International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL7 (ANTHELMINTICS GENERAL)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: GENERAL REQUIREMENTS (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS: GENERAL REQUIREMENTS (VICH GL7)

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 research and development 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, the definition of helminth claims, and an approach to new indications. 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 are generally preferred to develop induced infections, although in some cases laboratory strains can be used (see glossary). Field isolates are believed to reflect more accurately the current status of the parasite in nature. The characterisation of each of the laboratory strains used in the investigations should be included in the final report i.e. source, acquisition date, location of isolation, maintenance procedure, drug sensitivity profile, number of passages (including anthelmintic exposure during passage), and expected establishment rates in the target host. For field isolates, characterisation should include source, acquisition date, location of isolation, previous anthelmintic exposure, maintenance procedure, and number of passages.

In certain circumstances, such as for studies using products containing a previously approved active ingredient or an active ingredient within the same class as a previously approved drug, characterisation of the field isolate prior to its use in a study may include an evaluation of the sensitivity/resistance of the isolate to previously approved drugs and/or the proposed drug product, but is not required. If multiple candidate field isolates are characterised, the justification for field isolate selection should be determined *a priori* based on the study objectives. Any sensitivity/resistance characterisation performed on field isolates (e.g. number of field isolates examined and results of sensitivity/resistance characterisation) should be described in the final report. As for natural infections, induced

infection studies should use field isolates that reflect the current status of infections in the field.

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 targeted 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

For data analysis, either parametric or non-parametric procedures are acceptable. However, the statistical analyses process should be described
in the protocol prior to any data analyses. Parametric methods preserve the magnitude of observed parasite burdens and their biological interpretability. Parametric analysis also accommodates random effects (as needed) in the statistical model and provides an analysis that facilitates both group comparisons and an estimation of the means of the parasite counts for use in the calculation of percent efficacy. Non-parametric tests are appropriate when parametric methods are not applicable due to computational issues or the distribution of the count data.

If the results demonstrate significant statistical differences between the treated and control groups, then the next steps in the effectiveness evaluation should be performed as described in Section 4.2.

4.2 Calculation and Evaluation of Percent Efficacy

The choice of mean to estimate the central tendency of parasite or egg counts (e.g. geometric or arithmetic mean) may result in differences in the calculated percent efficacy. However, generally the measure of central tendency should be derived from the statistical analysis that is consistent with the distribution of the data. In the context of harmonization, recommendations are needed for how and when to use geometric or arithmetic means.

Log-transformed parasite or egg counts in untreated animals tend to follow a normal distribution more closely than do non-transformed parasite or egg counts. The geometric mean is therefore chosen as the initial estimate of the central tendency of parasite or egg counts for most dose determination, dose confirmation, and persistent efficacy studies. The log transformation includes the choice of a constant (e.g. c=1) added to the parasite or egg counts, which should be pre-defined and justified in the protocol.

For dose determination, dose confirmation, or persistent effectiveness studies in which adequate infections are established in the control group and a statistically significant difference was demonstrated between the groups, the percent efficacy should be calculated and evaluated using the following steps in order (as also shown by the decision tree in the Appendix). The process starts with calculation of efficacy based on geometric means which, if efficacy is ≥ 90%, is then complemented by calculation of efficacy based on arithmetic means. When efficacy based on arithmetic means is below 90%, a secondary assessment is applied to provide a predictable and harmonized approach to the evaluation of the biological relevance of such results. Such discrepancies between the % efficacy calculated based on geometric or arithmetic means typically occur when wide variations in worm counts are observed in the treated group at necropsy.

Steps in the interpretation of percent efficacy:

a. Calculate percent efficacy for the parasite or life stage using geometric means as follows:

   100 x ((Geometric mean for parasite count in control group – Geometric mean for parasite count in treated group) / Geometric mean for parasite count in control group)

   The geometric means should be calculated by back-transforming the least squares means estimated from a parametric model analysis of the log-transformed parasite counts, then subtracting the constant (e.g. c=1). If non-parametric methods are used for group comparison, the geometric means can be calculated directly from the observed values (parasite counts). If the experimental unit is a pen, rather than an individual animal, the initial calculation of efficacy should be performed by first computing pen averages (arithmetic mean of parasite counts in the pen); and then using these pen averages in the analysis to derive the geometric means. In situations where each experimental unit includes the same number of animals, pen totals may be used instead of pen averages.

b. Perform one of the following steps depending on the results from step a. above.

   1. If the % efficacy based on geometric means is <90% no further calculations or secondary assessment is performed. The % efficacy does not support a conclusion of effectiveness.

   2. If the % efficacy based on geometric means is ≥90%, calculate % efficacy using arithmetic means as shown below, where the arithmetic mean is computed as the average of parasite counts over all animals in each group:

      100 x ((Arithmetic mean for parasite count in control group – Arithmetic mean for parasite count in treated group) / Arithmetic mean for parasite count in control group)

If the experimental unit is a pen, rather than an individual animal, the secondary calculation of efficacy should be performed by first computing pen averages (arithmetic mean parasite counts in the pen); and then using these pen averages to compute the average parasite count in each treatment group. In situations where each experimental unit includes the same number of animals, pen totals may be used instead of pen averages.

Following the calculation of % efficacy based on arithmetic means, proceed to Step c below.

c. Perform one of the following steps depending on the results of Step b.2 above:

1. If the % efficacy based on arithmetic means is ≥90%, no further assessment is necessary. The % efficacy supports a conclusion of effectiveness.

2. If the % efficacy based on arithmetic means is <90%, a secondary assessment of the parasite counts of the experimental units (animal or pen) in both the treated and control groups should be performed.

   The methods used in the secondary assessment assume the use of appropriate animal (and pen, if applicable) selection and randomization procedures to minimize differences between treated and control groups. The control animal (or experimental unit) with the highest worm burden is used as the basis for estimating the proportion of treated animals that likely had at least a 90% reduction in worm counts to minimize the chance of overinterpreting higher worm burdens in the treated group as potential treatment failures.

   Perform the secondary assessment as follows

   Calculate the proportion of animals/experimental units in the treated group that appear to have at least a 90% reduction in parasite burden based on the highest parasite count within the experimental units of the control group.
   For sample sizes between 6 and 12 animals/experimental units:

   - If the proportion of experimental units in the treated group estimated to have a ≥90% reduction in parasite burden is at least 80%[1], effectiveness is supported.

