The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

CVMP/VICH/832/99-corr
London, 7 December 2000

VICH Topic GL7

Step 7 Consensus Guideline

EFFICACY REQUIREMENTS FOR ANTHELMINTICS: OVERALL GUIDELINES

TRANSMISSION TO CVMP	December 1998
TRANSMISSION TO INTERESTED PARTIES	December 1998
COMMENTS REQUESTED BEFORE	31 May 1999
FINAL APPROVAL BY CVMP	December 1999
DATE FOR COMING INTO OPERATION BY	December 2000
CORRIGENDUM APPROVED BY CVMP AND DATE FOR COMING INTO OPERATION	December 2000

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel (44 20) 74 18 84 00 Fax (44 20) 74 18 84 47
E-mail: mail@emea.eudra.org http://www.eudra.org/emea.html
EMEA 2000 Reproduction and/or distribution of this document is authorised for non-commercial purposes only provided the EMEA is acknowledged

EFFICACY OF ANTHELMINTICS: GENERAL REQUIREMENTS

Recommended for Implementation
at Step 7 of the VICH Process
on 21 November 2000
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.

EMEA 2000

EFFICACY OF ANTHELMINTICS:
GENERAL REQUIREMENTS (EAGR)

Introduction

The International harmonization of veterinary regulations has political and economical consequences.

The reduction or the elimination of the requirements to provide different sets of data for the marketing approvals could markedly reduce R&D costs and has a positive impact on the product approval process. Animal welfare will also benefit by eliminating unnecessary duplication of studies, which will lead to a reduction in the number of animals required for establishing the safety and effectiveness of veterinary antiparasitic drugs. An additional benefit would be the use of a single set of data to obtain marketing approval of products for the treatment of minor animal species.

Government regulatory authorities will also benefit by achieving recognition of uniform standards, which should have a positive impact on the resources dedicated to the approval process and should reduce the workload.

The present overall guideline will provide a major contribution towards the standardization and simplification of methods used for the evaluation of new anthelmintics and generic copies in domesticated animals. This overall guideline is supported by individual species guidelines for bovine, ovine, caprine, equine, swine, canine, feline, and poultry. These individual species guidelines are not intended for other animals.

Guidelines need to:

(1) Serve as models for government officials responsible for developing meaningful efficacy registration requirements within their country;

(2) Assist investigators in preparing basic plans to demonstrate effectively the efficacy of anthelmintics;

(3) Optimise the number of trials and experimental animals used for drug testing. This serves not only to diminish overall costs but is also an important welfare consideration.

The guidelines should not consist of rigid stipulations, but should make clear recommendations on the minimal standards needed. By their nature, guidelines address most, but not all possible eventualities. Each case has to be considered on its' merits, and if in a particular circumstance an alternative approach is deemed more fitting, a reasoned argument for the deviation should be prepared, and if possible discussed with appropriate authorities before work is initiated. Published data may be utilized also as substantial evidence to support effectiveness claims. This alternative approach should be discussed *a priori* with the corresponding regulatory authorities. It is important to emphasise that the acceptance of international data remains an important issue for the VICH guidelines.

Overall Anthelmintic Guidelines

Two sections have been identified in the guidelines: general elements, and specific evaluation studies. The General Elements section includes: good clinical practice, evaluation of effectiveness data, types of infection and parasite strains, product equivalence, recommendations for the calculation of effectiveness, standards of effectiveness and the definition of helminth claims. The Specific Evaluation Studies section describes: dose determination, dose confirmation, field and persistent efficacy studies.

A. General Elements

1 - Good Clinical Practice

The principles of Good Clinical Practice (GCP) should apply to all clinical studies and sponsors should work within the principles of the GCP recommendations. Non-GCP studies are considered as non-pivotal studies and may be used as supporting data.

2 - The evaluation of effectiveness data, use of natural or induced infections, definition of laboratory and field (helminth) strains

The evaluation of effectiveness data is based on parasite counts (adults, larvae) in dose determination and dose confirmation studies; egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies. Controlled and critical tests are acceptable both for the dose determination and dose confirmation studies (critical tests cannot be used for those drugs that destroy the parasite's body). However, controlled tests are preferable, and the option to utilize critical tests should be supported with an explanation from the sponsor.

