational labeling, if needed;
- an "Additional Comments" section. Include the boilerplate comments and add any comments determined to be appropriate from the DHFS review or your review; and
- If authorization is granted for a terrestrial species or catfish, include a cc: block with "USDA/FSIS" indicated below the enclosure line.[5] The RIM Team/Document Control Unit (DCU) will issue a copy of the letter and any other corresponding documents to USDA/FSIS;

NOTE: For aquaculture IFUA letters, only those authorizations that include catfish should have a copy sent to USDA/FSIS. Because USDA/FSIS only inspects catfish and terrestrial animals, all other aquaculture IFUA letters are not sent to USDA/FSIS.

VIII. PREPARING A SEPARATE ACKNOWLEDGEMENT LETTER TO TRANSMIT ADDITIONAL COMMENTS

In the rare situation in which we need to convey comments to the sponsor that do not relate directly to the IFUA and/or cannot be shared with USDA/FSIS (e.g., if the information is proprietary), prepare a separate acknowledgement (ACK) letter to the sponsor. For example, if agreed upon by the DHFS reviewer, this might include findings/recommendations from the DHFS review that will help the sponsor reduce their investigational withdrawal period and/or milk discard time for the investigational drug.

If you send separate letters (ACK and AUTH), add a sentence to the first paragraph of each of the letters indicating a separate letter transmits additional comments. Follow the format for letters provided in P&P 1243.3010. The TAD division director (DD) is the signature authority for the acknowledgement letter. Include both letters (ACK and AUTH) in the final action package, choose ACK/AUTH as the final action code in Appian, and send both letters to the sponsor.

IX. PREPARING A LETTER WHEN AN IFUA IS INCOMPLETE

In some instances, we will incomplete an IFUA. In these cases, prepare an IFUA incomplete letter using the IFUA incomplete letter template. The OD is the signature authority for authorization incomplete letters. For example, we will incomplete an IFUA:

- if the DHFS identifies potential HFS concerns that require additional information to mitigate the concern or make a decision; or
- if the sponsor has not submitted an appropriate claim of CE or EA and an EIS has not been prepared for the investigational use of the drug product under

5 USDA/FSIS is included in the cc: block in letters granting only a waiver of notification of slaughter (e.g., an amended authorization in which the sponsor did not request a waiver in the original authorization request).

the (J)INAD. Refer to P&P 1243.7220 Section III.A.2 for boilerplate language to include in the comment section of the letter.

Generally, when we incomplete an IFUA, we provide the information needed in order to complete the evaluation in the letter. If the sponsor provides the information in a new IFUA request and if we find that information acceptable, we may grant the IFUA. In final action package, choose AUTH INC as the final action code in Appian. Include the HFS DD in the Appian sign-off clearance chain for IFUAs that are incomplete.

X. PREPARING A LETTER WHEN AN IFUA IS DENIED

In some instances, we will not grant an IFUA. In these cases, prepare an IFUA denied letter denying the IFUA request. The TAD PR contacts the ONADE Policy Team to discuss the possibility of a denial and may ask the DHFS reviewer to participate in that discussion. The OD is the signature authority for authorization denied letters. For example, we will deny an IFUA:

- if the DHFS identifies potential HFS concerns that cannot be mitigated for the proposed investigational use;
- the sponsor is unduly prolonging investigational use.

Generally, when we deny an IFUA, we provide the reasons for the denial, and if applicable, we ask for additional information in the letter. If the sponsor provides the information in a new IFUA request and we find that information acceptable, we may grant the IFUA. In the final action package, choose AUTH DENY as the final action code in Appian. Include the HFS DD in the Appian sign-off clearance chain for IFUAs that are denied.

XI. ASSEMBLING AND ROUTING THE FINAL ACTION PACKAGE

A. Assembling the Final Action Package in Appian

Follow the procedures described in P&Ps 1243.3005 and 1243.3030 to prepare clean electronic documents and assemble the final action package. The final action package includes the PR's and CR's reviews and the letter(s) to the sponsor.

