
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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

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I. PURPOSE

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

The processes include:

- Defining the investigational food-use authorization;
- Assessing the submission and routing the consulting review request;
- Handling investigational food-use authorization requests included in a request to open an investigational file (A-0000 submission) and/or requests for categorical exclusion or an environmental assessment;
- Action needed when the consulting review is returned to the TAD reviewer;

¹ "Target animal divisions" with respect to investigational food-use authorizations are the Division of Production Drugs, the Division of Therapeutic Drugs for Food Animals, and the Division of Generic Animal Drugs. The principles in this document also apply to investigational food-use authorization requests submitted to the Animal Bioengineering and Cellular Therapies Team, 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.

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- Preparing an investigational food-use authorization letter granting original or amended investigational food-use authorizations;
 - Preparing an acknowledgement letter to transmit additional comments that cannot be communicated in the investigational food-use authorization letter, when applicable;
 - Preparing a letter incompleting an investigational food-use authorization request;
 - Handling a denial of an investigational food-use authorization request, and
 - Rescinding an investigational food-use authorization.

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

II. WHAT IS AN INVESTIGATIONAL FOOD-USE AUTHORIZATION?

An investigational food-use authorization permits edible tissues from animal species treated with investigational new animal drugs to be used for food. An investigational food-use authorization is issued after FDA has evaluated any potential public health hazards², and has determined appropriate mitigations (e.g., explantation or withdrawal period requirement) of those hazards to ensure the safety of the edible products (e.g., tissues, milk, eggs, and honey) entering the human food chain.

Sponsors of investigational new animal drug files (INADs) or generic investigational new animal drug files (JINADs)³ 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 investigational food-use authorization letter), before they use investigational animals for human food purposes (21 CFR 511.1(b)(4)(v)(a)). Sponsors of (J)INADs may request permission to use non-clinical investigational animals or their edible products as human food if they satisfy the criteria for animals used in clinical investigations (21 CFR 511.1(b)(5) and place the label statement contained in 21 CFR 511.1(b)(1) on the investigational new animal drug.

We code investigational food-use authorization requests as O (original) or D (amended) submissions in the Submission Tracking and Reporting System (STARS). All investigational food-use authorization requests are received by the

² In some cases, the investigational food-use authorization 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 Throughout this document, (J)INAD(s) is used and is intended to include INAD(s) and JINAD(s).

TADs (primary reviewer) and then, if necessary, are consulted to the DHFS (see Section III - Step 5 below).

CVM encourages drug sponsors to request an appropriate number of animals, commensurate for their anticipated investigational studies, when requesting the original investigational food-use authorization. In some instances, however, the sponsor may need to amend an original authorization to provide for additional animals or to refine the treatment regimen (i.e., changes in route of administration, drug formulation, dose, dosing frequency, or class of animals to be treated). Additionally, if the original authorization is limited by the amount of human food safety 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 investigational food-use authorization requests after the sponsor submits additional human food safety information to their (J)INAD.

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

The primary reviewer 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., primary reviewer 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 (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 investigational food-use authorization 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 name and drug product established name, 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 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 if 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 investigational food-use authorization, 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 investigational food-use authorization, 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 primary reviewer 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 investigational food-use authorization 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, and if appropriate, a team leader(s) in the DHFS. If the deficiencies are minor, an amendment may be requested.

If it is agreed that, on its face, the investigational food-use authorization request does not contain sufficient information for review, reviewers will follow the procedures in P&P 1243.2050 Refuse to File and Refuse to Review.

B. Step 2: Ensure consistency in the submission

Look through the entire submission to determine the purpose(s) of the 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 investigational food-use authorization request is included within an A-0000 submission, follow the instructions provided in P&P 1243.4000 Opening an Investigational File. If the investigational food-use authorization request includes a request for categorical exclusion or an environmental assessment, inform the sponsor that the information should be resubmitted, using the appropriate submission code, to the Environmental Safety Team. Document in your review and in the letter that the additional request was not reviewed under the investigational food-use authorization request and the sponsor was notified to resubmit the information.

D. Step 4: Request a consult from Environmental Safety Team

If a categorical exclusion (CE) or environmental assessment (EA) has not been submitted, the TAD reviewer should contact the sponsor and inform them that an appropriate claim of CE or an EA must be submitted prior to the granting of an investigational food-use authorization.