The use of natural or induced infections in effectiveness studies will be determined by the type of parasite and the claim proposed by the sponsor. In some rare, but epizootiologically important parasites, the use of induced infections is the only solution.

Recent field isolates generally are preferred to develop induced infections, although in some cases laboratory strains can be used (see glossary). Field strains are believed to reflect more accurately the current status of the parasite in nature. The characterisation of each of the laboratory isolates used in the investigations should be included in the final report i.e. source, maintenance procedure, drug sensitivity, number of passages and expected establishment rates in the target host. For field isolates, characterisation also needs to include source, date, location of isolation, previous anthelmintic exposure and maintenance procedure.

3 - Product equivalence

The principle of product equivalence can be used for two products containing the same approved active ingredient(s), e.g. generic(s) when used at the same dose, by the same route of administration and in the same host. For a formulation change to an approved product where the same approved active ingredient(s) remains, the pharmacokinetic attributes of the drug as well as the predilection site of the targetted parasites should dictate the study type that should be conducted for product equivalence.

In either case for absorbed drugs that can be measured in the blood plasma, and for which a relationship with effectiveness can be correlated with pharmacokinetic parameters, a blood level bioequivalence study may be used. Alternatively and particularly where pharmacokinetic parameters cannot demonstrate a relationship with effectiveness, 2 dose confirmation studies using the dose-limiting parasite for therapeutic claims and/or 2 persistence efficacy studies per species claimed will be needed.

4 - Recommendations for the calculation of effectiveness

The analysis of parasite data in support of effectiveness uses estimations of several parasitological parameters including faecal egg counts and worm counts, which may be a reflection of the success of the treatment. In most natural infections, and less in induced infections, large variations in data values between similarly treated animals have been observed. This may require additional studies to be conducted to increase the number of observations.

4.1 Data analysis recommendations

The statistical analysis of the study is a two-stage procedure. The requirements for approval of an anthelmintic product are based on significant statistical differences between the treated and control groups and on calculated percent effectiveness of 90% or more.

The type of statistical analyses must be determined by the sponsor in the protocol stage prior to any data analyses. Nonparametric or parametric procedures are acceptable. If the sponsor is able to demonstrate significant statistical differences between the treated and control groups, then percent effectiveness would be calculated using geometric means. For a product to be acceptable, the calculated percent effectiveness must be at least 90% (see Standards of Effectiveness).

4.2 Geometric versus arithmetic means

Differences in effectiveness may be seen whether geometric or arithmetic means are used. However, in the context of harmonization, recommendations are needed for one method of calculating the means. Log-transformed parasite counts or egg-counts tend to follow a normal distribution more closely than do non-transformed parasite counts. The geometric mean is therefore a more appropriate estimate of central tendency and has less potential for misinterpretation than the arithmetic mean. The use of arithmetic means to evaluate effectiveness has been considered to be a more stringent criterion reflected in a more conservative estimation of therapeutic activity of the product and may be acceptable in certain circumstances only.

For the calculation of percent of effectiveness geometric means are required for dose determination, dose confirmation, field trials and persistent efficacy studies. In certain circumstances there may be conditions acceptable for the use of arithmetic means.

4.3 Number of animals (dose determination, dose confirmation and persistency trials)

The minimum number of animals required per experimental group is a crucial point. The number of animals will depend on the type of statistical analysis used, however, the inclusion of at least 6 animals in each experimental group is a minimum recommended.

4.4 Pooling data

Pooling data is allowed when certain criteria are taken into account. For sponsors intending to pool data it is important to ensure that a general protocol is standardized for each type of study proposed, that is dose confirmation, field and persistency studies. There should be similarity among numbers of animals/group numbers of parasites, type of animals and experimental conditions. Where pooled data are used, any aberrant result should be explained to the regulatory authorities.

