

Guidance for Industry

EFFECTIVENESS OF ANTHELMINTICS: Specific Recommendations for Canine VICH GL19

DRAFT GUIDANCE

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This draft guidance is intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United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.

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Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 00D-1532.

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EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CANINE

Recommended for Consultation
at Step 4 of the VICH Process
on November 1998
by the VICH Steering Committee

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

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Endorsed by the VICH Steering Committee at Step 4 of the VICH Process
at its meeting on 18-20 May 1999

Introduction

The present guidance for canine was developed by the Working Group that was established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidances. They 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 canine are part of the "General Recommendations" document and the aim is: (1) to be more detailed for certain specific issues for canines and felines 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 guidance.

It is important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend that the sponsors refer to pertinent procedures described in details in other published documents, e.g. WAAVP Guidances for Evaluating the Effectiveness of Anthelmintics for Dogs and Cats, *Veterinary Parasitology* 52: 179-202, 1994.

General Elements

1 – The Evaluation of Effectiveness Data

The evaluation of effectiveness data is based on parasite counts (adults, larvae) in dose determination and dose confirmation studies; egg counts/larval identification is the preferred method to evaluate effectiveness in field studies.

The controlled test is the most widely accepted of the testing procedures for evaluation of anthelmintic drug effectiveness. However, the critical test may be appropriate for some intestinal species of parasites. 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 should be conducted using induced infections with either laboratory or recent field isolates.

Dose confirmation studies should be conducted using naturally or artificially infected animals, however, at least one study should be conducted in naturally infected animals for each parasite claimed on the label. *Echinococcus* spp. and *Dirofilaria* spp. testing may be conducted using only animals which harbour induced infections due to public health considerations for echinococcosis and the complexity of the claims for heartworm. For the following helminths, induced infections may also be the only method to determine effectiveness of the product because of difficulties in obtaining a sufficient number of infected animals: *Filaroides milksi*, *F. hirthei*, *Diocotophyma renale*, *Capillaria aerophila*, *C. plica*, *Spirocerca lupi*, *Physaloptera* spp, *Mesocestoides* spp. and *Crenosoma vulpis*. For claims against larval stages, only studies with induced infections are acceptable.

The history of the parasite cultures 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. The final number of larvae used in the infection should be included in the final report. Table 1 shows the range of numbers recommended for common helminths.

Table 1- Number of infective stages used to produce adequate infections in dogs for anthelmintic evaluation

Parasites	Range of eggs/larvae
Small Intestine	
<i>Toxocara canis</i>	100 - 500 *
<i>Toxascaris leonina</i>	200 - 3,000
<i>Ancylostoma caninum</i>	100 - 300
<i>Ancylostoma braziliense</i>	100 - 300
<i>Uncinaria stenocephala</i>	100 - 1,000
<i>Strongyloides stercoralis</i>	1,000 - 5,000
<i>Echinococcus granulosus</i>	20,000-40,000
<i>Taenia</i> spp.	5 - 15
<i>Dipylidium caninum</i>	15 - 30
Large Intestine	
<i>Trichuris vulpis</i>	100 - 500
Heart	
<i>Dirofilaria immitis</i>	30 - 100 **

* In suckling dogs or dogs less than 5 months of age.

** For adulticidal or microfilaricidal testing 5 – 15 pairs of adult worms can be transplanted.

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);
- b) The differences in parasite counts between treated and control should be statistically significant ($p < 0.05$);
- c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data. For *E. granulosus* and *D. immitis* with public health, animal welfare/clinical implications, respectively, higher effectiveness standards (i.e. up to 100%) may be applied. The regulatory authority of the region in which the product is intended to be registered should be consulted;
- d) The infection of the animals in the study will be deemed adequate based on historical, parasitological and/or statistical criteria;
- e) Effectiveness against helminths will be evaluated examining for the presence or absence of parasitic elements in faecal material or blood. An *E. granulosus* claim does not require field studies due to public health concerns.

4.2 Number of Animals (Dose Determination and Dose Confirmation 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 the adequate statistical analysis it has been recommended, to achieve harmonisation, 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 difference is 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

A universal definition of adequacy of infection cannot be formulated because of the diversity of genera, species and strains of helminths subject to evaluation. Furthermore, each strain under test may have unique characteristics of infectivity and pathogenicity. However, in the development of study protocols the adequacy of infection should be addressed, especially in terms of the statistical, parasitological and clinical relevance of the infection level in individual control animals, as well as the number of control animals.

