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

110

Guidance for Industry

Effectiveness of Anthelmintics: Specific Recommendations for Porcine

VICH GL16

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.

For questions regarding this document, contact Janis Messenheimer, Center for Veterinary Medicine, (HFV-135), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-8348, e-mail: janis.messenheimer@fda.hhs.gov.

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Center for Veterinary Medicine
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EFFECTIVENESS OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR PORCINE

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 porcine 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 porcine is part of this EAGR and the aim is (1) to be more specific for certain issues for porcine 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 Guidelines for Evaluating the Effectiveness of Anthelmintics in Swine. Veterinary Parasitology ***21*** : 69 - 82, 1986.

A. General Elements

1 - The Evaluation of Effectiveness Data

Only controlled tests are recommended both for the dose determination and dose confirmation studies. Critical tests are generally considered not to be very reliable for porcine.

Long-acting 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.

2 - Use of Natural or Induced Infections

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

Dose confirmation studies should be conducted using naturally infected animals. Induced infections with recent field isolates are also acceptable, as well as natural infections which can have

superimposed induced infections of certain parasites. This procedure should allow a wide range of parasites.

Persistent effectiveness studies should be conducted using induced infections with recent field isolates.

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

The number that should be used is approximate and should depend on the isolate that is used. The final number of larvae or eggs used in the infection should be included in the final report. Table 1 shows the range of viable L3 or eggs recommended.

Table 1 – Range of viable L3 or eggs recommended to produce adequate infections in porcine for anthelmintic evaluation.

Parasites	Range
Stomach	
Ascarops strongylina	200
Hyostrongylus rubidus	1,000 – 4,000
Physocephalus sexalatus	500
Intestines	
*Ascaris suum**	250 – 2,500
Oesophagostomum spp.	2,000 – 15,000
Strongyloides ransomi	1,500 – 5,000
Trichuris suis	1,000 – 5,000
Lungs	
Metastrongylus spp.	1,000 – 2,500
Kidney	
Stephanurus dentatus	1,000 – 2,000

* To maximize the establishment of adult worms a trickle infection with a low number of eggs is recommended.

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 six adequately infected non-medicated animals (control group) and six adequately infected medicated animals (treated group) in each study;

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 should be deemed adequate based on historical, parasitological and/or statistical criteria.

4.2 Number of Animals (dose determination, dose confirmation and persistency trials)

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 have 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 could then be 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 porcine 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 *A.suum, A. strongylina, P. sexalatus, S. dentatus*, *Metastrongylus* spp. and *Fasciola* spp.

4.4 Label Claims

For adult claims as a general rule the treatment should not be administered earlier than 35 days for *A. strongylina,* 26 days for *H. rubidus,* 55 days for *P. sexalatus*, 65 days for *A. suum,* 10 days for *S. ransomi*, 28 to 45 days for *O. dentatum* and *O. quadrispinulatum* , 50 days for *T. suis*, 35 days for *Metastrongylus* spp. and 10 months for *S. dentatus*.

For L4 claims treatments should be given as general rule 7 to 9 days days after infection with exceptions: 3 to 4 days for *S. ransomi* 11 to 15 days for *A. suum,* and 16 to 20 days for *T. suis.* The term immature on the labelling is not recommended.

For claims against transmammary transmission of *S. ransomi* somatic larvae, natural or artificially infected pregnant sows should be treated at various times prior to parturition and the effectiveness checked by counting the larvae in the sow milk and the adult worms in the small intestine of the litter.

5 - Treatment Procedures

The method of administration (oral, parenteral etc), formulation and extent of activity of a product will influence the protocol design. Slow-release products should be tested over the entire proposed effective time unless additional information suggests that this is unnecessary, e.g., for systemically 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 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 or group of animals should be recorded to ensure that the treatment satisfies the label recommendations.

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 2 to 6 months of age. 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 an adequate method to allocate the experimental animals.

For induced infections, the use of helminth naive animals is recommended. Animals not raised in a helminth-free environment should be treated with an approved anthelmintic drug to remove pre-existing infections followed by faecal examination to determine that the animals are helminth free.

Animal housing, feeding and care should follow recommendations for 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 and larvae. For additional descriptions of the procedures refer to EAGR.

3. Field Effectiveness Studies

No species specific recommendations.

4. Persistent Effectiveness Studies

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.

A minimum 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 six animals in the control group should be adequately infected. Persistent effectiveness claims should only be granted on a species-by-species basis.

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.