   - If the proportion of experimental units in the treated group estimated to have a ≥90% reduction in parasite burden is less than 80%, the results do not

[1] The 80% proportion cut-off was selected based on the typical sample sizes seen in these types of studies (6-12 animals), the assumption that parasite counts in the treated and control groups are similar before treatment, and a concern for protecting against overinterpretation of treated animals with positive parasite counts after treatment. The proposed cut-off allows 1 or 2 animals in the treated group to be potential treatment failures, with a potential treatment failure defined as an individual animal that does not have ≥90% reduction in worm count when compared to the control animal with the highest worm count. This method helps to distinguish whether the cause of the lower % efficacy based on AM is due to one or two animals with higher than expected worm counts or a more widespread issue that may reflect a true efficacy of <90%. The secondary assessment method was tested using historical data sets from over 100 studies submitted to regulatory authorities (multiple animal host species and more than one jurisdiction represented) to confirm that it could identify studies with high parasite counts in the treated group that were likely of biological concern without being overly conservative.

support a conclusion of effectiveness for the study.

See Tables 1-4 in the Appendix for specific examples of this secondary assessment.
For studies with sample sizes greater than 12 animals/experimental units, the threshold proportion of animals/experimental units with at least a 90% reduction in parasite burden used to support effectiveness should be justified in the protocol.

Due to the differences in parasite detection methods, animal species husbandry, and other factors, there is not a single harmonized recommendation for calculating percent efficacy from field studies. Furthermore, new endpoints and analysis methods for evaluating field effectiveness should be considered as they are developed and generally accepted by experts in veterinary parasitology.

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 following the procedure described in Section 4.2, i.e. minimally three studies with at least two of these demonstrating efficacy as described in Section 4.2 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 control 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 defined, 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. For some parasite species, low worm counts are expected and should be accounted for in the definition of adequate infection in the study protocol. If inadequate infections in a significant number of individual study animals are expected, increasing the number of animals in the study groups to achieve six adequately infected control animals should not, by itself, be considered an appropriate modification to the study design. In such cases, a statistical method of evaluating adequacy of infection, based on worm count distributions, may be needed in addition to the minimum requirement of six adequately infected animals as outlined in the relevant species-specific guidelines.

The adequacy of infection in at least 6 individual animals, as defined in each of the species specific guidelines, is intended to provide a guideline for when adequacy of infection should be considered acceptable without additional justification. However, if a study fails to meet the pre-defined adequacy of infection levels, investigators should consider the scientific validity of the model and investigate and discuss the reason for failing to meet expected infection levels in the study. 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. Justification for including the study to support efficacy should also be included as part of the submission file, as described above.

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, as described in Section 4.2, using pooled data (when appropriate), provided the control group was adequately infected with this parasite 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. These will be covered in the individual host species guidelines (e.g. zoonotic infections, *Dirofilaria* spp.). 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.

7 – Approach to New Indications

For new parasite indications (not currently addressed in VICH Guidelines), the following items should be taken into account according to the requirements of, or in collaboration with, the appropriate regulatory bod(ies):

- number and type of studies proposed: defined based on objective (e.g. dose

determination, dose confirmation, or field trial) and type (e.g. laboratory vs. field, if laboratory, natural vs. induced)
- justification for any deviations from GL7 recommendations
- availability of different parasitic isolates
- if available, justification of the model which may include how the experimental model was developed, details of its conduct, and how well the model reflects natural infection or if the use of the model may impact the inference of the results when considering the broader population
    - method of determining eligibility of animals for inoculation (e.g. age)
    - method of inoculation of test animals/ relevance of inoculate concentration to worm burden of naturally infected animals
    - the selection of the time between treatment and necropsy
    - the selection of the time between infection and treatment
    - minimum number of parasites to determine an adequate infection

Generally, the parasite should be present in the target animal species and in the geographic region in which registration is sought. Additionally, zoonotic parasitic diseases may have implications for study design which should also be addressed.

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 (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, there should be at least 6 (= recommended) adequately infected control 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 targeting 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 parasites, unless justified based on the objectives of the study. 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) control animals 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

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. Persistent efficacy 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.

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. 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% andmeeting the criteria described in Sections 4.1 and 4.2 of VICH GL7 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 evaluation studies (see Section B) and isolated from the field less than 10 years from the start of the study. The helminths are considered representative of current parasite infections in the field and have been characterised (see Section A.2).

LABORATORY STRAIN: A sub-population of helminths isolated from the field, which has been characterised 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. Characterisation should include the elements described in Section A.2.

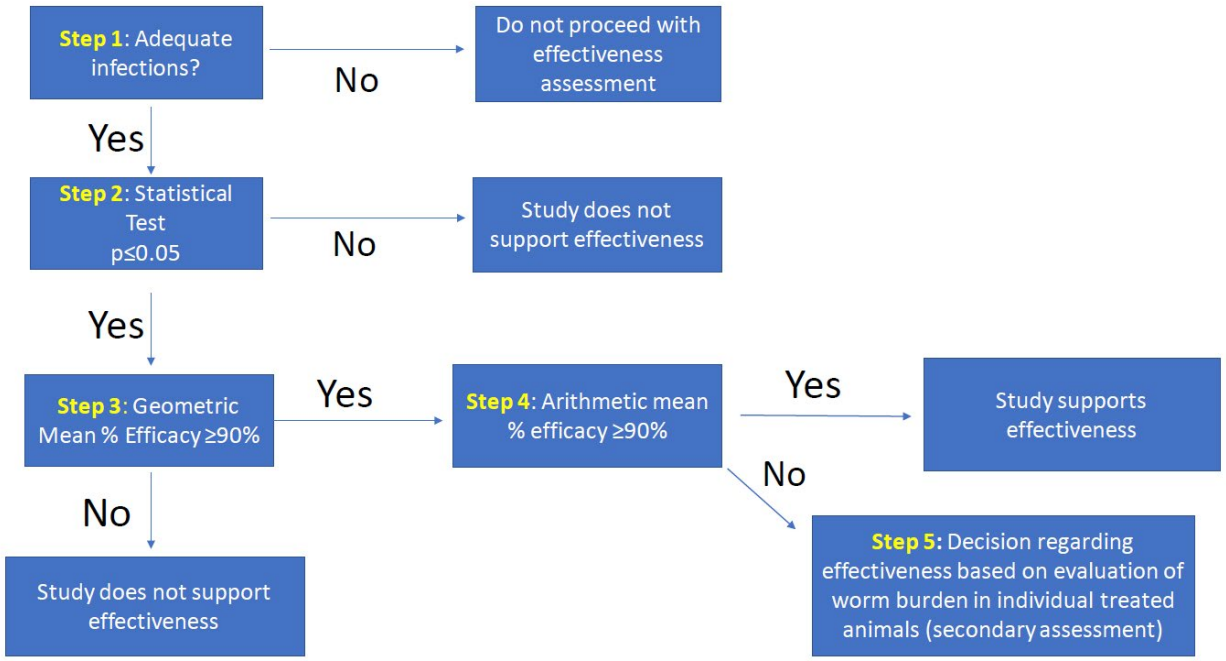
RARE PARASITE: Low prevalence parasite species which may or may not be able to produce significant morbidity and clinical symptoms, usually limited to certain geographic locations.