B. Routing the Final Action Package

After the consulting review from DHFS is returned, the PR completes their review and the appropriate letter(s) and forwards the electronic documents for review through the appropriate team or division supervisory chain following division procedures. Note: Appian sign-off is NOT initiated during the initial review of the package; instead, informal methods (i.e., email) should be used to notify the next person in the chain that the package is ready for their review.

When the package is ready for a Quality Control (QC) review from the Quality Assurance (QA) Team, follow the procedures in P&P 1243.3210. Allow approximately four (4) days for return of the QC consult.

In the final action package, choose AUTH GRNT, AUTH INC, AUTH DENY, or ACK/AUTH as the final action code in Appian. The IFUA Appian sign-off clearance chain includes the TAD AA reviewer, TAD TL, TAD DD, (HFS DD, if applicable), QA TL, and the OD. The TAD director is the signature authority for the acknowledgement letter when ACK/AUTH is the final action.

NOTE to the reviewer: Include the HFS DD in the Appian sign-off clearance chain for IFUAs that are denied, incomplete, or rescinded.

Table 2: The appropriate sign-off or clearance chain that should be used in Appian

If we:	**Choose this final action**	**TAD reviewer**	**TAD TL**	**HFS DD**	**TAD DD**	**QA TL**	**OD**
grant the FUA	AUTH GRNT	X	X	n/a	X	X	X
grant the FUA and provide separate comments	ACK/ AUTH	X (both letters)	X (both letters)	n/a	X (both letters)	X (auth letter)	X (auth letter)
incomplete the FUA	AUTH INC	X	X	X	X	X	X
deny the FUA	AUTH DENY	X	X	X	X	X	X
rescind the FUA	ACK	X	X	X	X	X	X

XII. RESCINDING AN IFUA

If, at some point after an IFUA is granted, CVM determines that investigational food-use is no longer consistent with the public health or that the sponsor is unduly prolonging investigational food-use, we will rescind that IFUA. For example, this can occur when data implicate an ingredient in an investigational formulation as a suspect carcinogen after we have granted an IFUA. In this case, we would rescind the IFUA until (or if) public health issues are resolved. Use the following procedure to rescind an IFUA:

1. The TAD PR initiates a Q submission (per 1243.3250) and sends a consulting review request to the DHFS. The DHFS prepares a review describing the circumstances that make it necessary to rescind the authorization. The "Transmit to Sponsor" section of the DHFS consulting review indicates why we are rescinding the authorization and any "next steps" that the sponsor could take to reinstate the authorization.

2. The TAD PR prepares a letter for the sponsor, and, for products used in terrestrial or catfish species, a separate letter notifying USDA/FSIS of the rescission. The OD signs both letters. Appendix 4 contains a sample letter for when we are rescinding an authorization. Appendix 5 contains a sample acknowledgment letter notifying USDA/FSIS that we have rescinded an authorization.

3. When the package is ready for a QC review, follow the procedures in P&P 1243.3210. Allow approximately four (4) days for return of the QC consult.

4. The TAD PR follows the procedures described in P&Ps 1243.3005 and 1243.3030 to prepare clean electronic documents and assemble the final action package that includes:

    a. the PR's and CR's reviews;

    b. the letter to the sponsor; and

    c. the letter for USDA/FSIS, *if applicable*.

The USDA address is:

USDA FSIS OPPD PDS
Attn: Internal information redacted
Stop Code 3786, Room 1255
1400 Independence Avenue, SW
Washington, DC 20250-3876

5. The Appian sign-off clearance chain includes the TAD PR, TAD TL, TAD DD, HFS DD, QA TL, and the OD. The final action code is ACK in Appian.

XIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 511 New Animal Drugs for Investigational Use

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

1243.2050 - Refuse to File and Refuse to Review

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

1243.3026 – Assessing Submission Quality and Amending and Resetting the Clock on Submissions

1243.3030 - Completing Final Action Packages for Submission Tracking and Reporting System (STARS) Submissions

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

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

1243.3250 – Q Submissions Agency-Initiated Actions

1243.4000 – Processing a Request to Open an Investigational (INAD) or Generic Investigational New Animal Drug (JINAD) File

1243.4041 - Investigational Food-Use Authorizations: The Role of the Division of Human Food Safety (DHFS) Reviewer

1243.7220 – Processing Environmental Impact Submissions for New Animal Drugs

FDA Guidance for Industry

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

XIV. VERSION HISTORY

March 31, 2009 – Original version

July 7, 2009 – Updated to include new address for FSIS and other minor modifications.

