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EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR PORCINES

Recommended for Implementation
on June 2001
by the VICH Steering Committee

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

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INTRODUCTION

The present guideline for porcines was developed by the Working Group established by the Veterinary International Co-operation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the VICH Efficacy of anthelmintics: General requirements (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 guideline for porcines is part of this EAGR and the aim is (1) to be more specific for certain issues for porcines not discussed in the EAGR; (2) to highlight differences with the EAGR on efficacy data requirements 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 guideline. We recommend to the sponsors to refer to the pertinent procedures described in details in other published document e.g WAAVP Guidelines for Evaluating the Efficacy of Anthelmintics in swine. Veterinary Parasitology ***21*** : 69 - 82, 1986.

A. General Elements

1. The evaluation of effectiveness data

Only controlled tests are acceptable 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 will allow a wide range of parasites.

Persistent efficacy 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 to be used is approximate and will depend of 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 used 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 6 adequately infected non-medicated animals (control group) and 6 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 will 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 required 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 harmonization, 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 have 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 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 will 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 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 *A.suum, A. strongylina, P. sexalatus, S. dentatus*, *Metastrongylus* spp. and *Fasciola* spp.

4.4 Label claims

The term immature on the labelling is not acceptable. 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*

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 efficacy 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 suggest that this is unnecessary e.g. for systemically acting compounds blood levels demonstrate steady state at all point**s** 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 required for medicated feed. Samples of medicated water or feed should be collected to confirm drug concentration. The amount of medicated product consumed to 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 strict requirements of welfare including vaccination 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

No species specific recommendations.

2. Dose Confirmation Studies

Confirmation studies are needed to support each claim: adult and larvae. For additional descriptions of the procedures refer to EAGR.

3. Field Efficacy Studies

No species specific recommendations.

4. Persistent Efficacy Studies

Two basic study designs have been used to pursue persistent efficacy 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 requirement for a persistent efficacy claim (for each duration and helminth claim) should include 2 trials (with worm counts) each with a non-treated and one or more treated groups. At least 6 animals in the control group shall be adequately infected. Persistent efficacy claims will only be granted on a species-by-species basis.

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