Regulatory Considerations for the Approval of Drugs against Histomoniasis (Blackhead Disease) in Turkeys and Game Birds in the United States

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Introduction

- Histomoniasis is an important disease of turkeys and game birds.
- The disease is caused by *Histomonas meleagridis; Heterakis gallinarum* is an important intermediate host for *H. meleagridis* transmission.
- Effective options for treatment/control of the disease are severely limited.
  - Current farm management techniques (e.g., changing the litter between flocks, physical separation of flocks of differing ages and species, and other biosecurity measures) are often not enough to prevent spread of the disease when they are used as the sole prevention strategy.
  - The use of phytoproduct feed additives have shown little success in adequately preventing or treating histomoniasis (Bleyen et al., 2010; Hess et al., 2015).
  - A vaccination against the disease is not available due to issues with maintaining pathogenicity or technical concerns associated with vaccine production and application (Pham et al., 2013).
  - There are currently no approved animal drugs against the disease in the US.
- The FDA Center for Veterinary Medicine (CVM) is responsible for the approval of new animal drugs in the United States, is eager to work with interested parties to align the research of promising drug products against histomoniasis with the drug approval requirements, such that it leads to the approval of a new animal drug.

New Animal Drug Approval Process

Drug Discovery
- A drug product with a potential therapeutic effect against histomoniasis in turkeys or game birds is identified.

Inform CVM
- The drug sponsor can contact the CVM Office of New Animal Drug Evaluation (ONADE) to discuss the best strategy for sharing scientific information related to the new drug with CVM. [Information may be shared at early stages or after the formal step of opening an INAD file.]

INAD File
- An INAD file is established to allow the sponsor to conduct studies using the investigational drug product.

Develop-ment Plan
- CVM and the drug sponsor discuss the development plan for the new animal drug to ensure that each of the seven technical sections are addressed appropriately.

Study Data
- The drug sponsor conducts studies and submits information necessary to support each of the seven technical sections. The sponsor is encouraged to submit study protocols and receive CVM concurrence prior to conducting pivotal studies.

Technical Section Complete
- If the submitted information adequately demonstrates that the requirement for a technical section has been met, CVM issues a technical section complete letter.

NADA
- Once each of the seven technical sections are complete, the sponsor submits an administrative NADA approval package.

Drug Approval
- CVM approves the drug if the data for all technical sections, when viewed as a whole, continue to support approval.

Alternatively, the sponsor can submit all information for all technical sections at one time as a traditional NADA.

New Animal Drug Approval Process: Technical Sections

- Section 512(b)(1) of the Federal Food, Drug, and Cosmetic Act describes the information that must be submitted as part of an New Animal Drug Application (NADA).
- CVM encourages drug sponsors to follow the "phased review process" when submitting data for an NADA. Under this process, a drug sponsor submits data separately for each of the seven technical sections under an Investigational New Animal Drug (INAD) file, rather than submitting data to support each of the technical sections at once as part of a traditional NADA approval package.
- The seven technical sections required to support approval of new animal drugs intended for food-producing animal species, such as turkeys are: 1) Target Animal Safety, 2) Effectiveness, 3) Chemistry, Manufacturing, and Controls, 4) Human Food Safety, 5) Environmental Impact, 6) Labeling, and 7) All Other Information.
- Guidance for Industry (GFI) documents are available on the CVM website to assist drug sponsors to meet the requirements for different technical sections (http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm042450.htm).

Table 1. Helpful Guidance for Industry (GFI) documents

Technical Section	GFI Number
Target Animal Safety	GFI #56, GFI #104, GFI #185, GFI #215, and GFI #226
Effectiveness	GFI #56, GFI #104, and GFI #215
Chemistry, Manufacturing, and Controls	GFI #169, GFI #227, and GFI #234
Human Food Safety	GFI #3, GFI #149, GFI #152, GFI #205, GFI #206, GFI #207, and GFI #208

Target Animal Safety Technical Section

- Data requirements depend on a number of factors including pharmacology and toxicology of the drug, animal class, route of administration, indication, and dosage(s).
- Margin of Safety study: Typically includes the drug at 1x, 3x, and 5x its highest use level for a period of time that may be up to three times the duration of the maximum administration of the drug product.
- Reproductive safety: Needs to be evaluated for drugs to be used in breeding animals.
- Alternative approaches include: use of information from the literature or data from studies conducted outside the United States.

