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Effectiveness of Anthelmintics: General Recommendations

VICH GL7

Guidance for Industry

Final Guidance

This version of the guidance replaces the version made available October 2001. This revision updates data analysis and isolate characterization recommendations, outlines how to approach new indications, and makes additional clarifying changes.

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

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October 2024
Revision at Step 9
For Implementation at Step 7

EFFICACY OF ANTHELMINTICS: GENERAL RECOMMENDATIONS (REVISION 1)

Revision at Step 9
Recommended for Adoption at Step 7 of the VICH Process
in October 2024
by the VICH Steering Committee

This Guidance has been developed by the appropriate VICH Expert Working Group and will be subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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Contains Nonbinding Recommendations

Effectiveness of Anthelmintics: General Recommendations

Guidance for Industry

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I. Introduction

The objective of this guidance is to provide study design recommendations that will facilitate the universal acceptance of the generated effectiveness data to fulfill the national/regional requirements for anthelmintic drugs in veterinary species. This guidance was prepared after consideration of the current national/regional requirements and recommendations for evaluating anthelmintic drugs in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) regions.

This guidance provides general recommendations for the design of effectiveness studies for anthelmintics, applicable to the most common veterinary species. Additional guidance for individual species-specific recommendations is provided in Guidance for Industry (GFI) #95/VICH GL12 (bovine); GFI #96/VICH GL13 (ovine); GFI #97/VICH GL14 (caprine); GFI #109/VICH GL15 (equine); GFI #110/VICH GL16 (porcine); GFI #111/VICH GL19 (canine); GFI #113/VICH GL20 (feline); and GFI #114/VICH GL21 (chicken).

It is also important to note that technical procedures to be followed in the studies are not the aim of this guideline. We recommend that sponsors refer to the pertinent procedures described in detail in other published documents, e.g., World association for the advancement of veterinary parasitology (WAAVP) guidelines and updated versions as they are published[1].

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II. General Anthelmintic Guidance

The guidance includes two sections: II.A. *General Elements* and II.B. *Specific Evaluation Studies*. The General Elements section includes: good clinical practice, evaluation of

[1] Geurden, T., Smith, E. R., Vercruysse, J., Yazwinski, T., Settje, T., & Nielsen, M. K. (2022). World association for the advancement of veterinary parasitology (WAAVP) guideline for the evaluation of the efficacy of anthelmintics in food-producing and companion animals: general guidelines. *Veterinary parasitology*, 304, 109698.

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 effectiveness studies.

A. General Elements

1. Good Clinical Practice

The principles described in CVM GFI #85 (VICH GL9), "Good Clinical Practice (GCP)" should apply to all clinical studies and sponsors should work within the principles of 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 should be 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 are not 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 should 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 should be used (see Appendix 1. *Glossary*). Field isolates are believed to reflect more accurately the current status of the parasite in nature. The characterization 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 susceptibility profile (as applicable to the study objectives), number of passages (including anthelmintic exposure during passage), and expected establishment rates in the target host. For field isolates, characterization 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 product containing a previously approved active ingredient or an active ingredient within the same class as a previously approved drug, characterization of the field isolate prior to its use in a study may include an evaluation of the susceptibility/resistance of the isolate to previously approved drugs and/or the proposed drug product. If multiple candidate field isolates are characterized, the justification for field isolate selection should be determined *a priori* based on the study objectives. Any susceptibility/resistance characterization performed on field isolates (e.g., number of field isolates examined and results of susceptibility/resistance characterization) should be described in the final report. As for natural infections, induced-infection studies should use field isolates that reflect the current status of infection in the field.

3. Product Equivalence

The principle of product equivalence may be used for certain formulation changes that do not significantly affect the safety or effectiveness of the same approved drug, when used at the same dose, by the same route of administration, and in the same host. For all formulation changes, the significance of the change (dose, route of administration, host, etc.), the pharmacokinetic attributes of the drug and the predilection site of the targeted parasites should dictate the study type that should be conducted for product equivalence.