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

VICH: Veterinary International Cooperation on Harmonization. The full title is the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

APPENDIX: Effectiveness decision criteria for dose determination, dose confirmation, and persistent effectiveness studies

Step 1: Assess adequacy of infection. If adequate infections are confirmed in the control group, proceed to Step 2. If adequate infections not confirmed, do not proceed.
Step 2: Perform the appropriate statistical analysis. If $p \leq 0.05$, proceed to step 3. If $p > 0.05$ do not proceed, study does not support effectiveness.
Step 3: Calculate % Efficacy using Geometric means. If % efficacy is **≥90%** (GM), proceed to Step 4. If % efficacy is <90%, do not proceed, study does not support effectiveness.
Step 4: Calculate % Efficacy using Arithmetic means. If % efficacy is **≥90%** (AM), the study supports effectiveness. If % efficacy is **<90%** (AM)**,** proceed to Step 5
Step 5: Perform a **secondary assessment** comparing the worm counts in individual treated animals to the counts in the control group. <u>See Section 4.2, Step C for details on this assessment, and examples in Tables 1-4 below.</u>



Examples:

Table 1

Animal Number	Treated	Control
1	1700	15880
2	13240	740
3	0	25300
4	5200	17600
5	13540	22200
6	20	21620

In this example, the experimental unit is the animal. The % efficacy based on the GM (c=1) is 95.1%. The % efficacy based on the AM is 67.4%. The highest control animal is 25300 worms. If this animal were to have 90% reduction in worm burden, the worm count would be 2530; therefore, there are 3/6 animals that are considered failures (only 50% meet the secondary criterion), and the conclusion is that the study does not support effectiveness.

Table 2

Animal Number	Treated	Control
1	2900	8250
2	1700	7950
3	1400	9360
4	400	15250
5	2700	15800
6	600	6000
7	350	28000
8	350	5800
9	300	8700
10	2300	17270

In this example, the experimental unit is the animal. The % efficacy based on the GM (c=1) is 91.6%. The % efficacy based on the AM is 89.4%. The highest control animal is 28000 worms. If this animal were to have 90% reduction in worm burden, the worm count would be 2800; therefore, there are 1/10 animals that are considered failures (90% meet the secondary criterion), and the study would support effectiveness.

Table 3

Animal Number	Treated	Control
1	0	350
2	71	95
3	37	10
4	0	6
5	1	35
6	2	22
7	0	2
8	0	27
9	0	67
10	1	4

In this example, the experimental unit is the animal. The % efficacy based on the GM (c=1) is 92.0%. The % efficacy based on the AM is 81.9%. The highest control animal is 350 worms. If this animal were to have 90% reduction in worm burden, the worm count would be 35; therefore, there are 2/10 animals that are considered failures (80% meet the secondary criterion), and the study would support effectiveness.

Table 4

In Table 4, each pen has 10 animals. The pen parasite counts listed are the pen averages (arithmetic mean pen counts). The experimental unit is the pen.

Pen number	Treated mean parasite count	Control mean parasite count
1	5.7	11.7
2	0.3	75.6
3	5.6	25.6
4	0.5	35.7
5	2.2	69.2
6	19.7	28.4
7	2.5	21.3
8	0	45.6

In this example, the % efficacy based on the GM (c=1) is 90.0%. The % efficacy based on the AM is 88.3%. The highest average worm burden in any of the control pens is 75.6 worms. If this pen were to have 90% reduction in worm burden, the worm count would be 7.6; therefore, there are 1/8 pens that are considered failures (> 80% of pens meet the secondary criterion), and the study would support effectiveness.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL12 (ANTHELMINTICS BOVINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR BOVINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR BOVINES

INTRODUCTION

These guidelines for bovines were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines and were subsequently revised in 2022. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General Requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the guidelines for bovines is (1) to be more specific for certain specific issues for bovines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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, and updated versions as they are published.

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 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 *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 to be present. For claims against 4^{th} 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.

Parasite Anatomical Location *Genus Species*	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 the non-medicated control group in each study. The infection of the 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 ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted using the procedures described in Section 4.2 of VICH GL7.

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

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 bovine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower counts are to be expected with *Bunostomum* spp, *Oesophagostomum* spp., *Trichuris* spp., and *Dictyocaulus* spp. For *Fasciola* spp. minimum counts of 20 adults are considered adequate.

Recommended worm counts (in individual control animals) to be considered adequate for specific parasites include:

Cooperia oncophora and *C. punctata:* 200 worms
All other Cooperia species: 100 worms
Haemonchus placei: 200 worms
Haemonchus contortus: 200 worms
Ostertagia ostertagi: 200 worms
Nematodirus helvetianus: 100 worms
Trichostrongylus axei, T. colubriformis, T. longispicularis: 100 worms
Bunostomum phlebotomum: 50 worms
Oesophagostomum radiatum: 50 worms
Dictyocaulus viviparus: 10 worms

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 labeling is not acceptable for these claims.

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 feed, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated feed. 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 should only be employed 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, 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

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 faecal samples will not be collected from

all available animals in the study), as appropriate, and the methods to be used for both faecal 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 faecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). 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. Efficacy should be calculated using post-treatment faecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of efficacy using pre- and post-treatment faecal egg counts 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 4.1 and 4.2 of VICH GL7.

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, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products

VICH GL13 (ANTHELMINTICS OVINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR OVINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR OVINES

INTRODUCTION

These guidelines for ovines were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines and subsequently revised in 2022. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General Requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the guidelines for ovines is (1) to be more specific for certain specific issues for ovines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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, and updated versions as they are published.

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 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. If no infection model exists for a parasite species (*Protostrongylidae*, cestodes, *Dicrocoelium* spp.), the use of natural infections instead of induced infections is 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 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, if needed. 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 parasites with existing infection models.

Table 1 - Number of Infective Stages Used to Produce Adequate Infections in Sheep 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)	
	100 - 200 (chronic)
	1,000 – 1,500 (acute)

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) in each study. The infection of the 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 ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted using the procedures described in Section 4.2 of VICH GL7.

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 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

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 ovine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower individual counts are to be expected with *Bunostomum* spp., *Oesophagostomum* spp., *Trichuris* spp., *Gaigeria pachyscelis* and *Dictyocaulus filaria*. 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. (28 to 41 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 *T.(O.) circumcincta*, 8 to 10 days for *Nematodirus* spp., and *D. filaria* and 15 to 17 days for *Oesophagostomum* spp. The term immature on the labelling is not acceptable for these claims.

