
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

INVESTIGATIONAL FOOD-USE AUTHORIZATIONS: THE ROLE OF THE DIVISION OF HUMAN FOOD SAFETY REVIEWER

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I. PURPOSE

This document describes the role of the Division of Human Food Safety (DHFS) in the review of investigational food-use authorization requests.

It explains:

- How investigational food-use authorizations are routed to and from the DHFS;
- The information the DHFS evaluates when responding to a request for an investigational food-use authorization; and
- The response the DHFS provides to a request for an investigational food-use authorization, including the format for the Authorization Table.

See P&P 1243.4040 for information on the role of the target animal division¹ (TAD) reviewer in the investigational food-use authorization process, including final processing of the investigational food-use authorization request and sample language for when we are rescinding an authorization.

II. HOW ARE INVESTIGATIONAL FOOD-USE AUTHORIZATIONS ROUTED TO DHFS?

DHFS receives requests for investigational food-use authorizations for evaluation as consulting reviews from the TAD primary reviewer. See P&P 1243.3200 for information on routing between divisions within the ONADE and P&P 1243.4040 for the role of the primary reviewer in the investigational food-use authorization process. Once completed, DHFS sends a consulting review through Appian to the primary reviewer (see P&P 1243.3005, Creating Clean Electronic Files; P&P 1243.3009,

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 as needed. Review assignments are determined per division procedures and are not addressed in this document.

Format and Style Conventions for Reviews and Submission Summaries; P&P 1243.3029, Closing Out a Consulting Review).

III. WHAT INFORMATION DOES DHFS EVALUATE FOR AN INVESTIGATIONAL FOOD-USE REQUEST?

Note: Investigational food-use authorization requests that do not require review by the DHFS are requests that:

- ONLY ask for additional animals
- ONLY ask for waiver of the requirement for notification of date and place of slaughter.

For investigational food-use authorizations that are consulted to the DHFS, the DHFS reviewer looks through the entire eSubmitter form and all attachments, or the entire paper submission, to determine the purpose(s) of the submission and the information included. Usually an investigational food-use authorization request will only be consulted from the TAD primary reviewer if it includes the following minimum information:

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). For example, this could include batch formulas. 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) information 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);
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;
7. *Target animal species and classes;
8. **Number(s) of animals requested;

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

*The TAD primary reviewer will determine the appropriate terminology for the target animal "Species" and "Class" for investigational food-use authorization letters and informs the DHFS reviewer of that terminology within a month of creating the consulting review.

**The TAD primary reviewer will verify that an adequate number of animals is requested for the studies likely needed to complete this phase of investigation, or the requirements for approval and will let the DHFS reviewer know if additional numbers should be considered in the authorization. Alternatively, the DHFS reviewer or the primary reviewer may grant fewer animals than the sponsor requested if the number seems excessive or would raise public health concerns based on the information provided.

Where a submission is deficient or incomplete on its face, reviewers should follow the procedures in P&P 1243.2050 Refuse to File and Refuse to Review. If a minor deficiency might be remedied by an amendment, the DHFS reviewer may request an amendment through the primary reviewer or directly from the sponsor. If the DHFS reviewer will request an amendment, the DHFS reviewer will alert the TAD primary reviewer prior to the request in order to minimize the number of amendments needed from the sponsor.

The DHFS determines which team has the "lead" and requests second level consults as needed (i.e., sub-consulted). Amendments submitted by the sponsor that are consulted to DHFS should also be sub-consulted as appropriate.

The DHFS uses the data and information available to evaluate the safety of residues of the investigational new animal drug to the human consumer. The primary issues addressed in any human food safety evaluation of an investigational food-use authorization request are toxicology, residue chemistry, and when the request involves products that include or target bacteria (e.g., competitive exclusion products or probiotics, antibiotics, and other drugs with antibacterial actions), microbial food safety.

The sponsor may ask to simultaneously administer specific approved new animal drugs to investigational animals. The DHFS reviewer should determine if this is acceptable. If acceptable, it should be addressed in the investigational food-use authorization letter (Section V), (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 to require a different investigational withdrawal period and/or milk discard time, these should be addressed in the investigational food-use authorization table.

If the DHFS reviewer recommends granting authorization (see Section IV.A.), the DHFS reviewer emails the primary reviewer and the TAD team leader a proposed investigational food-use authorization table (see Section V) at least 7 business days before the consulting due date. The DHFS reviewer will indicate in the email when

they would like to have a reply from the primary reviewer; however, they should give ample time for review of the table (at least 3 business days). The primary reviewer shares the proposed table with their team leader. The primary reviewer, TAD team leader, and 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. 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 (See Appendix 1 of P&P 1243.4040 for additional considerations for specific new animal drug products regarding cattle ear implants.)

If the DHFS reviewer recommends incompleting or denying the authorization (see Sections IV.B and IV.C.). The DHFS reviewer should first discuss their recommendation with their supervisor and division director. The DHFS reviewer should also communicate with the TAD primary reviewer and TAD team leader as early as possible if the request is going to be denied.

IV. WHAT WILL DHFS PROVIDE IN THEIR CONSULTING REVIEW FOR A REQUEST?

The DHFS provides recommendations to the TAD primary reviewer in a consulting review to either grant, incomplete, or deny an authorization.

A. Investigational Food-Use Authorization Granted

When the DHFS concludes that the request for an investigational food-use authorization is appropriate, the authorization letter to the sponsor conveys the conditions of the investigational food-use authorization. The consulting review from the DHFS provides, as part of the "Transmit to Sponsor" section, the conditions of the authorization in a table (Section V).

