AVIAN DISEASES 60:725–730, 2016

Review Article—

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

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Received 23 June 2016; Accepted 4 August 2016; Published ahead of print 8 August 2016

SUMMARY. Histomoniasis, commonly referred to as blackhead disease, is a serious threat to the turkey and game bird industries worldwide, and it is having an increasingly negative impact on the chicken industry as well. The Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM), charged with the approval and regulation of new animal drugs in the United States, understands the rising need for the availability of therapeutic options against histomoniasis. CVM has actively engaged in discussions with the poultry industry, academic institutions, and animal health companies regarding the current status of histomoniasis in the United States and varied success of past and current management, prophylactic, and therapeutic interventions that have been used against the disease. As effective options against the disease are severely limited, CVM encourages the poultry industry, academic institutions, and animal health companies to work together to research and develop viable management, prophylactic, and therapeutic strategies, such as litter management, deworming programs, vaccines or other biologics, novel technologies, and animal drugs. CVM also recognizes the potential challenges that the poultry industry, academic institutions, and animal health companies may encounter while working towards the approval of safe and effective drug products for the treatment and control of histomoniasis. With that recognition, CVM encourages interested parties to begin discussions with CVM early in order to align research of the drug product against histomoniasis with the drug approval requirements, such that it leads to the approval of a new animal drug in an efficient and expedient manner. This article provides information about the FDA's regulatory process for the approval of new animal drugs in the United States, with especial emphasis on drug products for the treatment and control of histomoniasis in turkeys, chickens, and game birds.

RESUMEN. Consideraciones reguladoras para la aprobación de medicamentos contra la histomoniasis (enfermedad de la cabeza negra) en pavos, pollos y aves de cacería en los Estados Unidos.

La histomoniasis, comúnmente conocida como enfermedad de la cabeza negra, es una seria amenaza para las industrias de los pavos y de las aves para cacería en todo el mundo y que está teniendo un impacto cada vez más negativo en la industria del pollo también. El Centro de Medicina Veterinaria (con las siglas en inglés CVM) de la Administración de Alimentos y Medicamentos (con las siglas en inglés FDA), encargado de la aprobación y regulación de los medicamentos veterinarios nuevos en los Estados Unidos, reconoce la creciente necesidad en la disponibilidad de opciones terapéuticas contra la histomoniasis. Este centro ha participado activamente en las discusiones con la industria avícola, instituciones académicas y con empresas relacionadas con la salud animal con respecto al estado actual de la histomoniasis en los Estados Unidos y acerca de los resultados variables de los tratamientos profilácticos y terapéuticos actuales y pasados que se han utilizado contra la enfermedad. Debido a que las opciones eficaces contra la enfermedad son muy limitadas, este centro está promoviendo que la industria avícola, las instituciones académicas y las empresas de salud animal trabajen en conjunto en la investigación y desarrollo de estrategias viables profilácticas y terapéuticas, como el manejo de la cama, los programas de desparasitación, vacunas u otro productos biológicos, nuevas tecnologías y medicamentos para los animales. El Centro de Medicina Veterinaria también reconoce los potenciales desafíos que la industria avícola, las instituciones académicas y empresas de salud animal pueden encontrar en el trabajo hacia la aprobación de medicamentos seguros y eficaces para el tratamiento y control de la histomoniasis. En este sentido, el Centro de Medicina Veterinaria estimula a las entidades interesadas a iniciar conversaciones con dicho centro de manera temprana con el fin de encaminar la investigación de medicamentos contra la histomoniasis de acuerdo con los requisitos para la aprobación de medicamentos, para poder conducir a la aprobación de un medicamento nuevo de una manera eficiente y oportuna. Este artículo proporciona información sobre el proceso de regulación de la FDA para la aprobación de nuevos medicamentos veterinarios en los Estados Unidos, con especial énfasis en los medicamentos para el tratamiento y control de la histomoniasis en los pavos, pollos y aves de cacería.