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 medicated feed, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated feed. 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. Randomization to treatment group should be performed using

an adequate method that should be described in the protocol and final report. Blocking should only be employed 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, 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

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 faecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both faecal 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 faecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). 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. Efficacy should be calculated using post-treatment faecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of efficacy using pre- and post-treatment faecal egg counts 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 4.1 and 4.2 of VICH GL7.

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 sheep 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, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL14 (ANTHELMINTICS CAPRINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CAPRINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR CAPRINES

INTRODUCTION

These guidelines for caprines were developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines and subsequently revised in 2022. They should be read in conjunction with the VICH Efficacy of Anthelmintics: General requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of the guidelines for caprines is (1) to be more specific for certain specific issues for caprines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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, and updated versions as they are published.

The cost of a full development programme 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.

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 subjected 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. If no infection model exists for a parasite species (*Protostrongylidae*, cestodes, *Dicrocoelium* spp.), the use of natural infections instead of induced infections is 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 4^{th} 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, if needed. 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 parasites with existing infection models.

Table 1 - Number of Infective Stages Used 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)	100 - 200 (chronic)
	1,000 – 1,500 (acute)

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 non- medicated animals (control group) in each study. The infection of the 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 ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted using the procedures described in Section 4.2 of VICH GL7.

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 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

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 will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower counts are to be expected with *Bunostomum* spp, *Oesophagostomum* spp., *Trichuris* spp., *Gaigeria pachyscelis* and *Dictyocaulus filaria*. 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. (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 *T. (O.) circumcinca*, 8 to 10 days for *Nematodirus* spp. and *D. filaria* and 15 to 17 days for *Oesophagostomum* spp*.* The term immature on the labelling is not acceptable for these claims.

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 medicated feed, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated feed. 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 should only be employed 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, 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

A dose determination trial 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 needed. If efficacy is demonstrated for the test parasites a claim can be supported for all the helminth species claimed for the sheep host.

3 - Field Efficacy 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 faecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both faecal 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 faecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). 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. Efficacy should be calculated using post-treatment faecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of efficacy using pre- and post-treatment faecal egg counts 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 4.1 and 4.2 of VICH GL7.

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 goats 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, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL15 (ANTHELMINTICS EQUINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR EQUINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR EQUINES

INTRODUCTION

The present guideline for equines was developed by the Working Group established by the Veterinary International Co-operation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the VICH Efficacy of anthelmintics: General requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of this guideline for equines is (1) to be more specific for certain issues for equines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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. World association for the advancement of veterinary parasitology (WAAVP): second edition of guidelines for evaluating the efficacy of equine anthelmintics. Veterinary Parasitology 103: 1-18, 2002, and updated versions as they are published.

A. General Elements

1. The Evaluation of Effectiveness Data

Controlled tests are recommended both for the dose determination and dose confirmation studies. Critical tests also can be used for certain adult large nematodes e.g. *Parascaris equorum* and *Oxyuris equi*. Long-acting products 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.

In the case of *Strongyloides westeri*, the evaluation of effectiveness data may be based on egg counts (at least 2 field efficacy studies). The justification for this is the fact that *S.westeri* is mainly observed in young animals. At this age few other helminths have matured and use of young animals in terminal tests is inappropriate from an ethical perspective.

2. Use of Natural or Induced Infections

Because of the difficulties involved in carrying out induced infections in worm-free equines, most studies can be carried out in naturally infected animals.

Dose determination studies can be conducted using natural or induced infections with either laboratory strains or recent field isolates.

Dose confirmation studies against adult stages for a wide range of parasites can be conducted using naturally infected animals which may be superimposed with induced infections of recent field isolates. Induced infections with recent field isolates are also acceptable. For claims against hypobiotic larvae (early L3 of small strongyles) only natural infections can be considered. In these cases, animals need to be housed for a minimum of 2 weeks before treatment to preclude unintended reinfection.

To determine the number of hypobiotic larvae, digestion of the large intestinal mucosa is required, the number of intramucosal developing stages (late L3/L4 of small strongyles) should be determined by using both the digestion technique and the transillumination technique due to the inherent limitation of each technique in isolation.

Persistent efficacy studies should be conducted using induced infections with recent field isolates and using young equines i.e. < 12 months of age.

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

As the use of induced infections in equines is not common (see above), only limited data on the number of infective larvae to administer are available. The following range of infective larvae/eggs to be administered can be recommended:

Parascaris equorum	100 - 500
Trichostrongylus axei	10,000 - 50,000
Strongylus vulgaris	500 - 750
Small strongyles (Cyathostominae)	100,000 - 1,000,000

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 non- medicated animals (control group) in each study; where a critical test is used only 6 animals are needed for each study as each animal acts as its own control. The infection of the 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 ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted using the procedures described in Section 4.2 of VICH GL7.

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 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 has 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 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 worm 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 equine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower counts are to be expected . with cestodes (e.g. *Anoplocephola perfoliata*, minimum number of 10), trematodes (*Fasciola* spp.), *Parascaris equorum,* and *Dictyocaulus arnfieldi*.

4.4 Label Claims

Adult or L3/ L4 stages: the term immature on the labelling is not acceptable. For adult and larval claims, treatment should correspond to life-cycle timing appropriate for the species claimed. In the case of small strongyles distinction needs to be made between early (hypobiotic) L3 stages, (developing) intramucosal L4 stages, luminal L4 stages, and adults.

Parasite identification will determine the type of claim proposed on the labelling. A species claim is highly recommended. For the small strongyles a genus claim should be acceptable on the assumption that generally speaking there is more than one species in that genus and the study was conducted with a mixed larval population.

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 this is unnecessary e.g. for systemic acting compounds blood levels demonstrate steady state at all points of the proposed therapeutic period. When the drug is to be administered in the water or via a medicated feed, it should be done as much as possible following the labelling recommendations. Palatability studies may be required for medicated feed. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product consumed by 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 3 to 12 months of age and raised helminth free, if induced infections are used because there is no guarantee that pre-existing infections can be removed. For natural infections animals between 12 to 24 months are preferred (except for *S. westeri*) and to reduce individual variations in worm counts it can be useful to graze the equines for at least 5 months together on the same infected pasture. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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.

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 supply 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. For additional descriptions of the procedures refer to VICH GL7.

3. Field Efficacy 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 faecal samples will not be collected from all available animals in the study), as appropriate, and the methods to be used for both faecal 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 faecal egg counts and should be performed using samples from the same animal before and after treatment in both study groups (control and treated). 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. Efficacy should be calculated using post-treatment faecal egg counts from the treated and control (typically placebo or untreated control) groups. Additionally, a calculation of efficacy using pre- and post-treatment faecal egg counts 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 Section 4.1 and 4.2 of VICH GL7.