If a CE or EA has been submitted, then the TAD reviewer should request a consult from the Environmental Safety Team. The reviewer on the Environmental Safety Team will determine if a claim of categorical exclusion (CE) or an environmental assessment (EA) for the investigational use of the drug product under the (J)INAD that has been submitted or accepted, or an Environmental Impact Statement (EIS) that has been prepared, for the investigational use of the drug product under the (J)INAD are appropriate for the investigational food-use authorization request.⁴ The CE, EA, or EIS must be for the same dose, duration, frequency, animal species/class, and indication, if applicable, as requested in the investigational food-use authorization. The Environmental Safety Team will check if any of these do

⁴ This information may be found in different STARS submission types. After 2008, the information should be in a P submission for EAs and an X submission for CEs.

not match, will determine if a new CE, EA, or EIS is necessary, and will inform the TAD reviewer of the decision.⁵

NOTE to the reviewer: Requests for amended investigational food-use authorizations that ONLY ask for additional animals do not typically require review by the Environmental Safety Team. Similarly, requests for amended investigational food-use authorizations that ONLY ask for a waiver of the requirement for notification of the date and place of slaughter do not typically require review by the Environmental Safety Team. Contact the Environmental Safety Team to determine if a consulting review request is appropriate.

If an appropriate⁶ CE or EA has been submitted, but not yet reviewed by the Environmental Safety Team, the investigational food-use authorization may be granted; however, the TAD reviewer should inform the sponsor in the authorization letter that the CE must be found acceptable or a Finding of No Significant Impact (FONSI) must have been prepared before any investigational use may be conducted.⁷

If a CE or EA is requested, the TAD primary reviewer should confirm in STARS that a CE or EA has been submitted to the Environmental Safety Team prior to due date for the investigational food-use authorization to determine if an incomplete letter should be prepared. If the claim for a CE or an EA is not received by the time that the investigational food-use authorization would be issued, the authorization should be incompleting (see Section IX).

E. Step 5: Request a DHFS consulting review

If the information is sufficiently complete for review, request a consulting review from the DHFS.⁸ 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 consulting reviewer when completing the request in Appian. If minor amendments are submitted by the sponsor, including increases in number of animals requested, be sure to consult them to DHFS.

NOTE to the reviewer: Requests for amended investigational food-use authorizations that ONLY ask for additional animals do not typically require review by DHFS. Similarly, requests for amended investigational food-use authorizations that ONLY ask for a waiver of the requirement for notification of the date and place of slaughter do not typically require review by the DHFS. Note, however, that original or amended investigational food-use authorizations that include discard of liver or kidney, injection site or implant removal, or other nonstandard slaughter practices cannot have the

⁵ See P&P 1243.7220 for further information on environmental review considerations.

⁶ Appropriate is defined as the conditions of use and species are the same as those requested in the investigational food-use authorization.

⁷ If an EIS needs to be prepared by the agency, then the agency will need to determine if it will allow investigational use to occur and will notify the sponsor once the decision has been made.

⁸ See P&P 1243.3200

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 consulting reviewer reviews the information in the submission and determines whether to recommend granting an investigational food-use authorization.⁹ The TAD primary reviewer and DHFS consulting reviewer should coordinate all amendment requests to minimize the number of amendments needed from the sponsor.¹⁰ Reminder to the TAD primary reviewer, be sure to consult minor amendments to the DHFS consulting reviewer.

The TAD primary reviewer:

- prepares the AA review and the accompanying letter for 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 primary reviewer's understanding of the investigations proposed under the (J)INAD, and with CVM's current standard terminology.¹¹

Once determined, inform the DHFS and Environmental Safety Team consulting reviewers of the "Species" and "Class" terminology as soon as possible, and no later than a 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 inconsistencies within the submission, discuss with your team leader 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 consulting reviewer(s).

Also, be sure to inform the consulting reviewers 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:

⁹ See P&P 1243.4041 for a description of the type of information the DHFS will review for an investigational food-use authorization.

¹⁰ See P&P 1243.3026 for further information on requesting amendments.

¹¹ Consider Appendix III in CVM's GFI #191 for recommended terminology for classes of major food animals. Note, however, 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.

Grant authorization - The request for an investigational food-use authorization is appropriate and conditions for the safe use of the investigational new animal drug in the requested target animal species and class are provided;

OR

Incomplete the request for authorization – The request for an investigational food-use authorization does not contain sufficient information to allow us to determine if the request is appropriate or if conditions for the safe use of the investigational new animal drug in the requested target animal species and class can be established. Therefore, we will close out the submission and issue an incomplete letter in response to the request. The FUA request will be incomplete until the sponsor provides the requested information in a new request and ONADE determines that the information is acceptable;

OR

Deny authorization – The request for an investigational food-use authorization is not appropriate and the target animals treated with the investigational new animal drug are not safe to be used as food and there are no means to mitigate that hazard.

