

# **Guidance for Industry**

## **Effectiveness of Anthelmintics: Specific Recommendations for Canine VICH GL19**

### **FINAL GUIDANCE**

This final 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.

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. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. All comments should be identified with the Docket No. 00D-1532.

For questions regarding this document, contact Thomas Letonja, Center for Veterinary Medicine, (HFV-135), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7576, e-mail: [tletonja@cvm.fda.gov](mailto:tletonja@cvm.fda.gov).

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Veterinary Medicine  
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# **EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CANINE**

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Recommended for Implementation  
on June 2001  
by the VICH Steering Committee

THIS GUIDANCE 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.

## **EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CANINE**

Endorsed by the VICH Steering Committee at Step 7 of the  
VICH process at its meeting from June 2001

***This guidance represents the agency's current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.***

### **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. It 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 is part of the EAGR and the aim is: (1) to be more detailed for certain specific issues for canines not discussed in the EAGR; (2) to highlight differences with the EAGR on 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 detail in other published documents, e.g., WAAVP Guidelines for Evaluating the Effectiveness of Anthelmintics for Dogs and Cats, Veterinary Parasitology **52**: 179-202, 1994.

### **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 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 animals harbouring 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. trials conducted using this genus should be carried out under high biosecurity provisions.

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*, *Diocotophyema renale*, *Capillaria aerophila*, *C. plica*, *Spirocerca lupi*, *Physaloptera* spp, *Mesocestoides* spp. and *Crenosoma vulpis*. For claims against larval stages, only 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.

Parasites	Range
<b>Small Intestine</b>	
<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>	1,000 – 1,500
<i>Strongyloides stercoralis</i>	1,000 - 5,000
<i>Echinococcus granulosus</i>	20,000-40,000
<i>Taenia</i> spp.	5 - 15
<b>Large Intestine</b>	
<i>Trichuris vulpis</i>	100 - 500
<b>Heart</b>	
<i>Dirofilaria immitis</i>	30 – 100 **

\* In suckling canine or canine 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 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 six adequately infected non-medicated animals (control group) and six 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 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;
- d) The infection of the animals in the study may be deemed adequate based on historical, parasitological and/or statistical criteria;
- e) Effectiveness against helminths should be evaluated by examining for the presence or absence of parasitic elements in faecal 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 Trials)**

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 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; 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**

With respect to the minimum adequate number of helminths, the decision should be made when the final report is submitted based on historical data, literature review, or expert testimony. Generally the minimal number of nematodes in canine recommended as 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.

Table 2. Recommended time of treatment after infection.

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

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

With the majority of parasites approximately seven 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. hirathi*: 42 days;
- *F. osleri*: one-half of the animals at 14 days and the other half at 28 days;
- *D. immitis*: varies by trial design.

For claims against transplacental and/or transmammary transmission of *T. canis* somatic larvae of natural 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 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 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 canine are suitable for effectiveness studies.

However, there are exceptions:

- *S. stercoralis* : less than six months;
- *A. caninum*, *A. braziliense*, *A. tubaeforme*, *U. stenocephala* : six to 12 weeks;
- *T. canis*, *T. leonina* : two to six weeks;
- *D. caninum* : three months or older;
- *Mesocestoides* spp.: eight weeks or older;
- *U. stenocephala* and *T. vulpis* : older canines 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*. 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 recommendations for welfare for canines. Animals should be acclimatized for at least seven-days to the experimental facilities and personnel. Animals should be monitored daily to determine adverse reactions.

### **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 canine infected with *Echinococcus* spp.

#### **4 - Persistent Effectiveness**

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