4. Persistent Efficacy

These claims can only be determined on the basis of actual worm counts and not on eggs per gram of faeces to demonstrate drug effectiveness.
A minimum requirement for a persistent efficacy claim (for each duration and helminth claim) should include two trials (with worm counts) each with a non-treated and one or more treated groups. At least 6 animals in the control group (of the same age) shall be adequately infected. Persistent efficacy claims will only be granted on a species-by-species basis, genus-by-genus in the case of small strongyles.

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 consistency of interpretation of results, a standardised study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature.

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 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, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

5. Egg Reappearance Period (ERP) Studies

ERP only relates to strongyles. ERP is a pasture contamination management tool and is not intended to be used to measure individual animal strongyle burdens. It is a tool to manage equine strongyles on a herd basis focusing on pasture contamination management. Claims for egg reduction during a certain period after treatment are only acceptable if the reduction in treated animals is at least 90% compared to pretreatment egg counts. In these studies animals should remain on infected pastures. Two studies are the minimum needed to determine the ERP. At least one of the two studies should be conducted in the geographical location where registration is being pursued. These studies should be conducted so that they are sufficiently representative of the various conditions under which the product will be authorised.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL16 (ANTHELMINTICS PORCINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR PORCINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR PORCINES

INTRODUCTION

The present guideline for porcines was developed by the Working Group established by the Veterinary International Co-operation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the VICH Efficacy of anthelmintics: General requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of this guideline for porcines is (1) to be more specific for certain issues for porcines not discussed in the VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7.

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 Swine. Veterinary Parasitology ***141***: 138-149, 2006, and updated versions as they are published.

A. General Elements

1. The Evaluation of Effectiveness Data

Only controlled tests are acceptable both for the dose determination and dose confirmation studies. Critical tests are generally considered not to be very reliable for porcine parasites.

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 strains or recent field isolates.

Dose confirmation studies should be conducted using naturally infected animals. Induced infections with recent field isolates are also acceptable, as well as natural infections which can have superimposed induced infections of certain parasites. This procedure will allow a wide range of parasites to be present.

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 or eggs used in the infection should be included in the final report. Table 1 shows the range of viable L3 or eggs recommended.

Table 1 – Range of Viable L3 or Eggs Used to Produce Adequate Infections in Porcine for Anthelmintic Evaluation.

Parasite Anatomical Location *Genus Species*	Range
Stomach	
Ascarops strongylina	200
Hyostrongylus rubidus	1,000 – 4,000
Physocephalus sexalatus	500
Intestines	
*Ascaris suum**	250 – 2,500
Oesophagostomum spp.	2,000 – 15,000
Strongyloides ransomi	1,500 – 5,000
Trichuris suis	1,000 – 5,000
Lungs	
Metastrongylus spp.	1,000 – 2,500
Kidney	
Stephanurus dentatus	1,000 – 2,000

* To maximize the establishment of adult worms a trickle infection with a low number of eggs is recommended.

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 experimental units (individual animals or pens, see Glossary) in the non-medicated control group in each study. The infection of the experimental units 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 experimental units should be statistically significant ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted as described in Section 4.2 of VICH GL7.

4.2 Number of Experimental Units in Dose Determination, Dose Confirmation and Persistency Trials

The minimum number of experimental units required per experimental group is a critical point. Although the number of experimental units will depend on the possibility to process the data statistically according to adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least 6 experimental units in each experimental group is a minimum.

In cases where there are several studies, none of which have 6 adequately infected

experimental units in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 experimental units 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 data, historical data, literature review, or expert testimony. If the experimental unit is a pen, an adequately infected pen should be defined by a minimum number of adequately infected animals out of the total number of animals in that pen (i.e. percentage of adequately infected animals in the pen). The range of porcine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection. Lower counts are to be expected with *A. suum, A. strongylina, P. sexalatus, S. dentatus*, *Metastrongylus* spp. and *Fasciola* spp.

4.4 Label Claims

The term immature on the labelling is not acceptable. Generally, for adult claims the treatment should not be administered earlier than 35 days for *A. strongylina,* 26 days for *H. rubidus,* 55 days for *P. sexalatus*, 49 to 63 days for *A. suum,* 10 days for *S. ransomi*, 28 to 45 days for *O. dentatum* and *O. quadrispinulatum*, 50 days for *T. suis*, 35 days for *Metastrongylus* spp. and 10 months after infection for *S. dentatus*.

Generally, for L4 claims treatments should be given 7 to 9 days after infection with exceptions: 3 to 4 days for *S. ransomi* 10 to 14 days for *A. suum,* and 16 to 20 days for *T. suis.*

For claims against migrating *A. suum* L3, treatment should be given between 2 and 6 days post-infection. Necropsy may be performed when larvae have accumulated in the small intestine either between 10 and 14 days post-infection (when parasites have matured to L4), or between approximately 23-28 days post-infection (after larvae have matured to the L5/adult stage).

For the majority of adult parasites, approximately 5 to 7 days is a sufficient time period from the termination of treatment until the animals are necropsied. For *Stephanurus dentatus* the recommended time between termination of treatment and necropsy is 6-8 weeks.

For claims against transmammary transmission of *S. ransomi* somatic larvae, natural or artificially infected pregnant sows should be treated at various times prior to parturition and the efficacy checked by counting the larvae in the sow milk and the adult worms in the small intestine of the litter.

5. Treatment Procedures

The method of administration (oral, parenteral etc), formulation and extent of activity of a product will influence the protocol design. Slow-release products should be tested over the entire proposed effective time unless additional information suggest that this is

unnecessary e.g. for systemically acting compounds blood levels demonstrate steady state at all points of the proposed therapeutic period. When the drug is to be administered in the water or via feed, it should be done following the labelling recommendations. Palatability studies may be required for medicated feed. Samples of medicated water or medicated feed should be collected to confirm drug concentration. The amount of medicated product consumed to each animal or group of animals should be recorded to ensure that the treatment satisfies the label recommendations.

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 2 to 6 months of age. If animals are housed in pens, the animals should be randomly assigned to each pen. The experimental units (animals or pens) should also be assigned randomly to each treatment group. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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 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 supply 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 and larvae. For additional descriptions of the procedures refer to VICH GL7.

3. Field Efficacy Studies

The experimental unit may be the individual animal or the pen. The design of the field studies should be representative of current commercial conditions and should be replicated in different geographic locations and in 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 and the faecal and/or urine sampling method. 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 faecal egg counts or urine egg counts. In some cases, identification of larvae or larvae counts (from faecal culture) can be performed to support faecal egg counts. Faecal egg count, urine egg count, and/or larval identification should be performed using samples from the same animal before and after treatment in both study groups (control and treated). Post-treatment counts are generally made 10-14 days after treatment, but the timing of post-treatment counts will depend on the parasite species evaluated. Efficacy should be calculated using post-treatment faecal egg or urine egg counts from the treated and control groups. A calculation of efficacy using pre- and post-treatment faecal egg or urine egg counts may be appropriate in some situations where significant individual animal variability is expected. The primary basis of the effectiveness determination should be defined in the protocol.