The level of infection, and its distribution, among control animals should be adequate to permit the appropriate standards of effectiveness to be met with acceptable statistical and biological certainty/confidence. Multiple infections are acceptable; however, each helminth species should reach acceptable minimums of infection.

In cases where the regulatory authority and sponsor cannot agree on a minimum adequate number, the decision will be made when the final report is submitted based on historical data, literature review, or expert testimony. Generally the minimal number of nematodes in dogs

considered to be adequate is in the range of 5 to 20. Higher counts are to be expected with *A. caninum* and *U. stenocephala*.

4.4 Label claims

A claim for effectiveness against life stages of each parasite should refer to each stage in the case of natural infections, or age in days in the case of induced infection. Table 2 is provided as a guide for the recommended time of treatment of induced infections.

With the majority of parasites approximately 7 days is a sufficient time period from the termination of treatment until the animals are necropsied. The following parasites are the exception to the above general recommendation:

- *Physaloptera* spp., *S. lupi*, *C. plica*, *D. renale*, *E. granulosus*, *Taenia* spp., *D. caninum*, *Mesocestoides* spp.: 10 to 14 days
- *C. vulpis*: 14 days
- *F. milksi*, *F. hirthi*: 42 days
- *F. osleri*: one-half of the animals 14 days and the other half 28 days
- *D. immitis*: varied by trial design

Table 2 – Recommended time of treatment after infection

Parasite	Adult Stages	Developing Stages
<i>S. stercoralis</i>	5 to 9 days	
<i>T. vulpis</i>	84 days	
<i>A. caninum</i>	> 21 days	6 to 8 days *
<i>A. braziliense</i>	> 21 days	6 to 8 days
<i>U. stenocephala</i>	> 21 days	6 to 8 days
<i>T. canis</i>	49 days	3 to 5 days (migrating **) 14 to 21 days (intestinal)
<i>T. leonina</i>	70 days	35 days
<i>D. immitis</i>	180 days	2 days (L3), 20 to 40 days (L4) 70 to 120 days (L5), 220 days (microfilaria)
<i>E. granulosus</i>	> 28 days	
<i>E. multilocularis</i>	> 18 days	
<i>Taenia</i> spp.	> 35 days	
<i>D. caninum</i>	> 28 days	

* For somatic larvae, treat within 2 days prior to parturition

** For breeding females, treat at 1 to 2 weeks prior to parturition

5. Treatment Procedures

The method of administration (oral, parenteral, topical), formulation and extent of activity of the product will influence the protocol design. It is advisable to consider the weather and animal relationship and bathing with regard to effectiveness of topical formulations.

For oral formulations, palatability studies should always be included in the evaluation of the effectiveness of the product. For products administered topically, the impact of weather (e.g.

rainfall, UV light), bathing and coat length should be included in the evaluation of the effectiveness of the product.

6. Animal Selection, Allocation and Handling

Approximately six month old dogs are suitable for effectiveness studies. However there are exceptions:

- *S. stercoralis* var. *canis* : less than 6 months:
- *A. caninum*, *A. braziliense*, *A. tubaeforme*, *U. stenocephala* : 6 to 12 weeks
- *T. canis*, *T. cati*, *T. leonina* : 2 to 6 weeks:
- *D. caninum* : 3 months or older
- *Mesocestoides* spp.: 8 weeks or older

Naturally infected animals are selected based on egg output or expelled proglottids for gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. They should be assigned to each group and replicated using an adequate method that should be described in the final report. Replications should cover each factor that may have an impact on the final evaluation of the effectiveness of the formulation. Animal housing, feeding and care should follow strict recommendations of welfare for dogs. Animals should be acclimated for at least 7 days to the experimental facilities and personnel.

B. Specific Evaluation Studies

1 - Dose Determination Studies

No species-specific recommendation.

2 – Dose Confirmation Studies

No species-specific recommendation.

3 - Field Effectiveness Studies

Field (clinical) studies should not be conducted with dogs infected with *Echinococcus* spp.

4 – Persistent Effectiveness

Due to the differing biologies for the helminths of dogs and the lack of experience with persistent effectiveness for these parasites, no recommendations can be provided.