Pooling of data only will be considered where more than two studies (as defined in Section B-2 below) have been conducted and the majority of individual studies provide 90% or greater efficacy, i.e. minimally three studies with at least two of these demonstrating efficacy of 90% or greater are required to pool data. The overall efficacy of the pooled studies should demonstrate efficacy of 90% or greater.

In the case of rare parasites an alternative approach will have to be used (i.e. more trials may be required).

The geometric means are calculated based on all controls values, i.e. dropping zero counts in control groups and a corresponding number of zero treated animals will not be allowed.

4.5 Adequacy of infection

A universal definition of adequacy of infection cannot be formulated because of the diversity of genera, species and strains of helminths subject to evaluation. Furthermore, each strain under test may have unique characteristics of infectivity and pathogenicity. However, in the development of study protocols, the adequacy of infection should be addressed, especially in terms of the statistical, parasitological and clinical relevance of the infection level in individual control animals, as well as the number of control animals in which infections are established. The level of infection, and its' distribution, among control animals should be adequate to permit the appropriate standards of efficacy to be met with acceptable statistical and biological certitude/confidence. Multiple infections are acceptable, however, each helminth species must reach acceptable minimums of infection.

In cases where all animals in the control group are infected, then *one possible* statistical method involves the use of calculating the lower 95% confidence limit of the control group geometric mean burden. If this value is greater than 10% of the control group geometric mean burden, then the infection can be said to be adequate. In the case where some of the animals in the control group are not infected (counts=zero), then the geometric means should be replaced by the median and the 95% confidence limit will be based on the control group median burden. However, whatever statistical method may be recommended, adequate infections are still required in (a minimum of) 6 control animals as outlined in the relevant species-specific guidelines.

4.6 Aliquot size

Aliquot size to determine parasite burdens should be at least 2%. Smaller aliquot size may be used with justification.

5 - Standards of Effectiveness

A compound should be declared effective only when effectiveness against each parasite declared on the labelling stands at 90% or above, based on calculation of geometric means using pooled data (when appropriate), and there is a statistically significant difference in parasite numbers between control and treated animals. However, there are regional differences where the epizootiology of certain parasitic infections may require higher minimal effectiveness, especially when the aim for drug effectiveness is focussed specifically on preventing pasture contamination. These will be covered in the individual host species guidelines. Effectiveness below 90% may be adequate when the claimed parasites do not have any other effective treatment.

6 - Definition of Helminth claims

Parasite identification will determine the type of claim proposed on the labelling. A species claim is highly recommended for adult stages. However, a genus claim should be acceptable for immature stages which cannot be specified where there is more than one species in that genus. If species claims are to be made then the presence of each should be confirmed including two dose confirmation studies for each parasite.

B. Specific evaluation studies

Three types of studies are used in the evaluation of all new anthelmintics: dose determination, dose confirmation and field efficacy studies. Special studies are also required to determine the persistent efficacy of an anthelmintic.

1 - Dose Determination Studies

Dose titration trials shall from now on be referred to as dose determination studies, their purpose being to determine the dose rate to be recommended for the particular target animal. The studies may or may not be conducted using the final formulation. However, if not, any changes in the formulation must be scientifically justified. Some regulatory authorities may waive the requirement for a dose determination study where alternative data are presented to support the intended dosage. For generic products, where the optimum dose of the active ingredient has already been generally adopted, dose determination studies are not necessary.

When broad spectrum activity is claimed for an anthelmintic preparation, dose determination studies should contain a dose-limiting species within the claimed spectrum, and should be independent of whether the dose limiting species is a high or a low (= rare) prevalence species. The sponsor should select the parasites taking into consideration their impact on animal health. Confirmation of effectiveness against the species for which a claim is made, would be completed in the dose confirmation studies.

When only one parasite is claimed (e.g. *Dirofilaria immitis*), the discussion on the number of species and the dose limiter becomes irrelevant.

