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Effectiveness of Anthelmintics: Specific Recommendations for Canines

VICH GL19

Guidance for Industry

Final Guidance

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

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For further information regarding this document, contact Center for Veterinary Medicine, Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740, email: AskCVM@fda.hhs.gov

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

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

This Guidance has been developed by the appropriate VICH Expert Working Group and 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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Contains Nonbinding Recommendations

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I. Introduction

The present guidance for canines 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 this canine guidance is: (1) to be more specific for certain specific canine 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 for dogs and cats. *Veterinary Parasitology* 312: 109815, 2022, and updated versions as they are published.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA's guidance documents should be viewed only as recommendations, unless specific

[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

The evaluation of effectiveness data is based on parasite counts (adults, larvae) in dose determination and dose confirmation studies. Egg counts/larval identification should be 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, e.g., ascarids.

Adequate parasite infection should be defined in the protocol according to regional prevalence or historical data and/or statistical analysis.

2. Use of Natural or Induced Infections

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

Dose confirmation studies should be conducted using naturally- or artificially-infected animals. Where possible, at least one study should be conducted in naturally-infected animals. An explanation should be provided if this is not possible, e.g., applicable laws or regulations prohibit sourcing of naturally-infected animals. Two studies should be conducted for each parasite claimed on the label. If both studies are conducted using experimentally-infected animals, then parasites should originate from naturally-occurring infections from different geographical regions no older than 10 years prior to use for inducing infection. In addition to two dose confirmation studies, effectiveness and safety is generally confirmed by data from field studies. *Echinococcus* spp. and *Dirofilaria* spp. testing may be conducted using animals harboring induced infections due to public health considerations for echinococcosis and the complexity of the claims for heartworm. Due to the zoonotic potential of *Echinococcus* spp., studies conducted using this genus should be carried out under high biosecurity provisions.

For the following helminths, induced infections may also be the only available method to determine effectiveness of the product because of difficulties in obtaining a sufficient number of infected animals*: Filaroides milksi*, *F. hirthi*, *Dioctophyma renale*, *Capillaria aerophila*, *C. plica*, *Spirocerca lupi*, *Physaloptera* spp., *Mesocestoides* spp., and *Crenosoma vulpis*. For claims against larval stages, studies with induced infections should be used.

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. 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. Range of infective stages recommended to produce adequate infections in canines for anthelmintic evaluation

Parasite Anatomical Location *Genus Species*	**Range**
Small Intestine	
Toxocara canis	100 – 500*
Toxascaris leonina	200 – 3,000
Ancylostoma caninum	100 – 300
Ancylostoma braziliense	100 – 300
Uncinaria stenocephala	1,000 – 1,500
Strongyloides stercoralis	1,000 – 5,000
Echinococcus granulosus	20,000 – 40,000
Taenia spp.	5 – 15
Large Intestine	
Trichuris vulpis	100 – 500
Heart	
Dirofilaria immitis	30 – 100 **

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

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

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 non-medicated animals (control group) in each study. The infection of animals 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 animals should be statistically significant ($p \leq 0.05$);

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. For some parasites with public health or animal welfare/clinical implications, e.g., *E. granulosus* and *D. immitis*, respectively, higher

effectiveness standards (i.e., up to 100%) may be appropriate. The regulatory authority of the region in which the product is intended to be registered should be consulted; and

d. In field studies, effectiveness against helminths should be evaluated by examining for the presence or absence of parasitic elements in fecal material or blood. An *Echinococcus* spp. claim does not need field studies due to public health concerns.

4.2. Number of Animals (Dose Determination and Dose Confirmation Studies)

The minimum number of animals used per experimental group is a critical point. Although the number of animals 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 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

The minimum adequate number of helminths in individual control animals should be defined in the protocol. However, final conclusions regarding adequacy of infection should be made as part of the final report based on statistical analysis, historical data, literature review, or expert testimony. Generally, a minimum of 5 nematodes in individual control animals is considered an adequate infection[2]. For *Dirofilaria immitis* microfilaria (mff) claims, 300 mff/mL (blood) is considered an adequate infection. Recommended counts (in individual control animals) to be considered adequate for cestodes include:

- *Echinococcus spp*. – 5 scolices
- *Taenia spp*. – 2 scolices
- *Dipylidium caninum* – 2 scolices

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.

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

Table 2. Recommended time of treatment after infection.

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

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

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 at 14 days and the other half at 28 days; and
- *D. immitis*: varies by trial design.

For claims against transplacental and/or transmammary transmission of *T. canis*, somatic larvae of naturally- or artificially-infected pregnant bitches should be treated prior to parturition and the effectiveness checked by counting the larvae in the bitch milk and/or the adult worms in the small intestines of the litter.

5. Treatment Procedures

The method of administration (oral, parenteral, topical), formulation, and extent of activity of a 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 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 6-month-old canines are suitable for effectiveness studies; however, there are exceptions:

- *S. stercoralis*: less than 6 months;
- *A.caninum*, *A. braziliense*: 6 to 12 weeks;
- *T. canis*, *T. leonina*: 2 to 6 weeks;
- *D. caninum*: 3 months or older;
- *Mesocestoides* spp.: 8 weeks or older; and
- *T. vulpis*: dogs older than 6 months can be used.

Naturally-infected animals should be selected based on egg output or expelled proglottids for gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. 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.

Animal housing, feeding, and care should follow recommendations for welfare for canines. Animals should be acclimatized for at least 7 days to the experimental facilities and personnel. Animals should be monitored daily for adverse reactions.

B. Specific Evaluation Studies

1. Dose Determination Studies

No species-specific recommendations.

2. Dose Confirmation Studies

No species-specific recommendation.

3. Field Effectiveness Studies

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

4. Persistent Effectiveness Studies

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