The potential for false positive and false negative faecal egg counts for *A. suum* and *T. suis,* and variability in daily egg output for *A. suum* should be considered in the study design and interpretation of results.

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 consistency of interpretation of results, a standardised 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 experimental units 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 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, and should take into consideration the pharmacological properties of the product.

Persistent efficacy claims should be supported by a minimum 90% efficacy at each time point and calculated and interpreted using the procedures described in Sections 4.1 and 4.2 of VICH GL7. Persistent efficacy 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.

GLOSSARY

EXPERIMENTAL UNIT: The entity (e.g., individual animal or pen) which can be independently and randomly assigned to a treatment, and whose response to the assigned treatment can be independently evaluated. The experimental unit is the basic unit for the statistical analysis. The experimental unit may be the individual pig or the pen depending on the circumstances of the study.

1) The pen is the experimental unit in the analysis if all pigs in a pen are provided the same treatment through medicated feed or water; or
2) The individual pig is the experimental unit in the analysis if the treatment can be individually administered, the treatments are randomly assigned to pigs within a pen, and the endpoint can be evaluated independently for each pig in a pen.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL19 (ANTHELMINTICS CANINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CANINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR CANINES

INTRODUCTION

The present guideline for canines was developed by the Working Group that was established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the VICH Efficacy of Anthelmintics: General Requirements (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of this guideline for canines is: (1) to be more detailed for certain specific issues for canines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on data requirements and (3) to give explanations for disparities with VICH GL7 guideline.

It is important to note that technical procedures to be followed in the studies are not the aim of this guideline. We recommend that the sponsors refer to pertinent procedures described in detail in other published documents, e.g. WAAVP Guidelines for Evaluating the Efficacy of Anthelmintics for Dogs and Cats, Veterinary Parasitology ***52***: 179-202, 1994, and updated versions as they are published.

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 is 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, historic data and/or statistical analysis.

2. Use of Natural or Induced Infections

Dose determination studies should be conducted using induced infections with either laboratory strains or recent field isolates.

Dose confirmation studies should be conducted using naturally or artificially infected animals. Where possible, at least one study should be conducted in naturally infected animals; deviation from this requirement should be justified, e.g., applicable laws or regulations prohibit sourcing of naturally infected animals. Two studies should be conducted for each parasite claimed on the label. If both studies are conducted using experimentally infected animals, then parasites must have originated from naturally occurring infections from different geographical regions no older than 10 years prior to use for inducing infection. In addition to two dose confirmation studies, the efficacy and safety is generally confirmed by data from field studies. *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. hirthi, Dioctophyma renale, Capillaria aerophila, C. plica, Spirocerca lupi, Physaloptera* spp*, Mesocestoides* spp*.* and *Crenosoma vulpis*. For claims against larval stages, only studies with induced infections are acceptable.

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 used to produce adequate infections in canines for anthelmintic evaluation

Parasite Anatomical Location ***Genus Species***	**Range**
Small Intestine	
Toxocara canis	100 – 500*
Toxascaris leonina	200 – 3,000
Ancylostoma caninum	100 – 300
Ancylostoma braziliense	100 – 300
Uncinaria stenocephala	1,000 – 1,500
Strongyloides stercoralis	1,000 – 5,000
Echinococcus granulosus	20,000 – 40,000
Taenia spp.	5 – 15
Large Intestine	
Trichuris vulpis	100 – 500
Heart	
Dirofilaria immitis	30 – 100 **

* In suckling canines or canines 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 6 adequately infected non-medicated animals (control group) in each study. The infection of the 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 should be statistically significant ($p \leq 0.05$).

Efficacy should be 90% or higher and calculated and interpreted using the procedure described in Section 4.2 of VICH GL7.

For some parasites with public health, animal welfare/clinical implications, e.g. *E. granulosus* and *D. immitis*, respectively, higher efficacy standards (i.e. up to 100%) may be imposed. The regulatory authority of the region in which the product is intended to be registered should be consulted.

c) Effectiveness against helminths will be evaluated examining for the presence or absence of parasitic elements in faecal material or blood. An *Echinococcus* spp. claim does not require field studies due to public health concerns.

4.2. Number of Animals (Dose Determination and Dose Confirmation Trials)

The minimum number of animals required 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 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 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. Generally, a minimum of 5 nematodes in individual control animals is considered an adequate infection. -For *Dirofilaria immitis* microfilaria (mff) claims, 300 mff/mL(blood) is considered an adequate infection. Recommended counts (in individual control animals) to be considered adequate for example cestodes include:

Echinococcus spp. - 5 scolices
Taenia spp. - 2 scolices
Dipylidum caninum - 2 scolices

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.

With the majority of parasites approximately 7 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. hirthi*: 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.

Table 2. Recommended time of treatment after infection

Parasite	Adult Stages	Larval Stages
S. stercoralis	5 to 9 days	
T. vulpis	84 days	
A. caninum	> 21 days	
A. braziliense	> 21 days	6 to 8 days * (L4)
U. stenocephala	> 21 days	6 to 8 days (L4)
T. canis	49 days	6 to 8 days (L4) 3 to 5 days (L3/L4)
T. leonina	70 days	14 to 21 days (L4/L5)
D. immitis	180 days	35 days (L4) 2 days (L3), 20 to 40 days (L4)
E. granulosu *s Taenia* spp.	> 28 days > 35 days	70 to 120 days (L5), 220 days (microfilariae)

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

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 efficacy 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 always 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 6 month old canines are suitable for effectiveness studies. However there are exceptions:
- *S. stercoralis*: less than 6 months;
- *A.caninum, A. braziliense*: 6 to 12 weeks;
- *T. canis, T. leonina*: 2 to 6 weeks;
- *D. caninum*: 3 months or older;
- *Mesocestoides* spp.: 8 weeks or older;
- *T. vulpis*: dogs older than 6 months can be used.

Naturally infected animals are selected based on egg output or expelled proglottids for gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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. Animal housing, feeding and care should follow strict requirements of welfare for canines. Animals should be acclimated for at least 7 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 Efficacy Studies

Field (clinical) studies should not be conducted with canines infected with *Echinococcus* spp.

4. Persistent Efficacy

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

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL20 (ANTHELMINTICS FELINES)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR FELINES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR FELINES

INTRODUCTION

The present guideline for felines was developed by the Working Group that was established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the "VICH Efficacy of Anthelmintics: General Requirements (VICH GL7)" which should be referred for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to VICH GL7 guideline with the aim of simplicity for readers comparing both documents.