Key words: histomoniasis, blackhead disease, *Histomonas meleagridis*, treatment and control, drug approval, turkey, chicken, game bird, FDA

Abbreviations: ADI = acceptable daily intake; AOI = all other information; CFR = Code of Federal Regulations; CMC = chemistry, manufacturing, and controls; CVM = Center for Veterinary Medicine; EA = environmental assessment; EFF = effectiveness; EI = environmental impact; FDA = Food and Drug Administration; HFS = human food safety; INAD = investigational new animal drug; LB = labeling; MUMS = minor use and minor species; NADA = new animal drug application; ONADE = Office of New Animal Drug Evaluation; TAS = target animal safety; VICH = International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

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Histomoniasis (commonly referred to as blackhead disease) is an important avian disease that affects a number of galliform and ratite birds, though turkeys and chukar partridges are typically the most susceptible (1,16). The disease is caused by the anaerobic protozoan parasite *Histomonas meleagridis*. *Heterakis gallinarum*, a nematode commonly present in the ceca of galliform birds, is an important intermediate host for *Hi. meleagridis*. Histomonads reside in the eggs of *He. gallinarum*, which have the ability to survive in the environment and remain infectious for several years (12,14); survival and transmission of histomonads are also perpetuated by invertebrate hosts, such as earthworms and flies.

A single histomonad-infected *He. gallinarum* egg can cause a histomoniasis outbreak in a flock of turkeys or game birds, resulting in a huge economic loss for the producer. Following infection in a turkey flock, histomonads can easily spread laterally between turkeys in the absence of any vector, resulting in rapid outbreaks and greater than 85% mortality (13,17). While mortality in other poultry species generally does not reach such high percentages, the disease can cause high morbidity, resulting in reduced performance and economic losses (10,15). Recent reports have shown an increase in the number of histomoniasis cases in chickens, especially in breeders and free-range flocks (9,13). Once recovered, these birds become carriers of the disease. Chickens, guinea fowl, chukar partridges, and pheasants are ideal hosts for the cecal worms and thereby may also act as a reservoir for histomonad infections (1,16). Poultry operations in close proximity to one another can lead to cross-contamination, and with a multitude of hosts available to perpetuate the survival of *Hi. meleagridis*, it is difficult to control the parasite once it enters a poultry facility.

Parasite biology, pathogenesis, disease epidemiology, diagnostic tools, and existing therapeutic and prophylactic strategies for histomoniasis have been extensively reviewed (1,13,17), but renewed attention to this parasite is needed because the availability of effective options for use against the disease are severely limited. Current farm management techniques, such as disinfecting the house and changing the litter in between flocks, physical separation of flocks of differing ages and species, and adequate 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 has shown little success in adequately preventing or treating histomoniasis (1,13). Vaccination programs have yet to be fully developed due to issues with maintaining pathogenicity or technical concerns associated with vaccine production and application (18,19). In addition, the number of approved animal drugs available against the disease has become increasingly limited. The recent withdrawal of nitarsone (Histostat® Type A medicated article) resulted in the loss of the last remaining Food and Drug Administration (FDA)–approved animal drug specifically indicated for the prevention of histomoniasis in turkeys and chickens. Fenbendazole (Safe-Guard® Type A medicated article), indicated for the removal and control of *He. gallinarum*, is the only drug currently approved for use in turkeys with the potential to control the disease by reducing the number of *He. gallinarum* nematodes, a major vector carrying the histomonads. [A Type A medicated article is a product that consists of one or more new animal drugs intended solely for use in manufacturing of another Type A article or in the manufacturing of a medicated feed.] Hygromycin B (Hygromix 8™ Type A medicated article) and fenbendazole (Safe-Guard® AquaSol oral suspension) are currently approved for the treatment and control of *He. gallinarum* in chickens. Use of these drugs to treat chickens, especially broiler breeders, may reduce the incidence of blackhead disease in turkeys in some areas, as anecdotal evidence suggests that turkey flocks in the vicinity of broiler breeder farms are more likely to encounter an outbreak of histomoniasis (Dr. Eric Gonder, veterinarian, Butterball, LLC, pers. comm. 2015). It is believed that infected breeding chickens and free-range laying hens can play a role in spreading the disease to other poultry, including wild bird reservoirs (11).