October 29, 2013 – Updated to reflect electronic submission process.

October 5, 2016 – Updated to update when an authorization may be denied and updated format.

February 9, 2018-- Updated Section III on the initial assessment, including an updated list of minimum information that should be in the investigational food-use authorization request. Added process to request consults from the Environmental Team. Emphasized that we should not remedy incomplete/poor quality submissions. Added much more clarity to Section IV on what to do if the investigational food-use authorization request is "bundled" with other requests/information. Added a new Section V on "Overview of Review Responsibilities." Some updates/additions to the Section VI. Moved up the Section on preparing a separate Ack letter to come before the section on preparing a letter for denying an investigational food-use authorization. Added Appendix 1.

August 15, 2019 – Updated Sections VI and VII to remove the inclusion of rendering statements that are no longer in the templates because CVM's Compliance Policy Guide 675.400, Rendered Animal Feed Ingredients was withdrawn. Added Section IX and clarification regarding issuance of an investigational food-use authorization incomplete letter. Updated titles of P&Ps in reference section.

March 5, 2020 – Updated to clarify instructions in Section III.D. and to include AUTH INC final action code.

June 16, 2020 – Updated with minor edits and clarification to Sections II and III.E. Included information regarding the request for waiver for slaughter notification does not apply to animals not inspected by USDA in Section V.A.5.

January 6, 2021 – Updated with minor edits to clarify that the term "investigational animals" as used in our authorization letters generally means animals treated with the investigational new animal drug (i.e., not control animals unless otherwise specified in the authorization table).

February 4, 2021 – Updated section III.D. to remove the instructions for TAD when the investigational food-use authorization is going to be granted and a CE or EA has been submitted, but not yet reviewed by the Environmental Team. The TAD primary reviewer was told to inform the sponsor in the authorization letter that the CE or EA must be found acceptable or a Finding of No Significant Impact (FONSI) must be prepared before any investigational use may be conducted. This was removed as it is not in line with the regulations.

February 23, 2021 – Updated section III.E. to clarify that for amended authorizations where the Division of Human Food Safety does not get a consult and does not create a new authorization table the TAD primary reviewer will generate the authorization table for the letter based on the most recently applicable authorization modified to reflect the current authorization.

August 9, 2021 – Revised add another appendix to clarify how and when to use the boilerplate language when the FUA is an amended FUA. Updated to inform the TAD primary reviewer that they may request a copy of the authorization table in MS Word from the DHFS reviewer to facilitate preparation and formatting of the letter.

February 24, 2022 – Updated to change "environmental safety team" to "environmental team" throughout the document. Updated to revise the note on page 6 to indicate that consults are not required (instead of not typically required) for requests that are just for additional number of animals and/or waivers of notification of slaughter.

April 8, 2022 – Updated Section III.D. to clarify the TAD primary reviewer instructions for requesting a consult from the appropriate Environmental Team.

May 12, 2022 – Clarify that the notes to the reviewer in section III.D and .E are for the TAD reviewer. In section III.D clarify which types of requests require a consult.

July 14, 2022 – Quality systems review for minor formatting updates.

March 6, 2023 – USDA/FSIS informed us they were closing their Omaha, Nebraska office and would no longer receive mail there. The Omaha address was removed and the new address added to section XII 4.

APPENDIX 1 – ADDITIONAL CONSIDERATIONS FOR SPECIFIC PRODUCTS

Cattle ear implants: Ear implants for beef cattle classes are intended to be approved without a requirement that they be removed before cattle are slaughtered.[6] However, sponsors of investigational cattle ear implants sometimes will propose to remove implants before the cattle are slaughtered to reduce the investigational withdrawal period and if size and/or condition of the implants at that stage of payout do not make removal prohibitive. In this case, removal of the implants before slaughter should be included as a required condition in the "Minimum Investigational Withdrawal Period" section of the IFUA table (e.g., 3 days following removal of implant(s)).

If the IFUA will require removal of the implants before slaughter, the minimum investigational withdrawal period should be identified as starting from the time of removal.

