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Effectiveness of Anthelmintics: Specific Recommendations for Porcines

VICH GL16

Guidance for Industry

Final Guidance

This version of the guidance replaces the version made available August 2022.

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Revision at Step 9
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EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR PORCINES (REVISION 1)

Revision at Step 9
Recommended for Adoption at Step 7 of the VICH Process
in October 2024
by the VICH Steering Committee

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Contains Nonbinding Recommendations

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I. Introduction

The present guidance for porcines was developed by the Working Group established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), Anthelmintic Guidances, and subsequently revised in 2024. It should be read in conjunction with Guidance for Industry (GFI) #90 (VICH GL7), "Effectiveness of Anthelmintics: General Recommendations," [1] 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 GFI #90/VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the porcine guidance is: (1) to be more specific for certain specific porcine issues not discussed in GFI #90/VICH GL7; (2) to highlight differences with GFI #90/VICH GL7 on effectiveness data recommendations; and (3) to give explanations for disparities with GFI #90/VICH GL7.

It is also important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend that sponsors refer to the pertinent procedures described in detail in other published documents, e.g., World association for the advancement of veterinary parasitology (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.

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[1] https://www.fda.gov/media/70349/download

regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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 helminth 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 should allow a wide range of parasites to be present.

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

Parasite Anatomical Location ***Genus Species***	**Range of Eggs/Larvae**
Stomach	
Ascarops strongylina	200
Hyostrongylus rubidus	1,000 – 4,000
Physocephalus sexalatus	500

Parasite Anatomical Location *Genus Species*	Range of Eggs/Larvae
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, trickle infections with a low number of eggs each (e.g., five times 50-500 eggs) can be considered.

4. Recommendations for the Calculation of Effectiveness

4.1 Factors to Support a Claim

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

a. Two dose confirmation studies conducted with a minimum of six adequately infected experimental units (individual animals or pens, see section II. *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 ($p \leq 0.05$); and

c. Percent effectiveness should be 90% or higher and calculated and interpreted using the procedures described in section A.4.5. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7.

4.2 Number of Experimental Units (Dose Determination, Dose Confirmation, and Persistency Studies)

The minimum number of experimental units used 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 the adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least six experimental units in each experimental group is a minimum.

In cases where there are several studies, none of which have six 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 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

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 analysis, 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 varies according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection[2]. Lower individual counts are to be expected with *A. suum*, *A. strongylina*, *P. sexalatus*, *S. dentatus*, *Metastrongylus* spp., and *Fasciola* spp.

4.4 Label Claims

Generally, for adult claims, 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*. The term "immature" on the labeling is not recommended.

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 10-14 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 *S. dentatus*, the recommended time between termination of treatment and necropsy is 6-8 weeks.

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

[2] The recommended minimum numbers are based on a review of published literature and data from studies submitted for regulatory review.

1. 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 feed, it should be done following the labeling recommendations. Palatability studies may be advisable for medicated feed. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product consumed by each animal or pen should be recorded to ensure that the treatment satisfies the label recommendations.

2. 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 are typically 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 is only recommended 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 fecal 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 acclimatization period of 7 days is recommended. Housing and feed/water supply should be adequate according to the geographical location. Animals should be monitored daily for 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 GFI #90/VICH GL7.

3. Field Effectiveness 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 fecal 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 fecal egg counts or urine egg counts. In some cases, identification of larvae or larvae counts (from fecal culture) can be performed to support fecal egg counts. Fecal 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. Effectiveness should be calculated using post-treatment fecal egg or urine egg counts from the treated and control groups. A calculation of effectiveness using pre- and post-treatment fecal 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. Furthermore, additional endpoints for evaluating field efficacy should be considered as they are developed and generally accepted by experts in veterinary parasitology.

The potential for false positive and false negative fecal 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 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 standardized study design is recommended using multiple daily challenges, as this most closely mimics what occurs under field conditions.

A minimum recommended for a persistent effectiveness claim (for each duration and helminth claim) should include two studies (with worm counts) each with a non-treated and one or more treated groups. At least six experimental units 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 3 weeks after the last challenge (or earlier) the animals should be

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 effectiveness claims should be supported by a minimum 90% effectiveness at each time point, and calculated and interpreted using the procedures described in sections A.4.4. *Data Analysis Recommendations* and A.4.5. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7. Persistent effectiveness 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.

II. 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 as follows:

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.