Development of viable management, prophylactic, and therapeutic strategies, such as litter management, deworming programs, vaccines or other biologics, novel technologies, and animal drugs, is critical for keeping turkey and game bird flocks adequately protected from histomoniasis. As the poultry industry, academic institutions, and animal health companies identify promising interventions, they are encouraged to begin working with government agencies, as applicable, to discuss alignment of their research with an appropriate regulatory pathway, such that they reach the marketplace in the most efficient and expedient manner. The FDA Center for Veterinary Medicine (CVM) is charged with the approval and regulation of new animal drugs in the United States. CVM 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. The goal of this article is to describe the regulatory processes and requirements for approval of new animal drugs, with emphasis on drug products intended for the treatment or control of histomoniasis in turkeys, chickens, and game birds.

NEW ANIMAL DRUG APPROVAL PROCESS IN THE UNITED STATES

The Federal Food, Drug, and Cosmetic Act prohibits the introduction into interstate commerce of animal drugs that are not the subject of an approved new animal drug application (NADA). Section 512(b)(1) of the Federal Food, Drug, and Cosmetic Act describes the information that must be submitted as part of an NADA. Guidance for industry documents are available on the CVM website (http://www.fda.gov/AnimalVeterinary) to assist drug sponsors in designing pivotal studies and to satisfy the requirements for approval of NADAs. [Drug sponsors are companies, research institutions, and other organizations that take responsibility for developing a drug.] While not legally binding requirements, these guidance documents represent the agency's current thinking on various topics related to the drug approval process. CVM encourages drug sponsors to follow the "phased review process" when submitting data for review by CVM. Under this process, a drug sponsor submits data independently to 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 complete 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 (TAS); 2) effectiveness (EFF); 3) chemistry, manufacturing, and controls (CMC); 4) human food safety (HFS); 5) environmental impact (EI); 6) labeling (LB); and 7) all other information (AOI). Once each technical section has been reviewed by CVM and the drug sponsor has received a technical section complete letter for each of the technical sections, the drug sponsor submits an administrative

NADA approval package. The administrative NADA is the culmination of the phased review process that leads to the approval of new animal drug products (6).

INAD file. Once a drug product with a potential therapeutic effect against histomoniasis in turkeys or game birds has been identified, a drug sponsor should contact the CVM Office of New Animal Drug Evaluation (ONADE) to discuss the best strategy for sharing scientific information related to the promising new animal drug with CVM. Drug sponsors are encouraged to have early discussions with CVM to create a development plan appropriate for the drug, target animal species, and intended use of the product. Information may be shared at early stages or after the formal step of opening an INAD file to discuss development plans that would be tailored toward moving the specific new animal drug for approval (7). The development plan for a new animal drug intended to be used in food-producing animals aids the drug sponsor in addressing the seven technical sections required for the approval of a new animal drug.

1) Target Animal Safety. The TAS technical section contains full reports of all studies that demonstrate whether or not the new animal drug is safe to the target species [21 CFR 514.1(b)(8)(i)]. Guidance for Industry 185, titled "Target Animal Safety for Veterinary Pharmaceutical Products" (4), was developed in concert with the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) to assist drug sponsors in the development of their TAS assessment for the drug product. The specific TAS information needed for approval is dependent on a number of factors, including the pharmacologic class of drug, class(es) of animals being targeted, route of administration, indication(s), dosage(s), and available scientific knowledge about the pharmacology and toxicology of the drug. For new animal drugs, TAS may be demonstrated in a margin of safety study, where the drug is administered at and above the intended dose for a period of time in excess of the recommended maximum duration of use.

