VICH GL12 (ANTHELMINTICS: BOVINES)
November 1999
For implementation at Step 7

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR BOVINES

Recommended for Implementation
at Step 7 of the VICH Process
on 16 November 1999
by the VICH Steering Committee

THIS GUIDELINE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND HAS BEEN 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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EFFICACY OF ANTHELMINTICS:
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Introduction

These guidelines for bovines were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General Requirements (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 guidelines for bovines are part of this EAGR and the aim is (1) to be more specific for certain specific issues for bovines not discussed in the overall guidelines; (2) to highlight differences with the EAGR on efficacy data requirements 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 guideline. We recommend to the sponsors to refer to the pertinent procedures described in detail in other published documents e.g. WAAVP Second Edition of Guidelines for Evaluating the Efficacy 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 acceptable 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, however, induced infections or superimposed induced infections can also be used. This procedure will allow a wide range of parasites. For claims against 4th stage larvae, induced infections must be used. For claims against hypobiotic larvae, only natural infections can 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 need to be housed (to preclude reinfection) for a minimum of 2 weeks before treatment.

Persistent efficacy 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 parasite species with existing infection models.

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

Parasites	Range of eggs/larvae
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 6 adequately infected animals in each of the non-medicated control group and the 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 will be deemed adequate based on historical, parasitological and/or statistical criteria.

This 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 efficacy 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 trials)

The minimum number of animals required 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 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

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 will vary according to the species. Generally the minimal mean number of nematodes considered to be 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 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 *Ostertagia* spp. and *Dictyocaulus viviparus*, 8 to 10 days for *Nematodirus* spp. and 15 to 17 days for *Oesophagostomum* spp. The term immature on the labelling is not acceptable. For early immature *Fasciola* spp., treatments should be given 1 to 5 weeks after infection and for late immatures at 6 to 9 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 as much as possible following the labelling 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 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, chemically not related to the test 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 7-day acclimatisation period is recommended. Housing and feed/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 needed to support each claim: adult, larvae and when applicable hypobiotic larvae.

3 - Field Efficacy Studies

No species specific recommendations.

4 - Persistent Efficacy Studies

Two basic study designs have been used to pursue persistent efficacy claims: one using a single challenge, another using multiple daily challenges following treatment. For both procedures, no standardised protocols have been developed. When conducting studies, protocols details should include among other things: determination of larval viability throughout the study, rationale for larval challenge and justification of slaughter-time. Parasite naive cattle are recommended in these studies. A study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature.

A minimum requirement for a persistent efficacy claim (for each duration and helminth claim) should include 2 trials (with worm counts) each with a non-treated and one or more treated groups. At least 6 animals in the control group shall be adequately infected. Persistent efficacy claims will only be granted on a species-by-species basis.

In the protocol using multiple daily challenges, different groups of animals are 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.

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