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, two dose confirmation studies using the dose-limiting parasite for therapeutic claims and/or two persistence effectiveness studies per species claimed may 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 fecal 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. In this case, additional studies may be recommended to increase the number of observations.

4.1 Number of Animals (Dose Determination, Dose Confirmation, and Persistency Studies)

The minimum number of animals used per experimental group is a critical point. The number of animals will depend on the type of statistical analysis used; however, a minimum of at least six animals in each experimental group is recommended.

4.2 Adequacy of Infection

A universal definition of adequacy of infection should not 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 effectiveness to be met with acceptable statistical and biological certitude/confidence. Multiple infections are acceptable; however, each helminth species should reach an acceptable minimum 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, an additional justification (e.g., a statistical method 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 six individual animals, as defined in each of the species-specific guidances, is intended to provide recommendations 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 effectiveness should also be included as part of the submission file.

4.3 Aliquot Size

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

4.4 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 effectiveness. 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 A.4.5. below.

4.5 Calculation and Evaluation of Percent Effectiveness

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 effectiveness. 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 effectiveness 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 effectiveness should be calculated and evaluated using the following steps in order (as also shown by the decision tree in Appendix 2. *Effectiveness Decision Criteria for Dose Determination, Dose Confirmation, and Persistent Effectiveness Studies*). The process starts with calculation of effectiveness based on geometric means which, if effectiveness is ≥ 90%, is then complemented by calculation of effectiveness based on arithmetic means. When effectiveness 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 % effectiveness 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 effectiveness:

a. Calculate percent effectiveness 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 group of animals (e.g., a pen), rather than an individual animal, the initial calculation of effectiveness should be performed by first computing the average for each experimental unit (arithmetic mean of parasite counts in the experimental unit) and then using these experimental unit averages in the analysis to derive the geometric means. In situations where each experimental unit includes the same number of animals, parasite count totals for each experimental unit may be used instead of experimental unit averages.

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

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

   2. If the % effectiveness based on geometric means is ≥ 90%, calculate % effectiveness 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 group of animals (e.g., a pen), rather than an individual animal, the secondary calculation of effectiveness should be performed by first computing the average for each experimental unit (arithmetic mean parasite counts in the experimental unit) and then using these experimental unit averages to compute the average parasite count in each treatment group. In situations where each experimental unit includes the same number of animals, parasite count totals for each experimental unit may be used instead of experimental unit averages.

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

2. If the % effectiveness based on arithmetic means is < 90%, a secondary assessment of the parasite counts of the experimental units (animal, pen, etc.) 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%,[2] effectiveness is supported.

[2] 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 one or two animals in the treated group to be potential treatment failures, with a potential treatment failure defined as an individual animal that does not have a ≥ 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 arithmetic means is due to one or two animals with higher-than-expected worm counts or a more widespread issue that may reflect a true effectiveness 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.

- 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 support a conclusion of effectiveness for the study.

See Tables 1-4 in Appendix 2. *Effectiveness Decision Criteria for Dose Determination, Dose Confirmation, and Persistent Effectiveness Studies* 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 effectiveness 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.

4.6 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 should only be considered where more than two studies (as defined in section B.2. *Dose Confirmation Studies* below) have been conducted and the majority of individual studies provide 90% or greater effectiveness following the procedure described in section A.4.5. *Calculation and Evaluation of Percent Effectiveness*, i.e., minimally three studies with at least two of these demonstrating effectiveness as described in section A.4.5. *Calculation and Evaluation of Percent Effectiveness* are recommended to pool data. The overall effectiveness of the pooled studies should demonstrate effectiveness of 90% or greater.

In the case of rare parasites, an alternative approach should be used (i.e., more studies may be recommended).

The geometric means should be calculated based on all control values, i.e., dropping zero counts in control groups and a corresponding number of zero-treated animals is not recommended.