One internationally accepted design includes a minimum of three groups receiving different levels of anthelmintic treatment together with a group of untreated controls should be included in the trials e.g., 0, 0.5, 1 and 2x the anticipated dose. It is suggested that the range of doses should be selected on the basis of preliminary studies to encompass the approximate effective dose. The reason for the dose selected should be explained. For each selected parasite, groups of treated and untreated controls should consist of at least 6 (= recommended) adequately infected animals, but if there is any doubt about the level of infection then the number should be increased accordingly (see data analysis).

This phase of the testing should be conducted using adult parasites unless there is information that larvae of a particular parasite could be a dose-limiting stage or the proposed product claim is only targetting a specific parasite at the larval stage (e.g. *Dirofilaria immitis*). Dose determination studies may be conducted using natural infections, however induced infections are preferred. Both laboratory strains and recent field isolates (see glossary) can be used to develop induced infections.

2 - Dose Confirmation Studies

These studies should be conducted using the final formulation of the drug to be commercialized. The dose confirmation work should not be conducted on known drug resistant strains of parasites. To investigate effectiveness against adult parasites, naturally infected animals are preferred. However, induced infections using recent field isolates in one of the studies are acceptable. For rare parasite species, laboratory strains may be used and they may be conducted outside the geographic location in which the product will be authorized for marketing. Dose confirmation for larval stages should be conducted using induced infections. The sponsor should explain deviations from this recommendation. Against inhibited stages only natural infections are recommended.

At least two controlled or, when appropriate, critical dose confirmation studies per individual claim are recommended (single or multiple infections). Two studies are the minimum needed to verify that efficacy can be achieved against various helminth strains in animals raised in disparate regions and climates and under respective husbandry conditions. At least one of the studies should be conducted in the geographic location where registration is being pursued and both studies should be conducted under conditions that are sufficiently representative of the various conditions under which the product will be authorised. In the event that in certain locations parasites are particularly rare then two trials from outside the location will be acceptable. A dose determination study can be used in place of one of the confirmation studies, if the final formulation was used and administered under label recommendations.

For each study, at least 6 (= recommended) animals per treatment group shall be adequately infected. The adequacy of the infection should be defined in the protocol phase. A sufficient number of infected animals should be examined before treatment to ensure that at least 6 (= recommended) adequately infected animals for the parasite or life stage of a parasite are present at the start of the trial (see recommendations for the calculation of effectiveness).

3 - Field Efficacy Studies

These studies shall be conducted using the final formulation of the drug product to be commercialized to confirm efficacy and safety. The number of field trials to be conducted and animals involved in each trial will depend on (1) the animal species, (2) the geographic location and (3) local/regional situations. The controls i.e. untreated animals or animals treated with a registered anthelmintic with a known profile, should equal a minimum of 25% of the treated animal numbers. Local/regional implies within a country and/or association with a climatic and/or management area (see also glossary). To achieve the requested numbers it is also acceptable to conduct multi-centre studies with sub-trials in each local/region. The request for additional (or fewer) studies, and/or animals (animal welfare considerations) by local regulatory authorities should be fully justified. The product should always be tested in the age range/class/production type of animal intended to be treated as indicated on the labelling.

4 - Persistent Efficacy Studies

Modern broad spectrum anti-parasitic compounds may show persistent effectiveness due to the presence of residual activity of either the parent compound, or the metabolites, in the treated animal. These claims can only be determined on the basis of actual worm counts and not on number of eggs per gram of faeces. Claims of activity of less than seven days should not be considered a persistent effect and claims should mention persistent efficacy for a certain number of days. The type of protocol depends on the animal species and will be discussed under the specific target species guidelines.

As described for dose confirmation, a minimum for a persistence claim (for each duration and parasite claim) should include 2 trials (with worm counts) each with a non-treated and treated group. At least 6 animals (= recommended) per treatment group shall be adequately infected. The adequacy of the infection should be defined in the protocol phase. Persistence claims will only be granted on a species-by-species basis.