Effectiveness Technical Section

- Includes dosage characterization and demonstration of substantial evidence of effectiveness under expected use/field conditions.
- Dosage characterization: Includes information such as a dose titration study using recent field isolates of the parasite, a pilot effectiveness study, *in vitro* studies, or scientific literature.
- Demonstration of substantial evidence of effectiveness:
  - Typically includes one or more adequate and well-controlled studies conducted in the U.S. that include the measurement of appropriate variables to show the effectiveness of the drug and provide inferential value.
- Alternative approaches include: Quantitative data synthesis methods, such as meta-analysis, data from studies conducted outside the United States, or results from validated model or *in vitro* studies.

Human Food Safety Technical Section

- Includes a description of practicable methods for determining 1) the quantity, if any, of a) residues including metabolites of the new animal drug or b) any substance formed in or on edible food products from treated target animals, and 2) a proposed tolerance, withdrawal period, or other use restrictions, in order to ensure that the proposed use of the drug will be safe to humans.
- Contains any relevant information or data relating to toxicology, microbial food safety (if the new animal drug is an antimicrobial or otherwise exhibits antimicrobial properties), and residue chemistry.

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Chemistry, Manufacturing, and Controls Technical Section

- Contains complete information regarding the manufacture of the new animal drug active ingredient and the new animal drug product.
  - Includes information on personnel; facilities; the drug's identity, strength, components, and composition; procedures to characterize drug substance and potential impurities, and packaging.
  - Includes manufacturing procedures to ensure consistent production of the drug, analytical specifications and method validations, and stability data to support the expiry periods and storage conditions.

Environmental Impact Technical Section

- Includes either an environmental assessment (EA) under 21 CFR 25.40, or a request for categorical exclusion under 21 CFR 25.30 or 25.33.
  - If a categorical exclusion is requested, the sponsor must include a statement of compliance with the categorical exclusion criteria and state that to the sponsor's knowledge, no extraordinary circumstances exist that requires the need for an EA.

Labeling Technical Section

- Includes facsimile or final printed labeling for all labeling components associated with the product (container labels, package inserts, and other labeling components).

All Other Information Technical Section

- Includes all other information that is pertinent to evaluation of the safety or effectiveness and is not included in the Effectiveness, Target Animal Safety, or Human Food Safety technical sections.

Considerations for Minor Use and Minor Species (MUMS)

- Conditional Approval: Provides for marketing of a MUMS drug when all requirements of its approval have been met except the "substantial evidence" standard for effectiveness, provided that the lower "reasonable expectation of effectiveness" standard has been met.
- Designation: Provides incentives to encourage MUMS new animal drug approval or conditional approval. These incentives are 1) eligibility to apply for competitive grants to support safety and effectiveness testing, and 2) seven years of exclusive marketing rights beginning when the drug is approved or conditionally approved.
- Marketing exclusivity for residue studies: Allows for three years of marketing exclusivity (*i.e.*, protection from generic copying) for approvals for minor uses and minor species based on the drug sponsor having conducted residue depletion studies.
- User fee waiver: Provides for a waiver of user fees associated with the establishment of an INAD file and the approval of a NADA for minor species/minor use indications.

Conclusions

- With no animal drugs currently approved for the treatment and control of histomoniasis, the disease remains a serious threat to the United States turkey and gamebird industries.
- Collaboration between the poultry industry, academic institutions, and animal health companies is integral in the effort to identify potential new drug therapies for histomoniasis.
- CVM encourages interested parties to contact ONADE to discuss their development plan for the approval of promising new animal drugs for the treatment and control of histomoniasis.

References

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2. Hess, M., D. Liebhart, I. Bilic, and P. Ganas. *Histomonas meleagridis* - New insights into an old pathogen. Vet. Parasitol. 208:67-76. 2015.
3. Pham, A. D., J. Mast, J. De Gussem, L. McDougald, and B.M. Goddeeris. Establishing mono-eukaryotic *Histomonas meleagridis* cultures from *in vivo* infection contaminated with *Tetratrichomonas gallinarum* and *Blastocystis* spp. Parasitol. 140:1266-1274. 2013.