The selection of dose and overdose levels and durations of treatment should be justified by the sponsor, taking into account the proposed use of the product and the known pharmacologic and toxicologic properties of the drug. For example, a margin of safety study may include the drug at 1×, 3×, and 5× 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 studies may also be required, if the drug is intended to be used in breeding animals. Alternative study designs or approaches to evaluate the safety of the drug in the target animal are also considered, when appropriate. For example, considerable information may be available from the literature or from studies conducted outside of the United States, which may also be used to support completion of the TAS technical section.

2) Effectiveness. The EFF technical section contains full reports of all studies conducted to demonstrate whether the new animal drug is effective for its intended use [21 CFR 514.1(b)(8)(i)]. This technical section includes dosage characterization (dose, frequency, and duration of administration) and a demonstration of the drug product's effectiveness as supported by substantial evidence under expected use/field conditions. For dosage characterization, information such as a dose titration study using recent field isolates of the parasite, a pilot effectiveness study, *in vitro* studies, scientific literature, or assessments based on pharmacokinetic and pharmacodynamic modeling can be submitted. Substantial evidence may be demonstrated through one or more adequate and well-controlled studies that include the measurement of appropriate variables that reflect the effectiveness of the specific drug and provide inferential value. Pharmacokinetic and pharmacodynamics studies may augment and further document the nature of the drug's effectiveness (20). Quantitative data synthesis methods, such as meta-analysis, data from studies conducted outside the United Studies, or results from validated model or *in vitro* studies can also be submitted for dosage characterization and provide substantial evidence of effectiveness. Because blackhead disease outbreaks occur sporadically, and the disease can lead to high mortality, validated model studies may also be considered in lieu of field studies.

3) Human Food Safety. The HFS technical section is required for all new animal drugs intended to be used in food-producing animal species. This technical section includes a description of practicable methods for determining i) 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 ii) 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 [21 CFR 514.1(b)(7)]. This technical section also should contain 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 (3).

Toxicology information is used to determine an acceptable daily intake (ADI) of a drug. The ADI represents drug residues that may be consumed daily for up to a lifetime in the human diet without adverse effects or harm to the health of the consumer. Using this ADI, CVM establishes safe concentrations for total residues of the drug in each of the edible tissues of treated animals (*e.g.*, meat, eggs).

Once safe concentrations are established, a target tissue and a marker residue are identified. A tolerance for the marker residue, which is the maximum legally permitted concentration for residues in or on a food, is determined in the target tissue using the official regulatory (analytical) method. Tolerances are established for the target tissue (*e.g.*, skin/fat, muscle, liver, eggs). Information on residue depletion is collected under conditions of use to establish a withdrawal period based on the respective tolerances. The withdrawal period is the interval between the last administration of a new animal drug and when the animal can be safely slaughtered for food, or the eggs can be safely consumed (20).

Drug products with potential genotoxicity/carcinogenicity concerns pose an additional level of complexity to the drug approval process, as a drug sponsor will also need to provide data to address human food safety concerns related to these end points. An animal drug should be tested for its potential for genotoxicity using a battery of genotoxicity tests (3). If a drug is genotoxic, or it is known to be a potential carcinogen, the sponsor of the drug may be required to conduct an appropriate carcinogenicity assessment, which can include conducting two chronic bioassays in rodents. If, on the basis of the results of the chronic cancer bioassays and other information, CVM determines a compound is carcinogenic, then it should be regulated as a carcinogen under the Delaney Clause Diethylstilbestrol proviso and subject to the 21 CFR 500, Subpart E—Regulation of Carcinogenic Compounds Used in Food-Producing Animals, to meet the FDA operational definition of no residue.

If a drug is an antimicrobial or exhibits antimicrobial properties, the drug sponsor must demonstrate that the use of the drug does not promote emergence or selection of antimicrobial resistance among bacteria of public health concern (*e.g.*, *Salmonella* spp., *Escherichia coli*, and *Campylobacter* spp.) in or on treated animals. As a result of this assessment, conditions of use or label language may be restricted to manage any risks to public health from antimicrobial-resistant organisms rising through the human food chain.

