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Effectiveness of Anthelmintics: Specific Recommendations for Caprines

VICH GL14

Guidance for Industry

Final Guidance

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

Submit comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2022-D-1494.

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

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EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CAPRINES (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

Effectiveness of Anthelmintics: Specific Recommendations for Caprines

Guidance for Industry

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I. Introduction

This caprine guidance 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 caprine guidance is: (1) to be more specific for certain specific caprine 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) Third edition of the guideline for evaluating efficacy of anthelmintics in ruminants (bovine, ovine, caprine) *Veterinary Parasitology* 329: 110187, 2024, and updated versions as they are published.

The cost of a full animal drug development program may preclude the development of products for this species, and since the helminth species of caprines are identical to those of ovines, it is recommended that consideration be given to an abbreviated schedule of studies to obtain approval.
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

Only controlled tests based on parasite counts of adults/larvae are recommended both for the dose determination and dose confirmation studies, since critical tests generally are not considered to be reliable for ruminants. Egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies. 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 historical data and/or statistical analysis.

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. Limited experience exists with induced infections of *Protostrongylidae*, cestodes, and *Dicrocoelium* spp. For these parasites, the use of natural infections instead of induced infections may be justified.

Dose confirmation studies should be conducted using naturally-infected animals; however, induced infections or superimposed induced infections can also be used. This procedure will allow a wide range of parasites to be present. For claims against 4th stage larvae, induced infections should be used. For claims against hypobiotic larvae, natural infections should be used. Sponsors should aim for a maximum period of accumulation of hypobiotic larvae for the particular parasite species being targeted in study animals. This will be area or regionally dependent. Specific details on area or regional situations should be obtained from experts on a case-by-case basis. In all cases, animals should be housed (to preclude reinfection) for a minimum of 2 weeks before treatment.

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 to be used is approximate and will depend on the isolate that is used. 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 parasites with existing infection models.

Table 1. Number of Infective Stages Recommended to Produce Adequate Infections in Goats for Anthelmintic Evaluation

Parasite Anatomical Location ***Genus Species***	**Range of Eggs/Larvae**
Abomasum	
Haemonchus contortus	400 – 4,000
Teladorsagia circumcincta	6,000 – 10,000
Trichostrongylus axei	3,000 – 6,000
Intestines	
Cooperia curticei	3,000 – 6,000
T. colubriformis & *T. vitrinus*	3,000 – 6,000
Nematodirus spp.	3,000 – 6,000
Oesophagostomum spp.	500 – 1,000
Chabertia ovina	800 – 1,000
Bunostomum trigonocephalum	500 – 1,000
Strongyloides papillosus	80,000
Gaigeria pachyscelis	400
Trichuris spp.	1,000
Lungs	
Dictyocaulus filaria	1,000 – 2,000
Liver	
Fasciola hepatica (metacercaria)	
Chronic	100 – 200
Acute	1,000 – 1,500

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 ($p \leq 0.05$); 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 Animals (Dose Determination, Dose Confirmation, and Persistency 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 has 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 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. The range of caprine 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 *Bunostomum* spp., *Oesophagostomum* spp., *Trichuris* spp., *Gaigeria pachyscelis*, and *Dictyocaulus filaria*. Generally, for *Fasciola* spp., minimum counts of 20 adults are considered adequate.

4.4 Label Claims

For adult claims, as a general rule, the treatment should not be administered earlier than 21 to 25 days after infection; optimum for most species is 28 to 32 days. Major exceptions are: *Oesophagostomum* spp. (34 to 49 days), *C. ovina* (49 days), *Bunostomum* spp. (52 to 56 days), *Strongyloides papillosus* (14 to 16 days), and *Fasciola* spp. (see below).

For L4 claims, treatments should be given on the following days after infection: 3 to 4 days for *Strongyloides papillosus*; 5 to 6 days for *Haemonchus* spp., *Trichostrongylus* spp., and *Cooperia* spp.; 7 days for *T. (O.) circumcincta*; 8 to 10 days for *Nematodirus* spp. and *D. filaria*; and 15 to

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

17 days for *Oesophagostomum* spp. The term "immature" on the labeling is not recommended for these claims.

For *Fasciola* spp. treatment should be administered as follows:

a. Early immature stages: Treatment should be administered at 1 to 4 weeks post-infection when flukes will be migrating in the liver parenchyma.
b. Late immature stages: Treatment should be administered at 6 to 8 weeks post-infection when flukes are still immature but starting to enter the hepatic bile ducts.
c. Mature flukes: Treatment should be administered at 12 to 14 weeks post-infection when all forms are in the bile ducts and gall bladder.

5. Treatment Procedures

The method of administration (oral, parenteral, topical, slow-release, etc.), formulation, and extent of activity of a product will influence the protocol design. It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations. Slow-release products should be tested over the entire proposed effective time unless additional information suggests that this is unnecessary, e.g., blood levels demonstrate steady state at all points of the proposed therapeutic period.

When the drug is to be administered in the water or in a medicated feed, it should be done following the labeling recommendations. Palatability studies may be required for medicated feeds. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product provided to each animal should be recorded to ensure that the treatment satisfies the label recommendations. For products used topically**,** the impact of weather (e.g., rainfall, UV light) and coat length should be included in the evaluation of the effectiveness of the product.

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 ruminating and older than 3 months of age. 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, chemically not related to the test drug, to remove pre-existing infections followed by fecal examination to determine that the animals are helminth-free. Extended-release anthelmintics should not be used. If possible, treatment using anthelmintics with persistent activity should be avoided or the study schedule adjusted to prevent interference of the treatment with the establishment of induced infections.

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 acclimatization period of 7 days is recommended. Housing, feed, and water should be adequate according to the geographical location. Animals should be monitored daily for adverse reactions.

B. Specific Evaluation Studies

1. Dose Determination Studies

A dose determination study and/or sheep/goat comparative pharmacokinetic studies where appropriate, should verify if the dose selected is effective in goats.

2. Dose Confirmation Studies

Confirmation studies including at least the dose limiting helminth(s) and stages in each study are recommended. If effectiveness is demonstrated for the test parasites a claim can be supported for all the helminth species claimed for the sheep host.

3. Field Effectiveness Studies

The field studies should be replicated in different geographic locations and in animal/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 (if fecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both fecal collection and examination. 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 larval counts for *D. filaria*) and should be performed using samples from the same animal before and after treatment. Post-treatment counts are generally made 10-14 days after treatment, but the timing of post-treatment counts will depend on the parasite species and class of anthelmintic evaluated. For example, due to the known effects of macrocyclic lactones on nematode egg suppression, post-treatment counts should be delayed until at least 14 days or longer. Unless otherwise justified, effectiveness should be calculated using post-treatment fecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of effectiveness using pre- and post-treatment fecal egg counts from animals in the treated group may provide further information on field effectiveness. Furthermore, additional endpoints for evaluating field effectiveness should be considered as they are developed and generally accepted by experts in veterinary parasitology.

See also sections A.4.4. *Data Analysis Recommendations* and A.4.5. *Calculation and Evaluation of Percent Effectiveness* of GFI #90/VICH GL7.

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 both procedures, no standardized protocols have been developed. When conducting studies, protocol details should include, among other things: determination of larval viability throughout the study, rationale for larval challenge, and justification for slaughter time. Parasite-naive goats are recommended for the studies. A study design is recommended using multiple daily challenges, as this most closely mimics what occurs under field conditions. Two studies (with parasite counts), each with a non-treated and one or more treated groups, are recommended for a persistent effectiveness claim (for each duration and helminth claim).

At least six animals 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 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 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.