OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

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

I. PURPOSE

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

- how IFUAs are routed to and from the DHFS;
- the information the DHFS evaluates when responding to a request for an IFUA; and
- the response the DHFS provides to a request for an IFUA, including the format for the Authorization Table.

See P&P 1243.4040 for information on the role of the target animal division[1] (TAD) reviewer in the IFUA process, including final processing of the IFUA request and sample language for when we are rescinding an authorization.

II. HOW ARE IFUAS ROUTED TO DHFS?

DHFS receives IFUA requests for evaluation as consulting reviews from the TAD primary reviewer (PR). See P&P 1243.3200 for information on routing between divisions within the ONADE and P&P 1243.4040 for the role of the PR in the IFUA process. Once completed, DHFS sends a consulting review through Appian to the pr (see P&PS 1243.3005 and 1243.3029).

III. WHAT INFORMATION DOES DHFS EVALUATE FOR AN IFUA REQUEST?

Note: IFUA 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.

[1] "Target Animal Divisions" 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; 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.

For IFUAs 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 request(s) of the submission and the information included. Usually an IFUA request will only be consulted from the TAD PR 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. Requested investigational withdrawal period and/or milk discard time[2] and, if applicable, conditions for the disposition of progeny of treated animals;
8. *Target animal species and classes;
9. **Number(s) of animals requested;
10. 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 PR determines the appropriate terminology for the target animal "Species" and "Class" for IFUA letters and informs the DHFS reviewer of that terminology within one month of creating the consulting review.

**The TAD PR verifies 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 lets the DHFS reviewer know if additional numbers should be considered in the authorization. Alternatively, the DHFS reviewer or the PR may grant fewer animals than the sponsor requested if the number seems excessive or would raise public health concerns based on the information provided.

[2] Typically, requests for zero-day investigational withdrawal periods or zero-day investigational milk discard times are not granted for investigational products early in development.

Where a submission is deficient or incomplete on its face, reviewers should follow the procedures in P&P 1243.2050. If a minor deficiency might be remedied by an amendment, the DHFS reviewer may request an amendment through the PR or directly from the sponsor. If the DHFS reviewer will request an amendment, the DHFS reviewer will alert the TAD PR 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 IFUA 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 determines if this is acceptable. If acceptable, it is addressed in the IFUA letter (Sections IV and V), (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 to require a different investigational withdrawal period and/or milk discard time, these should be addressed in the IFUA table.

If the DHFS reviewer recommends granting authorization (see Section IV.A), the DHFS reviewer emails a proposed IFUA table (see Section V) to the PR and the TAD team leader (TL) at least seven (7) business days before the consulting due date. The DHFS reviewer indicates in the email when they would like to have a reply from the PR; however, they should give ample time for review of the table [at least three (3) business days]. The PR shares the proposed table with their TL. The PR, TAD TL, 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 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 (see P&P 1243.4040, Appendix 1 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 first discusses their recommendation with their supervisor and division director. The DHFS reviewer also communicates with the TAD PR and TAD TL 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 PR in a consulting review to either grant, incomplete, or deny an authorization.

A. IFUA Granted

When the DHFS concludes that the request for an IFUA is appropriate, the authorization letter to the sponsor conveys the conditions of the IFUA. 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 United States Department of Agriculture's Food Safety and Inspection Service (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. Cleary identify comments appropriate for inclusion in a separate acknowledgement letter in the "Transmit to Sponsor" section of the consulting review. After the DHFS reviewer closes out the submission in Appian, they email a copy of the Word version of the final authorization table to the TAD PR. This will facilitate proper formatting of the table in the letter to the sponsor.

B. IFUA 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 IFUA does not contain sufficient information to complete an evaluation, the DHFS recommends incompletion of the IFUA request 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 IFUA in the "Transmit to Sponsor" section of the consulting review.

C. IFUA Request Denied

When the request for an IFUA 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, inform the TAD reviewer. The TAD reviewer then contacts 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 IFUA request in the "Transmit to Sponsor" section of the consulting review.

V. AUTHORIZATION TABLE FORMAT AND CONTENT

When an IFUA 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 PR, and TAD TL review the proposed IFUA 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 IFUAs 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 IFUA 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., products handled by the Division of Animal Bioengineering and Cellular Therapies) by deleting the rows that do not apply.

Sometimes the authorization table requires revision after the consulting review is returned to the requesting TAD PR. When minor revisions to the authorization table are needed, the PR 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 Reviews 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

1243.4040 - 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 P&P 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.

August 15, 2019 - Revised to add number 7 and footnote to section III.

June 16, 2020 – Added language to table and text in section III to include the conditions for disposition of progeny of treated animals.

August 9, 2021 – Added language to Section IV to tell the DHFS review to send an email to the TAD primary reviewer with a Microsoft Word version of the final authorization table

July 14, 2022 – Quality systems review for minor formatting updates. Update to the name of the Division of Food Animal Drugs.

Jube 23, 2023 - Quality system review conducted of the document and no updates or revisions were necessary at this time. To bring all office quality system documentation into compliance with the FDA Visual Identity Program approved fonts, ONADE has adopted Arial 11-point font. The font of this document was changed from Verdana 10-point font to Arial 11-point font.

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 PR
Class	Enter the description provided by the PR
Number of Animals	Enter the number of investigational animals being authorized for food use.
PERMITTED DOSING REGIMEN Maximum Dose (or range)	Enter the maximum dose (or dose range) of the investigational new animal drug.
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. When applicable, indicate any requirements at slaughter and/or the conditions for disposition of progeny of treated animals.