#109

Effectiveness of Anthelmintics: Specific Recommendations for Equines

VICH GL15

Guidance for Industry

Draft Guidance

This guidance document is being distributed for comment purposes only.

This version of the guidance replaces the version made available June 2002. This revision clarifies the definition of adequate infection in individual animals, updates considerations for field studies, and makes additional clarifying changes.

Submit comments on this draft guidance by the dated provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2022-D-1494.

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

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Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR EQUINES (REVISION 1)

Revision at Step 9
Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

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I. Introduction

This equine guidance was developed by the Working Group established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), Anthelmintic Guidances, and subsequently revised in 2022. It should be read in conjunction with Guidance for Industry (GFI) #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations,"[1] which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to GFI #90/VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the equine guidance is: (1) to be more specific for certain specific equine issues not discussed in GFI #90/VICH GL7; (2) to highlight differences with GFI #90/VICH GL7 on effectiveness data recommendations; and (3) to give explanations for disparities with GFI #90/VICH GL7.

It is also important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend that sponsors refer to the pertinent procedures described in detail in other published documents, e.g., World association for the advancement of veterinary parasitology (WAAVP): second edition of guidelines for evaluating the efficacy of equine anthelmintics. *Veterinary Parasitology* ***103***: 1-18, 2002, and updated versions as they are published.

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[1] https://www.fda.gov/media/70349/download

A. General Elements

1. The Evaluation of Effectiveness Data

Controlled tests are recommended both for the dose determination and dose confirmation studies. Critical tests also can be used for certain adult large nematodes, e.g., *Parascaris equorum* and *Oxyuris equi*. Long-acting products or sustained-release products should be subject to the same evaluation procedures as other therapeutic anthelmintics. Adequate parasite infection should be defined in the protocol according to regional prevalence or historical data and/or statistical analysis.

In the case of *Strongyloides westeri*, the evaluation of effectiveness data may be based on egg counts (at least two field effectiveness studies are recommended). The justification for this is the fact that *S. westeri* is mainly observed in young animals. At this age, few other helminths have matured and use of young animals in terminal tests is inappropriate from an ethical perspective.

2. Use of Natural or Induced Infections

Because of the difficulties involved in carrying out induced infections in worm-free equine, most studies can be carried out in naturally-infected animals.

Dose determination studies generally should be conducted using natural or induced infections with either laboratory strains or recent field isolates.

Dose confirmation studies against adult stages for a wide range of parasites should be conducted using naturally-infected animals, which may be superimposed with induced infections of recent field isolates. Induced infections with recent field isolates are also acceptable. For claims against hypobiotic larvae (early L3 of small strongyles), natural infections should be considered. In these cases, animals should be housed for a minimum of 2 weeks before treatment to preclude unintended reinfection.

To determine the number of hypobiotic larvae, digestion of the large intestinal mucosa is recommended; the number of intramucosal developing stages (late L3/L4 of small strongyles) should be determined by using both the digestion technique and the transillumination technique due to the inherent limitation of each technique in isolation.

Persistent effectiveness studies should be conducted using induced infections with recent field isolates and using young equine, i.e., < 12 months of age.

The history of the parasites used in the induced infection studies should be included in the final report.

3. Number of Infective Parasitic Forms Recommended for Induced Infections

As the use of induced infections in equines is not common (see above), only limited data on the number of infective larvae to administer are available. The following range of infective larvae/eggs to be administered can be recommended:

Parascaris equorum	100 - 500
Trichostrongylus axei	10,000 - 50,000
Strongylus vulgaris	500 - 750
Small strongyles (Cyathostominae)	100,000 - 1,000,000

4. Recommendations for the Calculation of Effectiveness

4.1 Factors to Support a Claim

To support a claim the following pivotal data should be included:

a. Two dose confirmation studies conducted with a minimum of six adequately infected non-medicated animals (control group) in each study. The infection of animals in the study will be deemed adequate based on historical, parasitological, and/or statistical criteria;

b. The differences in parasite counts between treated and control animals should be statistically significant ($p \leq 0.05$); and

c. Percent effectiveness should be 90% or higher and calculated and interpreted using the procedures described in section A.4.2. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7.

4.2 Number of Animals (Dose Determination, Dose Confirmation, and Persistency Studies)

The minimum number of animals used per experimental group is a critical point. Although the number of animals will depend on the possibility to process the data statistically according to the adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least six animals in each experimental group is a minimum.

In cases where there are several studies none of which has six adequately infected animals in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 animals in the studies and statistical significance calculated. If the differences are significant ($p < 0.05$), effectiveness may be calculated and if the infection is deemed adequate, the claim may be granted. Sampling techniques and estimation of worm burden should be similar among laboratories involved in the studies to allow adequate and meaningful extrapolation of the results to the population.

4.3 Adequacy of Infection

The minimum adequate number of helminths in individual control animals should be defined in the protocol. However, final conclusions regarding adequacy of infection will be made as part of the final report based on statistical analysis, historical data, literature review, or expert testimony. The range of equine helminths (adults) that has been considered adequate to grant a claim varies according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower individual counts are to be expected with cestodes (e.g., *Anoplocephala perfoliata*, minimum number of 10), trematodes (*Fasciola* spp.), *Parascaris equorum*, and *Dictyocaulus arnfieldi*.

4.4 Label Claims

For adult and larval claims, treatment should correspond to life-cycle timing appropriate for the species claimed. In the case of small strongyles, distinction should be made between early (hypobiotic) L3 stages, (developing) intramucosal L4 stages, luminal L4 stages, and adults. The term "immature" on the labeling is not recommended.