The aim of this guideline for felines is: (1) to be more detailed for certain specific issues for felines not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on data requirements, and (3) to give explanations for disparities with VICH GL7 guideline.

It is important to note that technical procedures to be followed in the studies are not the aim of this guideline. We recommend that the sponsors refer to the pertinent procedures described in detail in other published documents e.g. WAAVP Guidelines for Evaluating the Efficacy of Anthelmintics for Dogs and Cats, Veterinary Parasitology ***52***: 179-202, 1994, and updated versions as they are published.

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 is the preferred method to evaluate the effectiveness in field studies.

The controlled test is the most widely accepted of the testing procedures for the 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 historical data and/or statistical analysis.

2. Use of Natural or Induced Infections

Dose determination studies should be conducted using induced infections with either laboratory strains or recent field isolates.

Dose confirmation studies should be conducted using naturally or artificially infected animals. Where possible, at least one study should be conducted in naturally infected animals; deviation from this requirement should be justified, e.g., applicable laws or regulations prohibit sourcing of naturally infected animals. Two studies should be conducted for each parasite claimed on the label. If both studies are conducted using experimentally infected animals, then parasites must have originated from naturally occurring infections from different geographical regions no older than 10 years prior to use for inducing infection. In addition to two dose confirmation studies, the efficacy and safety is generally confirmed by data from field studies. *Echinococcus multilocularis* 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 *E. multilocularis* trials conducted using this parasite 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 the difficulties in obtaining a sufficient number of infected animals: *Capillaria aerophile* and *Physaloptera* spp. For claims against larval stages, only studies with induced infections are acceptable.

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 common helminths.

Table 1. Range of infective stages used to produce adequate infections in felines for anthelmintic evaluation

Parasite Anatomical Location ***Genus Species***	**Range**
Small Intestine	
Toxocara cati	100 – 500
Toxascaris leonina	200 – 3,000
Ancylostoma tubaeforme	100 – 300
Ancylostoma braziliense	100 – 300
Strongyloides stercoralis	1,000 – 5,000
Taenia taeniaeformis	5 – 15
Large Intestine	
Trichuris campanula	100 – 500
Heart	
Dirofilaria immitis	30 – 100 *

* 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 6 adequately infected non-medicated animals (control group) in each study. The infection of the 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 should be statistically significant ($p \leq 0.05$).

c) Efficacy should be 90% or higher and calculated and interpreted using the procedure described in Section 4.2 of VICH GL7. For some parasites with public health, animal welfare/clinical implications e.g. *E. multilocularis* and *D. immitis*, respectively, higher

efficacy standards (i.e. up to 100%) may be imposed. The regulatory authority of the region in which the product is intended to be registered should be consulted.

d) Effectiveness against helminths will be evaluated examining for the presence or absence of parasitic elements in faecal material or blood. An *E. multilocularis* claim does not require field studies due to public health concerns.

4.2. Number of Animals (Dose Determination and Dose Confirmation Trials)

The minimum number of animals required 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 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 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. Generally, a minimum of 5 nematodes in individual control animals is considered an adequate infection. For *D. immitis*, adequacy of infection may generally be established if at least six control cats have 2 or more worms. In cases where efficacy and statistical criteria are met for an individual study, but the study does not meet the pre-defined adequacy of infection criterion, justification that the study is valid to support efficacy should be provided, using information about the infection model and isolate, and considerations from literature review and expert testimony.

Recommended counts (in individual control animals) to be considered adequate for example cestodes include:
Echinococcus spp. – 5 scolices
Taenia spp. – 2 scolices
Dipylidium caninum – 2 scolices

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.

With the majority of parasites approximately 7 days is a sufficient time period from the termination of treatment until the test animals are necropsied. The following parasites are the exception to the above general recommendation:

Physaloptera spp.*, C. aerophila, E. multilocularis, T. taeniaeformis*, *Dipylidium caninum*: 10 to 14 days; *D. immitis:* varies by trial design.

Table 2. Recommended time of treatment after infection

Parasite	Adult Stages	Larval Stages
S. stercoralis	5 to 9 days	
T. campanula	84 days	
A. tubaeforme	> 21 days	
A. braziliense	> 21 days	6 to 8 days (L4)
T. cati	60 days	6 to 8 days (L4) 3 to 5 days (L3/L4)
T. leonina	70 days	28 days (L4/L5)
D. immitis	180 days	35 days (L4) 2 days (L3), 20 to 40 days (L4)
T. taeniaeformis	> 35 days	70 to 120 days (L5), 220 days (microfilariae)

For claims against transmammary transmission of *T. cati* somatic larvae of natural or artificially infected pregnant queens should be treated prior to or just after parturition and the efficacy checked by counting the larvae in the queen milk and/or the adult worms in the small intestines of the litter.

5. Treatment Procedures

The method of administration (oral, parenteral, and topical) 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 always 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 6-month-old felines are generally suitable for controlled studies, however, older and younger animals can also be used and the following exceptions have to be taken into account:

- *S. stercoralis*: less than 6 months;
- *A. braziliense, A. tubaeforme:* 6 to 16 weeks;
- *T. cati, T. leonina:* 4 to 16 weeks;
- *D. caninum:* 3 months or older.

Naturally infected animals are selected based on egg output or expelled proglottids in gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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. Animal housing, feeding and care should follow strict requirements of welfare for felines. Animals should be acclimated for at least
7 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 recommendations.

2. Dose Confirmation Studies

No species specific recommendations.

3. Field Efficacy Studies

Field (clinical) studies should not be conducted with felines infected with *E. multilocularis* and *D. immitis.*

4. Persistent Efficacy Studies

Due to the differing biology of helminths in felines and the lack of experience with persistent efficacy for these parasites, no recommendations can be provided.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL21 (ANTHELMINTICS CHICKENS – *GALLUS GALLUS*)
May 2022
Revision at Step 9
For consultation at Step 4

EFFICACY OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR CHICKENS – *GALLUS GALLUS* (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in May 2022
by the VICH Steering Committee

This Guideline has been developed by the appropriate VICH Expert Working Group 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.

Secretariat: c/o HealthforAnimals, 168 Av de Tervueren, B-1150 Brussels (Belgium) - Tel. +32 2 543 75 72
e-mail : sec@vichsec.org - Website : http://www.vichsec.org

EFFICACY OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR CHICKENS - *GALLUS GALLUS*

INTRODUCTION

The present guideline for chickens (*Gallus gallus*) was developed by the Working Group established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidelines. It should be read in conjunction with the VICH Efficacy of Anthelmintic: General Requirements Guidelines (VICH GL7) 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 VICH GL7 with the aim of simplicity for readers comparing both documents.

