VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Guidance for Industry

Effectiveness of Anthelmintics: Specific Recommendations for Equine

VICH GL15

FINAL GUIDANCE

This final 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.

Comments and suggestions regarding the document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the Docket No 00D-1532.

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EFFECTIVENESS OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR EQUINE

Recommended for Implementation
on June 2001
by the VICH Steering Committee

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Endorsed by the VICH Steering Committee at Step 7 of the
VICH process at its meeting from June 2001

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 and regulations.

Introduction

The present guidance for equines was developed by the Working Group established by the Veterinary International Co-operation on Harmonization (VICH), Anthelmintic Guidances. It 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 is part of this EAGR and the aim is (1) to be more specific for certain issues for equines not discussed in the EAGR; (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 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 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). 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 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 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 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 six adequately infected medicated animals (treated group) in each study; where a critical test is used only six animals are needed for each study as each animal acts 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 using transformed (geometric means) data;

d) The infection of the animals in the study may 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 ability to process the data statistically according to 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

With respect to the minimum adequate number of helminths, the decision should 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 varies according to the species. Generally, the minimal mean number of nematodes recommended as adequate is 100. Lower mean counts are to be expected with *P. equorum, Dictyocaulus arnfieldi* and *Fasciola* spp.

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, lumenal L4 stages and adults. The term immature on the labelling is not recommended.

Parasite identification should determine the type of claim proposed on the labelling. 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 premix, it should be done as much as possible following the labelling recommendations. Palatability studies may be advisable 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 equines 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. Faecal egg/larval counts are also useful to allocate the experimental animals. 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 seven-day acclimatization 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

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 EAGR.

3. Field Effectiveness Studies

No species specific recommendations.

4. Persistency Studies

These claims should only be determined on the basis of actual worm counts and not on eggs per gram of faeces 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 standardised 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 three weeks after the last challenge (or earlier) the animals should be examined for parasite burden.

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

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 developing new tool to manage equine strongyles on a herd basis focussing 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.