If the DHFS recommends that authorization be granted:

- At least 7 business days before the consulting due date, the DHFS reviewer will email the TAD primary reviewer and the TAD team leader a proposed investigational food-use authorization table. The DHFS reviewer will indicate in the email when they would like to have a reply from the primary reviewer and should give ample time for review of the table (at least 3 business days). The TAD primary reviewer discusses the proposed table with their team leader. Together the reviewer and their team leader and the DHFS reviewer should 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 primary reviewer prepares an AA review (see section V.A), making sure that all requests and information in the submission and amendments are addressed in the investigational food-use authorization table or letter, e.g., investigational labeling, request for a waiver from the requirements for notification of the date and place of slaughter, etc. (see Section V.A.4).
- The TAD primary reviewer prepares the appropriate investigational food-use authorization letter, (e.g., terrestrial, aquaculture, original or amended) (see Sections VI and VII, respectively).
- If applicable, the TAD primary reviewer prepares a separate Acknowledgement Letter to transmit additional comments (see Section VIII).

If the DHFS recommends that authorization be incompleated, see Section V.B. and Section IX. If the DHFS recommends that authorization be denied, see Section V.C. and Section X.

V. CONTENTS OF THE TAD (AA) REVIEW

Prepare a review document using the Office template and the instructions provided in P&P 1243.3009.

A. If the investigational food-use authorization request is being granted.

The AA review document should:

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 primary reviewer should describe in their review any minor changes that the TAD primary reviewer made to the authorization table. Generally, you will transmit the authorization conditions as provided in the table from the DHFS consulting review. If you need to make changes to the authorization table 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 submissions submitted electronically, be sure to check if 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 treated animals will remain under investigational conditions and under their supervision for the established drug investigational withdrawal period. Use the boilerplate language provided in the template for the letter. However, remember that investigational food-use authorizations 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.

- 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 should be addressed in the investigational food-use authorization letter, e.g., in the "Additional Comments" section below the investigational food-use authorization 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 should be addressed in the investigational food-use authorization table.

NOTE to the reviewer: such requests may be intended only for pilot studies; acceptability of simultaneous use of other drugs for an investigational food-use authorization 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 investigational food-use authorization request, summarize the status of previous authorizations granted under the (J)INAD.

Amended investigational food-use authorizations 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 investigational food-use authorization(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 investigational food-use authorization, refer to Appendix 2 for examples.

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

Table 1. An example of a table created in the TAD AA review that summarizes the status of previous investigational food-use authorizations

Submission Identification	Date of Authorization Letter	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 consulting reviewers to transmit in the letter(s). These comments vary depending on the type of information submitted, and/or division procedures.

B. If the investigational food-use authorization request is being incompletd.

The TAD primary reviewer will summarize the basis for incompleting the request for authorization and any decisions or discussions beyond the information in the DHFS review in their review. In the review, the reviewer should indicate that an incomplete letter will be issued.

C. If the investigational food-use authorization request is being denied.

The TAD primary reviewer will summarize the basis for the denial and contact the ONADE Policy Team to discuss the decision and preparation of the denial letter. The discussion may need to include the consulting reviewer and team leader(s) from the Division of Human Food Safety as well. The TAD reviewer will document any discussions with the Policy Team and any subsequent discussions with the ONADE Office Director and the final decision in their review.

VI. PREPARING AN ORIGINAL INVESTIGATIONAL FOOD-USE AUTHORIZATION LETTER

Use the applicable original investigational food-use authorization letter template. The ONADE Director is the signature authority for investigational food-use authorization letters.

In addition to the authorization table, the original investigational food-use authorization letter includes:

- boilerplate language regarding the Notice of Claimed Investigational Exemption (NCIE) forms, rendering, 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 United States Department of Agriculture/Food Safety and Inspection Service (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 investigational food-use authorization). 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.
- If authorization is granted for a terrestrial species or catfish, include a cc: block with "USDA/FSIS" indicated below the enclosure line. The Records and Information Management (RIM) Team/Document Control Unit (DCU) will issue a copy of the letter and any other corresponding documents to USDA/FSIS.

NOTE to the reviewer: For aquaculture investigational food-use authorization 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 investigational food-use authorization letters are not sent to USDA/FSIS.

VII. PREPARING AN AMENDED INVESTIGATIONAL FOOD-USE AUTHORIZATION LETTER

Use the applicable amended investigational food-use authorization letter template. The ONADE Director is the signature authority for amended investigational food-use authorization letters.

