

**109**

# **Guidance for Industry**

## **EFFECTIVENESS OF ANTHELMINTICS: Specific Recommendations for Equine VICH GL15**

### **DRAFT GUIDANCE**

*This guidance document is being distributed for comment purposes only*

This draft guidance is intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

This guidance represents the agency's current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes, regulations or both.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 00D-1532.

For questions regarding this document, contact Thomas Letonja, Center for Veterinary Medicine, (HFV-135), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7576, e-mail: [tletonja@cvm.fda.gov](mailto:tletonja@cvm.fda.gov).

---

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Veterinary Medicine  
September 26, 2000**

---

# **EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR EQUINE**

---

Recommended for Consultation  
at Step 4 of the VICH Process  
on November 1998  
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

# EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR EQUINE

Endorsed by the VICH Steering Committee at Step 4 of the VICH Process  
at its meeting on 16 - 19 November 1999

## Introduction

These guidances for equine were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidances. They should be read in conjunction with the VICH Effectiveness of Anthelmintics: General Recommendations (EAGR) 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 the EAGR with the aim of simplicity for readers comparing both documents.

The guidance for equine are part of this EAGR and the aim is (1) to be more specific for certain specific issues for equines not discussed in the overall guidances; (2) to highlight differences with the EAGR on effectiveness data recommendations and (3) to give explanations for disparities with the EAGR.

It is also important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend to the sponsors to refer to the pertinent procedures described in detail in other published documents, e.g. WAAVP Guidances for Evaluating the Effectiveness of Equine Anthelmintics. *Veterinary Parasitology*, 30: 57-72, 1988.

## 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 under certain circumstances. 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 historic and/or statistical data.

In the case of *Strongyloides westeri*, the evaluation of effectiveness data may be based on egg counts (at least 2 field effectiveness studies are recommended). The justification for this is the fact that *S.westeri*, is mainly observed in young animals; at this age other helminth infections are very rare and eggs are easily differentiated from those of other helminth species.

### 2 - Use of Natural or Induced Infections

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

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

Dose confirmation studies against adult stages for a wide range of parasites should be conducted using naturally-infected animals which were superimposed with induced infections of recent field isolates. Induced infections with recent field isolates are also acceptable. For claims against (developing) larval stages (e.g. L4 stages) only induced infections of recent field isolates should be considered. For claims against hypobiotic larvae (early L3 of small strongyles) only natural infections should be considered. In these cases, animals need to 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 should be used and the number of intramucosal developing stages (late L3/L4 of small strongyles) should be determined by either the digestion or transillumination technique.

Persistent effectiveness studies should be conducted using induced infections with recent field isolates and using young horses 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 horses is not common (see above), only limited data on the number of infective larvae to administer are available. The following numbers of infective larvae/eggs to be administered can be recommended :

<i>Parascaris equorum</i>	100 - 500
<i>Trichostrongylus axei</i>	10,000 - 50,000
<i>Strongylus vulgaris</i>	500 - 750
Small strongyles (Cyathostominae)	100,000 - 500,000

### **4 - Recommendations for the Calculation of Effectiveness**

#### **4.1 Criteria to Grant a Claim**

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

- a) Two dose confirmation studies conducted with a minimum of 6 adequately infected non-medicated animals (control group) and 6 adequately infected medicated animals (treated group) in each study; where a critical test is used only 6 animals are needed for each study as each animal act as its own control.
- b) The differences in parasite counts between treated and control animals should be statistically significant ( $p < 0.05$ );
- c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data.
- d) The infection of the animals in the study will be deemed adequate based on historical, parasitological and/or statistical criteria.

#### **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 adequate statistical analysis, it has been recommended, to achieve harmonisation, that the inclusion of at least 6 animals in each experimental group is a minimum.

In cases where there are several studies, none of which has 6 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 difference 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**

With respect to the minimum adequate number of helminths, the decision will be made when the final report is submitted based on statistical and historical data, literature review, or expert testimony. The range of equine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally the minimal mean number of nematodes considered to be adequate is 100. Lower mean counts are to be expected with *Parascaris equorum*, *Dictyocaulus* spp. For *Fasciola* spp. minimal mean counts of 20 adults may be considered adequate.

#### **4.4 Label Claims**

Adult or L3/ L4 parasites: the term immature on the labeling is not acceptable. 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, intraluminal L4 stages and adults.

Parasite identification will 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**

**5.1 Product Type.** 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.

**5.2 Treatment Route.** When the drug is to be administered in the water or via a premix, it should be done as much as possible following the labeling recommendations. Palatability studies may be required for medicated feed. Samples of medicated water or 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 horses for at least 5 months together on the same infected pasture. Animals should be assigned randomly to each treatment. Blocking in replicates by weight, sex, age, and/or exposure to parasites may aid in reducing trial variance. Fecal egg/larval counts are also useful to allocate the experimental animals. Good husbandry practices should be followed and the animals should be vaccinated according to local practices. This information should be provided in the final report. A minimum 7 day acclimatisation period is recommended. Housing and feed-water supply 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**

#### **2. Dose Confirmation Studies**

A minimum of 2 dose confirmation studies is recommended to support each claim: adult or larvae. For additional descriptions of the procedures refer to EAGR.

#### **3. Field Effectiveness Studies**

Claims for egg reductions during a certain period ("Egg reappearance period") after treatment are only acceptable if the reduction in the treated animals, compared to the controls, is at least 90% and if in the treated animals faecal egg counts are lower than 50.

#### **4 - Persistency Studies**

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

The minimum data recommended for 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 6 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 are treated and exposed to a daily natural or induced challenge for 7, 14, 21 or more days after the treatment.

Then at approximately three weeks after the last challenge (or earlier) the animals are examined for parasite burden.

Persistent effectiveness claims should be supported by a minimum 90% effectiveness based on geometric means.