The potential for turkeys and chickens of any age to be infected with histomoniasis may complicate the use of therapeutic agents in these species. Drugs proposed for short duration of use or that are intended for use earlier in the grow-out phase may pose less of a risk to human consumers from drug residues or antimicrobial-resistant bacteria in or on treated animal–derived foods as compared to those proposed for a long duration of use or that are intended for use late in the grow-out phase, especially up to the date of slaughter.

4) Chemistry, Manufacturing, and Controls. The CMC technical section contains complete information regarding the manufacture of the new animal drug active ingredient and the new animal drug product. It includes information on personnel, facilities, the drug's identity, strength, components, and composition, procedures to characterize drug substance and potential impurities, and packaging. The technical section 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. In addition, the technical section should include good manufacturing practice compliance, and other aspects of the chemistry and manufacturing processes as outlined in 21 CFR 514.1(b)(3) and (b)(4).

In order to improve the process for submission and review of CMC information for animal drugs, CVM has developed a process called "question-based review." In this process, drug sponsors provide answers to a series of questions that focus on the critical scientific and regulatory issues and pharmaceutical attributes essential for ensuring the quality of new animal drug substances and products (8).

5) Environmental Impact. As described in 21 CFR 514.1(b)(14), the EI technical section should contain either an environmental assessment (EA) under 21 CFR 25.40, or a request for categorical exclusion under 21 CFR 25.30 or 25.33. Under 21 CFR 25.15(a), a claim of categorical exclusion must include a statement of compliance with the categorical exclusion criteria and must state that to the drug sponsor's knowledge, no extraordinary circumstances exist that require the need for an EA. "Environmental impact considerations" and directions for preparing an EA can be found in 21 CFR Part 25 (6).

6) Labeling. The LB technical section, described in 21 CFR 514.1(b)(6), includes facsimile or final copies of container labels, package inserts, and other labeling components that will be associated with the product. Facsimile labeling is nearly final labeling that adequately represents the package size (actual or to scale); graphics; pictures; type size, font, and color of text; and the substance of the text to demonstrate to the reviewing divisions at ONADE and Office of Surveillance and Compliance that the final printed labeling will be in compliance with applicable regulations (6). For drug products intended for use in creating medicated feeds, representative Type B (as applicable) and Type C medicated feed labels, commonly referred to as "Blue Bird labels," are also required.

[A Type B medicated feed is a feed that contains a new animal drug plus a substantial quantity of nutrients (not less than 25% by weight) and is intended solely for use in the manufacturing of another Type B medicated feed or a Type C medicated feed. A Type C medicated feed is a feed that consists of a new animal drug that is intended to be offered as a complete feed for the animal or may be fed top dressed or offered free-choice in conjunction with other animal feed to supplement the animal's total daily ration.]

In addition, antimicrobial drugs for use in feed that are considered to be of human importance or that are otherwise not marketed as over-the-counter) require a veterinary feed directive form, which should also be submitted with the labeling components. [A veterinary feed directive is a written order from the veterinarian authorizing the distribution of a specific quantity of medicated feed for a specific producer and animal(s).]

7) All other information. The AOI technical section includes all other information that is pertinent to an evaluation of the safety or effectiveness of the new animal drug for which approval is sought and is not included in the EFF, TAS, HFS, or EI technical sections [21 CFR 514.1(b)(8)(i)]. All other information includes, but is not limited to, any information derived from other marketing (domestic or foreign) and favorable and unfavorable reports in the scientific literature. If there is no additional information that has not been previously submitted, the drug sponsor's AOI technical section should contain a statement to that effect (6).