In addition to the authorization table, the amended investigational food-use authorization letter includes:

- language clarifying the status of previous authorization(s). Use the appropriate paragraph(s).
- boilerplate language regarding the Notice of Claimed Investigational Exemption (NCIE) forms, rendering, 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 investigational food-use authorization). 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.
- If authorization is granted for a terrestrial species or catfish, include a cc: block with "USDA/FSIS" indicated below the enclosure line.¹² The RIM Team/DCU will issue a copy of the letter and any other corresponding documents to USDA/FSIS.

NOTE to the reviewer: For aquaculture investigational food-use authorization 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 investigational food-use authorization 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 investigational food-use authorization and/or cannot

¹² USDA/FSIS should also be included in the cc: block in letters granting only a waiver of notification of slaughter (for example, an amended authorization in which the sponsor did not request a waiver in the original authorization request).

be shared with USDA/FIS (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 director 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 INVESTIGATIONAL FOOD-USE AUTHORIZATION REQUEST IS INCOMPLETED

In some instances, an investigational food-use authorization request will be insufficient. In these cases, prepare an investigational food-use authorization incomplete letter setting forth the deficiencies in the investigational food-use authorization request that must be addressed to permit ONADE to grant the request. Use the investigational food-use authorization incomplete letter template. The TAD division director is the signature authority for authorization incomplete letters.

For example, we will incomplete an investigational food-use authorization request:

- if the DHFS identifies potential human food safety concerns that have not been mitigated for the proposed investigational use;
- 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 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 investigational food-use authorization request, we provide the reasons for the incomplete, and we ask for additional information in the letter, as appropriate. If the sponsor provides the information in a new investigational food-use authorization request and if we find that information acceptable, we may grant the investigational food-use authorization. For the time being, there is no final action code 'AUTH INC', so, until that code is implemented, in the final action package, choose ACK as the final action code in Appian. Once the AUTH INC code is available, use it for these situations. In the interim, the TAD reviewer will identify this as an incomplete food-use authorization request when filling in the review summary in Appian.

X. PREPARING A LETTER WHEN AN INVESTIGATIONAL FOOD-USE AUTHORIZATION REQUEST IS DENIED

In rare instances, an investigational food-use authorization request cannot be granted. In these cases, prepare an investigational food-use authorization denial letter. After discussing with their team leader and division director, the TAD primary reviewer should contact the ONADE Policy Team as early as possible and communicate with them about the decision to issue a denial letter. There may be additional conversations with the ONADE Office Director, as well, to communicate the intent regarding the authorization. The TAD primary reviewer prepares the denial letter for the sponsor. Follow the format for letters provided in P&P 1243.3010.

When we deny an investigational food-use authorization request, we provide the reasons for the denial. The TAD and, if applicable, the DHFS reviewers prepare a review describing the circumstances that make it necessary to deny the authorization. If the sponsor provides information to address the concerns in a new investigational food-use authorization request and if we find that information acceptable, we may grant the investigational food-use authorization. Choose AUTH DENY as the final action code in Appian. The ONADE Office Director is the signature authority for authorization denial letters.

XI. ASSEMBLING AND ROUTING THE FINAL ACTION PACKAGE**A. Assembling the Final Action Package in Appian**

Follow the procedures described in P&P 1243.3005 and P&P 1243.3030 to prepare clean electronic documents and assemble the final action package.

The final action package includes:

1. The AA and consulting reviewer's reviews.
2. The letter(s) to the sponsor.

B. Routing the Final Action Package

Once the consulting review from DHFS has been returned, the primary reviewer should complete their review and the appropriate letter(s) and forward 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. See Table 2 for information on routing and sign of for all final actions for an authorization request.

For authorizations that are granted, denied, or rescinded, the Office Director is the signing authority and require a Quality Control (QC) review. When the package is ready for a Quality Control (QC) review, follow the procedures in P&P 1243.3210, Requesting a Quality Control Review from the Quality Assurance Team. Allow approximately four days for return of the QC consult.

When we are incompleting an authorization request, the TAD division director is the signature authority for the letter. The TAD division director is also the signature authority for the acknowledgement letter when we are sending an acknowledgement letter with the authorization. Choose the ACK/AUTH final action code if we are sending an acknowledgement letter with the authorization.

In the final action package, choose AUTH GRNT, ACK/AUTH, ACK, or AUTH DENY as the final action code in Appian, as appropriate. The Appian sign-off clearance chain for investigational food-use authorizations includes the TAD primary reviewer, TAD team leader, TAD division director, (HFS Division Director, if applicable), QA Team Leader (if applicable), and the Office Director (if applicable). For information on the sign off chain for each potential outcome see Table 2.

NOTE to the reviewer: Include the HFS Division Director in the Appian sign-off clearance chain for investigational food-use authorizations that are incompleting, denied, or rescinded. (see Table 2).