If the IFUA will not require removal of the implants before slaughter, the minimum investigational withdrawal period should be identified as starting from the time of implantation, not after an estimated "pay-out" period after implantation.

Although ears of cattle are typically discarded after slaughter in U.S. packing plants, the IFUA table should still include in the "Other Restrictions or Conditions" section a statement that ears must be discarded at slaughter, even if implants are removed before slaughter.

Note: original or amended IFUAs that include implant removal cannot have the notification of the date and place of slaughter requirement waived. Include the following sentences to the IFUA letter. You had requested a waiver of the requirement to notify FDA of the date and place of slaughter. Please note, CVM no longer grants this waiver for authorizations that require non-standard slaughter practices, including implant or injection site removal.

6 All cattle ear implants approved by the FDA have a zero-day withdrawal period with no requirement to remove the implants before slaughter.

APPENDIX 2 – EXAMPLES OF NUMBER OF ANIMALS GRANTED FOR AMENDED AUTHORIZATIONS

Example 1- When the amended IFUA will replace the original IFUA:

In the original IFUA, the sponsor was authorized 200 lactating dairy cows treated with up to 10 mg/kg (drugimycin) once by subcutaneous (SC) injection. The current submission is a request for 1,000 additional animals treated under the same conditions. Because this authorization will replace the previous one, the number of animals requested also replaces the number previously authorized. There is no need to add or modify the number of animals based on the previous authorization. Thus, the current request should replace the previous authorization, and the total number of animals authorized should start over as of the date the sponsor receives the letter, so the number authorized in the amended authorization would be 1,000.

Example 2 - Amended IFUA to be granted in addition to original IFUA:

We previously granted the sponsor an IFUA for 1,200 lactating dairy cows treated with drugimycin at up to 10 mg/kg once by subcutaneous (SC) injection. The current submission requests 600 lactating dairy cows treated with drugimycin at up to 10 mg/kg once by intramuscular (IM) injection. Typically, this would result in concurrent IFUAs. In other words, we had previously authorized the sponsor to treat 1,200 lactating dairy cows under the initial conditions (SC injection; the actual number remaining is 1,200 minus those animals already used) AND now are also authorizing 600 lactating dairy cows under different conditions (IM injection) under the separate but concurrent amended IFUA. In this case, do not add the number of animals together, because the IFUAs differ in their treatment conditions (for this example, route of administration).

Example 3 - Amended IFUAs for aquaculture drugs:

Amended IFUAs for aquaculture drugs generally replace the previous authorization when the sponsor is asking for additional fish numbers. With each amended IFUA, the total number of animals authorized starts over as of the date the sponsor receives the letter.

APPENDIX 3 – USING THE AMENDED FUA LETTER BOILERPLATE PARAGRAPHS TO CLARIFY THE STATUS OF PREVIOUS AUTHORIZATIONS

There are three boilerplate paragraphs in the terrestrial amended FUA letter template. Typically, only one paragraph will apply to the current submission. Use the paragraph(s) that applies to your submission and delete the others.

1. Include the following paragraph when the current submission will replace (supersede) one or more previous authorizations (i.e., the previous authorization(s) named in this paragraph is/are no longer valid). See Section V.A.6 above for examples of when it is appropriate to replace (supersede) a previous authorization. Delete the paragraph if no authorizations are being replaced.

   "This authorization replaces our previous authorization letter(s) dated <January 1, 1901> (<X-0000>). The <X-0000> and <X-0000> authorization letter(s) are no longer valid. You should begin counting the number of animals used starting at zero on the date you receive our letter."

2. In most cases, it is preferable to replace (supersede) an authorization when the sponsor requests additional animals and start the animal count over at zero, as described in Appendix 2 above. However, in some cases reviewers instead choose to keep the previous authorization in place and grant additional animals (e.g., add more animals to the previously granted total). If this is the case, include the following paragraph to help the sponsor understand how many total animals they have been granted and how many they have remaining. Delete this paragraph if the current submission will replace (supersede) a previous authorization. "The total number of animals that have now been authorized for these conditions under this <INAD> (<X-0000> and <X-0000>) is <insert number>. The actual number of animals remaining is <insert number> minus any animals you have already <treated/slaughtered> for <human consumption and use in animal food>."