ACKNOWLEDGEMENTS

The workgroup acknowledge the help of J Reid (FEDESA, EU), L Maes (FEDESA, EU), T Kennedy (AHI, USA), P Jones (EMEA), J Messenheimer (FDA/CVM, USA), D J Shaw (EU), M Lamb (FDA/CVM, USA), A Nevius (FDA/CVM, USA), K Hamamoto (JMAFF, Japan) and N Hirayama (JMAFF, Japan).

GLOSSARY

ADEQUATE INFECTION: Natural or induced infection level defined in the study protocol that will allow the evaluation of the therapeutic effectiveness of the drug when comparing parasitological parameters (e.g., number of parasites) in medicated and control animals.

ALIQUOT SIZE: A sample (known volume) of gastrointestinal or other (lung etc) content collected to determine the number of parasites.

CLAIM: A parasite species or genus (adult and/or larvae) listed on the labelling with proven susceptibility (90% or better effectiveness) to an anthelmintic drug

CONTROLLED TEST: A procedure to study the effectiveness of a drug using two groups: a control and at least one treated group of experimental animals. Adequately parasitized animals are included in each treated and control group; after a suitable period of time after treatment the animals are necropsied and the parasites are enumerated and identified. The effectiveness of the compound is calculated as follows: 100 [(GM of Nº of parasites in control group) - (GM of Nº parasites in treated animals)] divided by [GM of Nº of parasites in control animals] is equal to % Effectiveness for the parasite or life stage (GM = geometric mean). This test is the most widely used and accepted when the sample size is the same.

CRITICAL TEST: A procedure whereby the number of parasites recovered from an animal after the treatment is added to the number counted in the intestine at necropsy which are considered to be the total number of parasites in the animal at the time of treatment. The effectiveness is calculated as follows: [Nº of parasites expelled] divided by [(Nº of parasites expelled) plus (Nº of parasites remaining)] X100 is equal to % effectiveness in the individual animal.

DOSE CONFIRMATION STUDY: *In-vivo* study to confirm the effectiveness of a selected drug dose and formulation; may be conducted in the laboratory or in the field.

DOSE DETERMINATION STUDY: *In-vivo* study conducted to determine the most appropriate dose or range of effectiveness of a veterinary drug.

DOSE-LIMITING PARASITE: A parasite that will be identified during dose determination studies that will identify the dosage of the drug at which it shows 90% effectiveness. Any lower concentration of the product will show an effectiveness below 90% for the dose-limiting parasite even though it will adequately treat other parasites (90% or better effectiveness) in the host.

EFFECTIVENESS: The degree to which the manufacturers claims on the labelling have been supported by adequate data i.e. providing control of at least 90% on the basis of the calculation of geometric means using pooled data from controlled studies.

FIELD EFFICACY STUDY: Larger scale study to determine effectiveness and safety of a veterinary drug under actual use conditions.

GCP: Good Clinical Practice: A set of recommendations intended to promote the quality and validity of test data. It covers the organizational process and the conditions under which studies are planned, performed, monitored, recorded and reported.

GENERIC(S) : A generic may be approved by providing evidence that it has the same active ingredient(s), in the same dosage, as the approved animal drug, and that it is bioequivalent to the approved animal drug product. Local regulatory requirements should be addressed accordingly.

GEOGRAPHICAL LOCATION: A subdivision where the guidelines will be implemented: Japan, European Union, USA and Australia/New Zealand.

FIELD ISOLATE*:* A collection of a sub-population of helminths for the conduct of drug effectiveness tests isolated from the field less than 10 years ago. The helminths are considered representative of

current parasitic infections in the field and have been characterized (source, date, location, previous anthelmintic exposure and maitenance procedures).

LABORATORY STRAIN: A sub-population of helminths isolated form the field at least 10 years ago, which has been characterized and segregated in the laboratory. Segregation is based on a particular property making it unique for areas of research such as resistance to certain antiparasitic compounds.

RARE PARASITE: Low prevalence parasite species which may or may not be able to produce significant morbidity and clinical symptoms, usually limited to certain geographic locations.

REGION: An area within a geographical location defined by climatic conditions, target animal husbandry, and parasite resistance prevalence.

VICH: Veterinary International Cooperation on Harmonization.