Table 2. Summary of Appian Sign-Off Clearance Chain

If we are:	Choose this final action:	Appian sign-off:					
		TAD reviewer	TAD TL	HFS DD	TAD DD	QA TL	OD
granting the FUA	AUTH GRNT	X	X		X	X	X
granting the FUA and providing separate comments	ACK/AUTH	X both letters	X both letters		X both letters	X Auth letter	X Auth letter
incompleting the FUA	ACK	X	X	X	X		
denying the FUA	AUTH DENY	X	X	X	X	X	X
rescinding the FUA	ACK	X	X	X	X	X	X

XII. RESCINDING AN INVESTIGATIONAL FOOD-USE AUTHORIZATION

If, at some point after an investigational food-use authorization 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 investigational food-use authorization. For example, this can occur when data implicate an ingredient in an investigational formulation as a suspect carcinogen after we have granted an investigational food-use authorization. In this case, we would rescind the investigational food-use authorization until (or if) public health issues are resolved.

Use the following procedure to rescind an investigational food-use authorization:

1. The TAD primary reviewer initiates a Q submission 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 primary reviewer 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 Office Director signs both letters.

Appendix 3 contains a sample letter for when we are rescinding an authorization. Appendix 4 contains a sample acknowledgment letter notifying USDA/FSIS that we have rescinded an authorization.

3. When the package is ready for a quality control (QC) review, follow the procedures in P&P 1243.3210, Requesting a Quality Control Review from the Quality Assurance Team. Allow approximately four days for return of the QC consult.
4. The TAD primary reviewer follows the procedures described in P&P 1243.3005 and P&P 1243.3030 to prepare clean electronic documents and assemble the final action package that includes:
 - a. The TAD primary and consulting reviewer's reviews.
 - b. The letter to the sponsor.
 - c. The letter for USDA/FSIS, *if applicable*. The USDA address is:

Residue Staff, USDA/FSIS/PDD
Attn: John Doe, Policy Development Division
Edward Zorinsky Federal Building
1616 Capitol Avenue, Suite 260
Omaha, NE 68102
5. The Appian sign-off clearance chain includes the TAD primary reviewer, TAD team leader, TAD division director, HFS Division Director, QA Team Leader,

and the Office Director. The final action code is ACK in Appian (see Table 2 in Section XI.B.).

XIII. REFERENCES

Code of Federal Regulations (Title 21)

Part 511 New Animal Drugs for Investigational Use

CVM Program Policy and Procedure Manual

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 - Amending STARS Submissions

1243.3030 - Completing Final Action Packages for STARS Submissions

1243.3200 - Routing a Request to Obtain a Review of an INAD, JINAD, ANADA, NADA, or VMF Submission

1243.3210 - Requesting a Quality Control Review from the Quality Assurance Team

1243.4000 – Processing a Request to Open a (J)INAD 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 Drug

FDA 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 Safety 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.

April 12, 2018 – Updated to clarify there are three potential options for a request for a food-use authorization (e.g., authorization granted, authorization incomplete, and authorization denied) and update the process for signing incomplete letters.

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.¹³ 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 investigational food-use authorization table (e.g., 3 days following removal of implant(s)).

If the investigational food-use authorization 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 investigational food-use authorization 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 investigational food-use authorization 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 investigational food-use authorizations that include implant removal cannot have the notification of the date and place of slaughter requirement waived. Include the following sentences to the investigational food-use authorization 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.

¹³ 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 investigational food-use authorization will replace the original investigational food-use authorization:

In the original investigational food-use authorization, 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 1000.

Example 2 - Amended investigational food-use authorization to be granted in addition to original investigational food-use authorization:

We previously granted the sponsor an investigational food-use authorization 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 investigational food-use authorizations. 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 investigational food-use authorization. In this case, do not add the number of animals together, because the investigational food-use authorizations differ in their treatment conditions (for this example, route of administration).

Example 3 - Amended investigational food-use authorizations for aquaculture drugs:

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

APPENDIX 3 – SAMPLE LANGUAGE FOR A RESCIND NOTIFICATION FOR A SPONSOR

[Note: that this is example language that notifies the sponsor that we are rescinding an investigational food-use authorization that we previously granted.]

Effective immediately, we rescind the investigational food-use authorization(s) for species or class treated with <drug product 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<®™> (drug 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 4 – SAMPLE LANGUAGE FOR A RESCIND NOTIFICATION FOR USDA/FSIS

[Note that this is example language that notifies USDA/FSIS that we are rescinding an investigational food-use authorization that we previously granted.]

We recently became aware of new information regarding the human food safety of <Proprietary Name<®™> (drug 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 product 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.