3. Include the following paragraph if there are any concurrent (i.e., still valid) authorizations, to explain how the sponsors should count animals under each valid authorization, including the current submission. See Section V.A.6 above for examples of when it is appropriate to have concurrent authorizations. Delete the paragraph if there are no concurrent authorizations."Your <X-0000> authorization remains valid for the conditions described in our authorization letter dated <January 1, 2018>. You should continue to count <species and if applicable, class, or conditions of treatment> under the <X-0000> authorization. You should only count <species/class or conditions of treatment> under the <X-0000> authorization.

The first two sentences should include the information for the previous authorization(s), repeated as needed for each valid concurrent authorization. The last sentence should include the information for the current submission.

Example 1: The previous authorization (O-0001) was granted for steers and will remain valid. The current submission (D-0002) grants authorization for heifers (i.e., the table in the letter only includes the information for heifers). The paragraph would look like this:

> Your O-0001 authorization remains valid for the conditions described in our authorization letter dated March 1, 2018. You should continue to count growing beef steers fed in confinement for slaughter under the O-0001 authorization. You should only count growing beef heifers fed in confinement for slaughter under the D-0002 authorization.

Example 2: For more complex situations, you may need to include more information and/or repeat the first two sentences to make it clearer to the sponsor which authorization(s) we are referring to. For example. if previous authorizations for steers (O-0006) and heifers (D-0007) treated with a subcutaneous injection of 10 mg/kg BW are still valid, and the current submission (D-0010) is authorizing food use of steers and heifers treated with a different regimen (one intramuscular injection of 15 mg/kg BW), the paragraph would look like this:

> Your O-0006 authorization remains valid for the conditions described in our authorization letter dated December 5, 2018. You should continue to count beef steers treated with one subcutaneous injection of drugimycin at 10 mg/kg BW under the O-0006 authorization. Your D-0007 authorization remains valid for the conditions described in our authorization letter dated April 17, 2019. You should continue to count beef heifers treated with one subcutaneous injection of drugimycin at 10 mg/kg BW under the D-0007 authorization. You should only count beef steers and heifers treated with one intramuscular injection of 15 mg/kg BW under the D-0010 authorization.

APPENDIX 4 – SAMPLE LANGUAGE FOR A RESCIND NOTIFICATION FOR A SPONSOR

[Note: that this is example language that notifies the sponsor that we are rescinding an IFUA that we previously granted.]

Effective immediately, we rescind the investigational food-use authorization(s) for species or class treated with <drug established name(s)> under the (generic) investigational new animal drug ((J)INAD) file J/I-XXXXXX. We rescind the authorization because we recently became aware of new information regarding the human food safety of <Proprietary Name<®™> (product established name) dosage form if not part of the proprietary or established name>. The specific information that raises new human food safety concerns is <describe the basis of the decision to rescind investigational food-use authorization>.

This letter supersedes our authorization letter dated <Month XX, XXXX (X-XXXX)>. Our decision to rescind your investigational food-use authorization(s) is based on the information described above and our desire to limit the public's exposure to a public health hazard. Please communicate this decision to your (J)INAD investigators immediately. <*For drugs used in terrestrial species or catfish, add the following sentence*: "We will notify the United States Department of Agriculture/Food Safety and Inspection Service of this decision.">

APPENDIX 5 – SAMPLE LANGUAGE FOR A RESCIND NOTIFICATION FOR USDA/FSIS

[Note that this is example language that notifies USDA/FSIS that we are rescinding an IFUA that we previously granted.]

We recently became aware of new information regarding the human food safety of <Proprietary Name<®™> (product established name) dosage form if not part of the proprietary or established name>. <Company name> is investigating the use of this product in food-producing animals under the (generic) investigational new animal drug ((J)INAD) file (J)I-XXXXXX. As a result of our findings, effective immediately, we are rescinding the investigational food-use authorization(s) for species or class treated with <drug established name> under this (J)INAD originally granted in an investigational food-use authorization letter(s) dated <Month XX, XXXX>. We are notifying <company name> of our decision in a separate letter.