Where applicable, the authorization or a separate acknowledgement letter also identifies the information needed to shorten the investigational withdrawal period or milk discard time. Note that a copy of the authorization letter is typically sent to USDA's Food Safety and Inspection Service (FSIS) (see P&P 1243.4040). A separate acknowledgement letter is better suited for information that is detailed, includes proprietary comments to the sponsor, and/or includes comments otherwise not appropriate to include in the authorization letter. Clearly identify comments appropriate for inclusion in a separate acknowledgement letter in the "Transmit to Sponsor" section of the consulting review.

B. Investigational Food-Use Authorization Request Incompleted

Typically, a long investigational withdrawal period or milk discard time can be assigned in order to mitigate human food safety concerns. However, when the request for an investigational food-use authorization does not contain sufficient information to complete an evaluation, the DHFS recommends incompleting of the request for the investigational food-use authorization until the requested information is provided and ONADE determines that the information is acceptable.

Include the information that the DHFS needs to continue its evaluation of the investigational food-use authorization in the "Transmit to Sponsor" section of the consulting review.

C. Investigational Food-Use Authorization Request Denied

When the request for an investigational food-use authorization contains a human food safety concern for the investigational use that cannot be mitigated, the DHFS recommends denial of the request. As soon as you become aware there is a possibility the request will be denied, contact the TAD reviewer and let them know. The TAD reviewer will contact the ONADE Policy Team to discuss the possibility of a denial and should ask the DHFS reviewer to participate in that discussion. Include the basis for the denial of the investigational food-use authorization request in the "Transmit to Sponsor" section of the consulting review.

V. AUTHORIZATION TABLE FORMAT AND CONTENT

When an investigational food-use authorization is appropriate, DHFS provides an authorization table. The format for the table is included as Appendix 1. The DHFS, except where noted below, completes the table for inclusion with the response to the sponsor. The guiding principle when filling out the authorization table is to convey clearly and concisely all necessary information associated with the conditions of the authorization. As described in Section III, the DHFS reviewer, TAD primary reviewer, and TAD team leader review the proposed investigational food-use authorization table before the consulting due date to ensure that all parties agree on its accuracy in describing the authorized investigational use of the drug.

The authorization table in the appendix assumes the simplest scenario: one investigational drug, one species, one class, one permitted dosing regimen. However, some requests for investigational food-use authorizations are more complex. When necessary, modify the basic table structure to accommodate the increased complexity for multiple classes, dosage forms, or dosing regimens within the same authorization. Alternatively, prepare separate authorization tables in response to a single investigational food-use authorization request to describe complex dosing regimens or to address concerns for positive control or vehicle control treatments. The authorization table should be modified to describe unique drug products (e.g., animal bioengineering technologies) by deleting the rows that do not apply.

Sometimes the authorization table requires revision after the consulting review is returned to the requesting TAD primary reviewer. When minor revisions to the authorization table are needed, the primary reviewer discusses the proposed changes with the reviewer in the DHFS, and agreement by all appropriate DHFS parties is documented by email. These discussions are summarized in the TAD primary review, and the email string is attached to the review.

VI. REFERENCES

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

1243.3029 – Closing Out a Consulting Review for STARS Submissions

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

1243.4040 - Investigational Food-Use Authorizations: The Role of the Target Animal Division (AA) Reviewer

VII. VERSION HISTORY

March 31, 2009 – Original version

April 7, 2009 – Revised to update authorization table (i.e., change milk discard period to milk discard time and change drug identity to drug ingredient/feed identity, add feed ingredient identity, and remove rendering).

April 23, 2013 – Revised to update version date and consulting review routing procedure.

June 15, 2016 – Modified to current format.

February 9, 2018 – Updated Section III to include the revised list of minimum information that should be in the request consistent with 1243.4040, Updated authorization table to provide clarity. Combined previous section headings into one Section V.

April 12, 2018 – Revised to clarify there are three potential outcomes for a food-use authorization request (e.g., authorization granted, authorization incomplete, and authorization denied).

August 1, 2018 – Revised to change the word 'may' to 'should' in section IV. C. This now reads that when there is a possibility the food-use authorization will be denied, the TAD reviewer should have the Division of Human Food Safety reviewer participate in the discussions with the ONADE Policy Team.

APPENDIX 1 – AUTHORIZATION TABLE FORMAT AND INSTRUCTIONS

DRUG PRODUCT IDENTITY	Enter the chemical name of the investigational new animal drug and prominent excipients to distinguish the product and appropriately limit the food use authorization. If investigational use is requested for an already approved new animal drug or human drug, instead enter the proprietary name and drug product established name.
Dosage Form	Enter the physical description of the investigational new animal drug (e.g., implant, solution, Type A medicated article).
SPECIES	Enter the name provided by the primary reviewer
Class	Enter the description provided by the primary reviewer
Number of Animals	Enter the number of investigational animals being authorized for food use.
PERMITTED DOSING REGIMEN	Enter the maximum dose (or dose range) of the investigational new animal drug.
Maximum Dose (or range)	
Route of Administration	Enter the method by which the investigational new animal drug is introduced into the animal.
Frequency and Duration of Dosing	Enter the maximum timing (frequency) and length (duration) of treatment with the investigational new animal drug.
MINIMUM INVESTIGATIONAL WITHDRAWAL PERIOD	Enter the length of time from the last administration of the investigational new animal drug until the treated animals can be slaughtered for human or animal food.
MINIMUM INVESTIGATIONAL MILK DISCARD TIME	Enter the length of time from the last administration of the investigational new animal drug until the milk from treated animals can be used as human or animal food.
OTHER RESTRICTIONS OR CONDITIONS	Enter any other restrictions on the use of the investigational new animal drug or investigational animals.