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Draft

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

VICH GL16 (ANTHELMINTICS PORCINES)
May 2022
Revision at Step 9
For consultation at Step 4

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

Revision at Step 9

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

This Guideline has been developed by the appropriate VICH Expert Working Group will be 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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EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR PORCINES

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 (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of this guideline for porcines is (1) to be more specific for certain issues for porcines not discussed in the VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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 detail in other published documents e.g WAAVP Second edition of Guidelines for Evaluating the Efficacy of Anthelmintics in Swine. Veterinary Parasitology ***141***: 138-149, 2006, and updated versions as they are published.

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 parasites.

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 strains 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 to be present.

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 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 Used to Produce Adequate Infections in Porcine for Anthelmintic Evaluation.

Parasite Anatomical Location *Genus Species*	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 experimental units (individual animals or pens, see Glossary) in the non-medicated control group in each study. The infection of the experimental units 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 experimental units should be statistically significant ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted as described in Section 4.2 of VICH GL7.

4.2 Number of Experimental Units in Dose Determination, Dose Confirmation and Persistency Trials

The minimum number of experimental units required per experimental group is a critical point. Although the number of experimental units 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 experimental units in each experimental group is a minimum.

In cases where there are several studies, none of which have 6 adequately infected

experimental units in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 experimental units 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 data, historical data, literature review, or expert testimony. If the experimental unit is a pen, an adequately infected pen should be defined by a minimum number of adequately infected animals out of the total number of animals in that pen (i.e. percentage of adequately infected animals in the pen). The range of porcine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower 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. Generally, for adult claims the treatment should not be administered earlier than 35 days for *A. strongylina,* 26 days for *H. rubidus,* 55 days for *P. sexalatus*, 49 to 63 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 after infection for *S. dentatus*.

Generally, for L4 claims treatments should be given 7 to 9 days after infection with exceptions: 3 to 4 days for *S. ransomi* 10 to 14 days for *A. suum,* and 16 to 20 days for *T. suis.*

For claims against migrating *A. suum* L3, treatment should be given between 2 and 6 days post-infection. Necropsy may be performed when larvae have accumulated in the small intestine either between 10 and 14 days post-infection (when parasites have matured to L4), or between approximately 23-28 days post-infection (after larvae have matured to the L5/adult stage).

For the majority of adult parasites, approximately 5 to 7 days is a sufficient time period from the termination of treatment until the animals are necropsied. For *Stephanurus dentatus* the recommended time between termination of treatment and necropsy is 6-8 weeks.

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 points of the proposed therapeutic period. When the drug is to be administered in the water or via feed, it should be done following the labelling recommendations. Palatability studies may be required for medicated feed. Samples of medicated water or medicated 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. If animals are housed in pens, the animals should be randomly assigned to each pen. The experimental units (animals or pens) should also be assigned randomly to each treatment group. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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.

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 VICH GL7.

3. Field Efficacy Studies

The experimental unit may be the individual animal or the pen. The design of the field studies should be representative of current commercial conditions and should be replicated in different geographic locations and in 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 and the faecal and/or urine sampling method. 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 faecal egg counts or urine egg counts. In some cases, identification of larvae or larvae counts (from faecal culture) can be performed to support faecal egg counts. Faecal egg count, urine egg count, and/or larval identification 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 evaluated. Efficacy should be calculated using post-treatment faecal egg or urine egg counts from the treated and control groups. A calculation of efficacy using pre- and post-treatment faecal egg or urine egg counts may be appropriate in some situations where significant individual animal variability is expected. The primary basis of the effectiveness determination should be defined in the protocol.

The potential for false positive and false negative faecal egg counts for *A. suum* and *T. suis,* and variability in daily egg output for *A. suum* should be considered in the study design and interpretation of results.

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 experimental units 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. The challenge interval and schedule may vary for longer acting products, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

GLOSSARY

EXPERIMENTAL UNIT: The entity (e.g., individual animal or pen) which can be independently and randomly assigned to a treatment, and whose response to the assigned treatment can be independently evaluated. The experimental unit is the basic unit for the statistical analysis. The experimental unit may be the individual pig or the pen depending on the circumstances of the study.

1) The pen is the experimental unit in the analysis if all pigs in a pen are provided the same treatment through medicated feed or water; or
2) The individual pig is the experimental unit in the analysis if the treatment can be individually administered, the treatments are randomly assigned to pigs within a pen, and the endpoint can be evaluated independently for each pig in a pen.