Special considerations and programs to support the approval of new animal drugs for minor uses and minor species. The Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act) established several incentives to encourage new animal drug approval for minor uses and minor species. Turkeys and chickens are *major species*, and game birds such as pheasants, partridges, and quail are *minor species*. A *minor use* is defined as "the intended use of a drug in a major species for an indication that occurs infrequently and in only a small number of animals or in limited geographic areas and in only a small number of animals annually." For turkeys, the small number is defined as $\leq$14 million animals; for chickens, the small number is defined as $\leq$72 million animals (5).

Based on United States Department of Agriculture reports, 233.1 million turkeys, 8.7 billion broiler chickens, and 349.5 million layers (includes both table egg type and hatching egg type layers) were raised in the United States in 2015 (21,22). A turkey health survey of professionals representing the majority of the U.S. turkey production industry reported 52 to 108 annual histomoniasis outbreaks from 2009 to 2015 (2). As of this writing, the authors were not aware of any published information regarding the number of turkeys and chickens in the United States that require therapeutic interventions against histomoniasis on an annual basis.

If the estimated total number of turkeys or chickens to which a drug could potentially be administered on an annual basis for the treatment of histomoniasis meets the small number requirement, then the proposed intended use of that drug could be considered a minor use in a major species (21 CFR 516.21). Minor use status would make a potential drug product eligible for the incentives available to encourage minor uses and minor species drug approval.

Under the MUMS Act, drugs intended for a minor use in a major species or for use in food-producing minor species are eligible for the following incentives:

1) Conditional approval. Conditional approval provides for marketing of a MUMS drug when all requirements for its approval have been met except the "substantial evidence" standard for

effectiveness provided that the lower "reasonable expectation of effectiveness" standard has been met.

2) Designation. Designation provides incentives to encourage MUMS new animal drug approval or conditional approval. These incentives are i) eligibility to apply for competitive grants to support safety and effectiveness testing, and ii) 7 yr of exclusive marketing rights beginning when the drug is approved or conditionally approved. During the time that exclusive marketing rights are in effect, the FDA cannot approve the same drug/dosage form/intended use for a generic copy or another pioneer.

3) Marketing exclusivity for residue studies. Marketing exclusivity for residue studies allows for 3 yr of market 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.

4) Scope of review. Scope of review for minor use and minor species applications allows CVM to reevaluate only the relevant information in an approved application to determine whether a supplemental application for an intended use for a minor species or a minor use in a major species can be approved. Note that the agency can reexamine any approval at any time with just cause. This provision simply states that a MUMS supplement will not trigger any such reexamination.

In addition to the above incentives, a drug sponsor of a minor use indication can request an animal drug user fee waiver of all associated user fees.

If a drug sponsor is interested in pursuing a new animal drug as a minor use in turkeys, they can submit a request to CVM to determine the minor use status of the new animal drug involved. The request should justify that the intended use of the product will be for an eligible population of turkeys that is smaller than 14 million. While published literature, surveys, and veterinary hospital databases are possible sources of useful information, drug sponsors are encouraged to contact CVM's Office of Minor Use and Minor Species to discuss demonstrating a minor use and determining the eligible population.

In general, CVM does not consider a production class to be an appropriate population for determining minor use. For example, it would not be appropriate to limit an indication against histomoniasis for use in only breeding turkeys or chickens because the disease has the potential to affect the animals at any age. As such, all classes of a major species must be considered when determining eligibility. However, it may be appropriate to further reduce the eligible population to only a subset of animals if administration of the drug is only medically justified for this subset. To establish this, a sponsor must demonstrate that administration of the drug to animals other than the subset is not medically justified.

CONCLUSION

The approval of safe and effective new animal drugs for use against unmet animal health needs, such as histomoniasis, is considered an important part of the mission of CVM with regard to protecting human and animal health. With no animal drugs currently approved for use against histomoniasis, the disease remains a serious threat to the U.S. turkey and game bird industries. CVM considers collaboration among the poultry industry, academic institutions, and animal health companies to be an integral part of the effort to identify potential new drug therapies for histomoniasis. CVM encourages interested parties to contact ONADE to discuss strategies for the approval of promising new animal drugs for the treatment and control of histomoniasis.

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