The aim of this guideline for chickens is (1) to be more specific for certain specific issues for chickens not discussed in VICH GL7; (2) to highlight differences with VICH GL7 on efficacy data requirements and (3) to give explanations for disparities with VICH GL7. We recommend to the sponsors to refer to the pertinent procedures described in detail in other published documents e.g. WAAVP Guidelines for Evaluating the Efficacy of Anthelmintics in Chickens and Turkeys. Veterinary Parasitology 116: 159-173, 2003, and updated versions as they are published. For other poultry, the principles outlined in this guideline should be used where applicable.

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 chickens. Egg counts with identification of the genus is the preferred method to evaluate the effectiveness in field studies. Adequate parasite infection should be defined in the protocol according to regional prevalence or historic 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.

Dose confirmation studies could be conducted using naturally infected birds which can have superimposed induced infections. This procedure will allow a wide range of parasites to be present in the experimental birds. Also induced infections in one of the studies is acceptable. Studies for larval stages should be conducted with induced infections only.

The history of the parasites used in the induced infection studies should be included in the final report.

3. Number of Infective Forms Recommended for Induced Infections

Table 1 indicates the number of eggs/cysticercoids recommended to be used and will depend on the isolate that is used. The final number of eggs/cysticercoids used in the infection should be included in the final report.

Table 1. Range of Infective Stages Used to Produce Adequate Infections in Chickens for Anthelmintic Evaluation.

Parasites	Range
Ascaridia galli	200-500
Capillaria obsignata	100-300
Heterakis gallinarum	200-300
Raillietina cesticillus	50-100
Syngamus trachea	200 - 600

Some factors to consider for induced infections in chickens are:

a) Young birds should be used in the studies;

b) To maximize the establishment of adequate infections it is recommended to use low numbers of infective stages;

c) Stress (e.g. poor diets) is not required to generate helminth infections;

d) Housing conditions should not allow accidental infections.

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 experimental units (individual birds or pens, see Glossary) in the non-medicated control group in each study. The infection of the experimental units 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 experimental units should be statistically significant ($p \leq 0.05$).

c) Percent efficacy should be 90% or higher and calculated and interpreted as described in Section 4.2 of VICH GL7.

4.2 Number of Experimental Units in Dose Determination and Dose Confirmation Trials

The minimum number of experimental units required per experimental group is a crucial point. Although the number of experimental units will depend on the possibility to process the data according to an adequate statistical analysis, it has been recommended, to achieve harmonization, that the inclusion of at least 6 experimental units in each experimental group is a minimum.

4.3 Adequacy of Infection

The minimum adequate number of helminths in individual control birds 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. If the experimental unit is a pen, an adequately infected pen should be defined by

a minimum number of adequately infected birds out of the total number of birds in the pen (i.e. percentage of adequately infected birds in the pen). The range of chicken helminths (adults) considered adequate to grant a claim will vary according to the species. Generally, a minimum of 20 *A. galli* in individual control birds is considered an adequate infection. Lower counts may be expected with *H. gallinarum*, *C. obsignata* and *R. cesticellus.* Necropsies should be conducted within 10 days of treatment.

4.4 Label Claims

For adult claims, as a general rule, the treatment should not be administered earlier than 28 days after infection. It is recommended to include at least 6 sentinel birds for helminth characterization and quantification before treatment is initiated. For L4 claims, treatments should be given, as a general rule, 7 days after infection, except for *A. galli and H. gallinarum* which should be 16 days after infection.

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.

When the drug is to be administered in the water or in a feed, it should be done as much as possible following the labelling recommendations. Palatability/consumption 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.

6. Bird Selection, Allocation and Handling

Test birds 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, birds should be young and from a breed that is susceptible to helminth infections. If birds are housed in pens (e.g. cages or floor pens), the birds should be randomly assigned to each pen. The experimental units should also be randomly assigned to each treatment group. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report. Blocking should only be employed 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.

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 10-day acclimatisation period is recommended. Housing and feed/water should be adequate according to the geographical location. Birds should be monitored daily to determine adverse reactions.

B. Specific Evaluation Studies

1. Dose Determination Studies

If the treatment requires extended administration, one or more studies are required to determine the minimum treatment period for efficacy.

2. Dose Confirmation

No species specific recommendations.

3. Field Efficacy Studies

Depending on the facilities available, the experimental unit may be the animal, pen, or the shed/house (see glossary). The design of the field studies should represent current commercial conditions and should be replicated in different geographic locations and in different production class(es), depending on the indication being pursued. Housing will differ based on the production class under investigation (e.g. layers vs. broilers). 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. 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.

When commercial facilities (or similar) are used, the shed/house should be subdivided, when possible, to allow for sufficient replication to enable a statistical analysis. If the shed/house is the experimental unit and there is only one replicate per treatment group at a study site, the study may need to utilize additional sites with the same housing conditions to achieve sufficient replication and enable a statistical analysis. Otherwise, a study with one replicate can only be summarized using descriptive statistics and may not provide sufficient inferential value.

Effectiveness should be assessed by the reduction of worm counts in all birds or in representative birds as determined by comparing the treated and control groups. If representative birds are used for worm counts the protocol should describe procedures for random selection of animals (number and percentage) to be necropsied. Faecal egg counts may be used to establish pre-treatment infection levels and parasite species present. A comparison of pre- and post-treatment faecal egg counts may be included but is not required. If faecal egg counts are evaluated, fresh, clean droppings should be collected immediately before treatment, and at 7 to 14 days after treatment. The faecal sampling method, number of pens/animals sampled, and egg counting technique should be defined in the protocol. Standard, well accepted techniques should be used and fully described in the protocol and final report.

Clinical observations, production variables, and records of culls and mortality should be maintained and compared to control birds and historical data of the commercial establishment. If birds are processed at the end of the study, slaughterhouse inspection reports with final observations regarding possible abnormalities which are collected per the standard practices of the slaughterhouse should be included in the final report. However, if the study duration does not coincide with or include slaughterhouse processing, these data are not required.

GLOSSARY

EXPERIMENTAL UNIT: The entity (e.g. individual animal, cage, pen, or shed/house) which can be independently and randomly assigned to a treatment, and whose response to the assigned treatment can be independently evaluated. The experimental unit is the basic unit for the statistical analysis. The experimental unit may be the individual bird or the pen/shed/house depending on the circumstances of the study:

1) The pen/shed/house is the experimental unit in the analysis if all birds in a pen/shed/house are provided the same treatment through medicated feed or water; or
2) The individual bird is the experimental unit in the analysis if the treatment can be individually administered, the treatments are randomly assigned to birds within a pen/shed/house, and the endpoint can be evaluated independently for each bird in a pen/shed/house.