Parasite identification should determine the type of claim proposed on the labeling. A species claim is highly recommended. For the small strongyles, a genus claim should be acceptable on the assumption that, generally speaking, there is more than one species in that genus and the study was conducted with a mixed larval population.

5. Treatment Procedures

The method of administration (oral, parenteral, topical, slow-release, etc.), formulation, and extent of activity of a product will influence the protocol design. It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations. Slow-release products should be tested over the entire proposed effective time unless additional information suggests this is unnecessary, e.g., for systemic acting compounds, blood levels demonstrate steady state at all points of the proposed therapeutic period. When the drug is to be administered in the water or via a medicated feed, it should be done as much as possible following the labeling recommendations. Palatability studies may be advisable for medicated feed. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product consumed by each animal should be recorded to ensure that the treatment satisfies the label recommendations. For products used topically**,** the impact of weather (e.g., rainfall, UV light) and coat length should be included in the evaluation of the effectiveness of the product.

6. Animal Selection, Allocation, and Handling

Test animals should be clinically healthy and representative of the age, sex, and class for which the claim of the test anthelmintic is to be made. In general, the animals should be 3 to 12 months of age and raised helminth-free, if induced infections are used, because there is no guarantee that pre-existing infections can be removed. For natural infections, animals between 12 to 24 months are preferred (except for *S. westeri*) and to reduce individual variations in worm counts, it can be

useful to graze the equids for at least 5 months together on the same infected pasture. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking is only recommended if it is expected to reduce residual error in the study. If blocking is used, blocks should be included as a random effect in the statistical model. Nevertheless, blocking is not always the most appropriate method for reducing residual error. Alternative methods may therefore be considered, e.g., a suitably selected covariate.

Animal housing, feeding, and care should follow strict requirements of welfare, including vaccination according to local practices. This information should be provided in the final report. A minimum 7-day acclimatization period is recommended. Housing, feed, and water should be adequate according to the geographical location. Animals should be monitored daily to determine adverse reactions.

B. Specific Evaluation Studies

1. Dose Determination Studies

No species-specific recommendations.

2. Dose Confirmation Studies

Confirmation studies are recommended to support each claim: adult, larvae, and, when applicable, hypobiotic larvae. For additional descriptions of the procedures refer to GFI #90/VICH GL7.

3. Field Effectiveness Studies

The field studies should be replicated in different geographic locations and in animal/production class(es) that represent the conditions of use for the indication being pursued. The protocol should state the number of experimental units per treatment group (sample size), describe allocation (proportion) to treatment groups, and include a brief description of how the sample size was determined. The protocol should also describe procedures for random selection of animals (number and percentage) to be sampled (if fecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both fecal collection and examination. Regardless of whether one or multiple parasites are being evaluated within a study, an appropriate sample size calculation or justification is necessary prior to study conduct.

Effectiveness against adult nematodes can be assessed by the reduction of fecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). Post-treatment counts are generally made 10-14 days after treatment, but the timing of post-treatment counts will depend on the parasite species and class of anthelmintic evaluated. For example, due to the known effects of macrocyclic lactones on nematode egg suppression, post-treatment counts should be delayed until at least 14 days or longer. Effectiveness should be calculated using post-treatment fecal egg counts from the treated

and control (typically placebo or untreated control) groups. Additionally, a calculation of effectiveness using pre- and post-treatment fecal egg counts may provide further information on field effectiveness. Furthermore, additional endpoints for evaluating field effectiveness should be considered as they are developed and generally accepted by experts in veterinary parasitology.

See also sections A.4.1. *Data Analysis Recommendations* and A.4.2. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7.

4. Persistent Effectiveness Studies

These claims should only be determined on the basis of actual worm counts and not on eggs per gram of feces to demonstrate drug effectiveness.

A persistent effectiveness claim (for each duration and helminth claim) should include two trials (with worm counts), each with a non-treated and one or more treated groups. At least six animals in the control group (of the same age) should be adequately infected. Persistent effectiveness claims should only be granted on a species-by-species basis, genus-by-genus in the case of small strongyles.

Two basic study designs have been used to pursue persistent effectiveness claims: one using a single challenge, another using multiple daily challenges following treatment. For consistency of interpretation of results, a standardized study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature.

In the protocol using multiple daily challenges, different groups of animals should be treated and exposed to a daily natural or induced challenge for 7, 14, 21, or more days after the treatment, then at approximately 3 weeks after the last challenge (or earlier) the animals are examined for parasite burden. The challenge interval and schedule may vary for longer-acting products and should take into consideration the pharmacological properties of the product.

Persistent effectiveness claims should be supported by a minimum 90% effectiveness at each time point, and calculated and interpreted using the procedures described in sections A.4.1. *Data Analysis Recommendations* and A.4.2. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7. Persistent effectiveness claims should be granted for the longest period between treatment and the last challenge where effectiveness criteria are met, and all preceding time points tested meet the criteria as well.

5. Egg Reappearance Period (ERP) Studies

ERP only relates to strongyles. ERP is a pasture contamination management tool and is not intended to be used to measure individual animal strongyle burdens. It is a tool to manage equine strongyles on a herd basis focusing on pasture contamination management. Claims for egg reduction during a certain period after treatment should be acceptable if the reduction in treated animals is at least 90% compared to pretreatment egg counts. In these studies, animals should remain on infected pastures. Two studies should be the minimum needed to determine the ERP. At least one of the two studies should be conducted in the geographical location where

registration is being pursued. These studies should be conducted so that they are sufficiently representative of the various conditions under which the product will be authorized.