95

Guidance for Industry

EFFECTIVENESS OF ANTHELMINTICS: Specific Recommendations for Bovine VICH GL12

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 this document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Comments should be identified with the full title of the guidance document and the Docket No. 99D-2248.

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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
March 26, 2001

EFFECTIVENESS OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR BOVINE

Recommended for Consultation
at Step 7 of the VICH Process
in November 1999
by the VICH Steering Committee

EFFECTIVENESS OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR BOVINE

Endorsed by the VICH Steering Committee at Step 7 of the VICH Process at its meeting from 16-19 November 1999

This guidance represents FDA's current thinking on this matter 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 applicable statutes and regulations.

Introduction

These guidances for bovine were developed by the Working Group 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 guidances for bovine are part of this EAGR and the aim is (1) to be more specific for certain specific issues for bovine not discussed in the overall guidances; (2) to highlight differences with the EAGR on effectiveness data recommendations and (3) to give explanations for disparities with the EAGR.

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 the sponsors refer to the pertinent procedures described in detail in other published documents e.g. WAAVP Second Edition of Guidances for Evaluating the Effectiveness of Anthelmintics in Ruminants (Bovine, Ovine, Caprine) Veterinary Parasitology ***58***: 181-213, 1995.

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 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 or recent field isolates. Limited experience exists with induced infections of *Toxocara vitulorum*, cestodes and *Dicrocoelium dendriticum*. 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 which can have superimposed induced infections of certain parasites that will not interfere with the resident intestinal population. This procedure will allow a wide range of parasites. For claims against hypobiotic larvae, only natural infections should be considered. Sponsors should aim for a maximum period of accumulation of hypobiotic larvae for the particular parasite species being targeted in trial 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 cattle for anthelmintic evaluation.

Parasites	**VICH**
Abomasum	
Haemonchus placei	5,000 - 10,000
Ostertagia ostertagi	10,000 - 30,000
Trichostrongylus axei	10,000 - 30,000
Intestines	
Cooperia oncophora	10,000 - 30,000
C. punctata	10,000 - 15,000
T. colubriformis	10,000 - 30,000
Nematodirus spathiger	3,000 - 10,000
N. helvetianus	3,000 - 10,000
N. battus	3,000 - 6,000
Oesophagostomum radiatum	1,000 - 2,500
O. venulosum	1,000 - 2,000
Chabertia ovina	500 - 1,500
Bunostomum phlebotomum	500 - 1,500
Strongyloides papillosus	1,000 - 200,000
Trichuris spp.	1,000
Lungs	
Dictyocaulus viviparus	500 - 6,000
Liver	
Fasciola hepatica (metacercaria)	
Adult cattle	1,000
Young cattle	500-1,000

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 animals should be statistically significant ($p<0.05$);

c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data;

d) Infection of the animals in the study may be deemed adequate based on historical, parasitological and/or statistical criteria.

This recommended effectiveness standard (= 90% or higher) is based on helminth removal from the host. If, however, the focus of regional anthelmintic treatment is to target prevention of pasture contamination due to the epizootiology of gastrointestinal helminth parasites, then a higher minimum effectiveness standard may be applied. Sponsors should discuss such situations with the regulatory authorities prior to commencement of trial work.

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 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 calculated. If the differences are significant ($p<0.05$), effectiveness may be calculated and if the infection is deemed adequate in each study, 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

Concerning minimum adequate number of helminths, the decision will be made when the final report is submitted based on statistical and historical data, literature review, or expert testimony. The range of bovine helminths (adults) that has been considered adequate to grant a claim varies according to the species. Generally the minimal mean number of nematodes recommended as adequate is 100. Lower mean counts are to be expected with *Bunostomum* spp, *Oesophagostomum* spp., *Trichuris* spp., and *Dictyocaulus* spp. For *Fasciola* spp. minimal mean counts of 20 adults may be 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), *Bunostomum* spp. (52 to 56 days), *Strongyloides papillosus* (14 to 16 days) and *Fasciola* spp. (8 to 12 weeks).

For L4 claims, treatments should be given as a general rule 7 days after infection with the following recommended exceptions: 3 to 4 days for *Strongyloides papillosus*., 5 to 6 days for *Haemonchus* spp., *Trichostrongylus* spp. and *Cooperia* spp., 8 to 10 days for *Nematodirus* spp. and 15 to 17 days for *Oesophagostomum* spp . The term immature on the labeling is not recommended. For early immature *Fasciola* spp., treatments should be given 1 to 4 weeks after infection and for late immatures at 6 to 8 weeks.

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 premix, it should be done following the labeling recommendations. Palatability studies may be required for medicated premixes. Samples of medicated water or 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 impact 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. Animals should be assigned randomly to each treatment. Blocking in replicates by weight, sex, age, and/or exposure to parasites may aid in reducing trial variance. Faecal egg/larval counts are also useful to allocate the experimental animals.

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 faecal examination to determine that the animals are helminth free.

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 seven-day acclimatization period is recommended. Housing, feed, and water should be adequate according to the geographical location. Animals should be monitored daily to determine 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, larvae and when applicable hypobiotic larvae.

3 - Field Effectiveness Studies

No species specific recommendations

4 - Persistent Effectiveness Studies

Two basic study designs have been used to pursue persistent effectiveness claims. One is 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 naïve cattle are recommended in these studies. A study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature. Two trials (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 three 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.

Persistent effectiveness claims should be supported by a minimum 90% effectiveness based on geometric means.