5. Standards of Effectiveness

A compound should be declared effective only when effectiveness against each parasite declared on the labeling stands at 90% or above, as described in section A.4.5. *Calculation and Evaluation of Percent Effectiveness*, 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 recommend higher minimal effectiveness. These will be covered in the individual host species guidances (e.g., zoonotic infections, *Dirofilaria* spp.). Effectiveness below 90% may be adequate when no other effective treatment against the parasite in question is available.

6. Definition of Helminth Claims

Parasite identification will determine the type of claim proposed on the labeling. A species claim is highly recommended. However, a genus claim may be acceptable if the parasites cannot be speciated and 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 guidances), the following items should be taken into account according to the requirements of, or in collaboration with, the appropriate regulatory bodies:

- 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 GFI #90/VICH GL7 recommendations;
- Availability of different parasitic isolates; and
- If available, justification of the model, which should 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; and
    - 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 should be used in the evaluation of all new anthelmintics: dose determination, dose confirmation, and field effectiveness studies. Special studies may also be used to determine the persistent effectiveness of an anthelmintic.

1. Dose Determination Studies

Dose titration studies should 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 should 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 should 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 limiting species becomes irrelevant.

One internationally accepted design includes a minimum of three groups of animals receiving different levels of anthelmintic treatment (e.g., 0, 0.5, 1, and 2x the anticipated dose together with a group of untreated control animals). 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 six (= recommended) adequately infected control animals.

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., *D. immitis*). Dose determination studies may be conducted using natural infections; however, induced infections are preferred. Both laboratory strains and recent field isolates (see Appendix 1. *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 by 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. Only natural infections are recommended for evaluating efficacy against inhibited stages.

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 suggested to verify that effectiveness 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 authorized. In the event that in certain locations parasites are particularly rare, then two studies from outside the location should 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, it is recommended that at least six control animals should 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 section A.4.5. *Calculation and Evaluation of Percent Effectiveness*).

3. Field Effectiveness Studies

These studies should be conducted using the final formulation of the drug product to be commercialized to confirm effectiveness and safety. The number of field studies to be conducted and animals involved in each trial should depend on: (1) the animal species, (2) the geographic location, and (3) local/regional situations. The controls, i.e., non-treated animals or animals treated with a registered anthelmintic with a known profile, should equal a minimum of 25% of the treated animal numbers. The term local/regional means within a country and/or association with a climatic and/or management area (see also Appendix 1. *Glossary*). To achieve the requested numbers, it is also acceptable to conduct multi-center studies with sub-studies in each locality/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 breed/age range/class/production type of animal intended to be treated as indicated on the labeling.

4. Persistent Effectiveness Studies

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 should be based on actual worm counts and not on number of eggs per gram of feces. Claims of activity of less than 7 days should not be considered a persistent effect and claims should mention persistent effectiveness for a specific number of days. The type of protocol depends on the animal species and will be discussed under the specific target species guidance.

As described for dose confirmation, a persistence claim (for each duration and parasite claim) should include two studies (with worm counts), each with a non-treated and treated group. It is

recommended that at least six animals per treatment group should be adequately infected. The adequacy of the infection should be defined in the protocol phase. Persistence claims should be in terms of a species-by-species basis. Persistent effectiveness claims should be granted for the longest period between treatment and the last challenge where effectiveness criteria are met, and all preceding time points tested meet the criteria as well.

III. Appendix 1. 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 labeling 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 is 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)] X 100 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 manufacturer's claims on the labeling have been supported by adequate data, i.e., providing control of at least 90% and meeting the criteria described in sections A.4.4. *Data Analysis Recommendations* and A.4.5. *Calculation and Evaluation of Percent Effectiveness* using pooled data from controlled studies.

FIELD EFFECTIVENESS 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.

GEOGRAPHICAL LOCATION: A subdivision where the guidances 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. *Specific Evaluation Studies*) 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 characterized (see section A.2. *The Evaluation of Effectiveness Data, Use of Natural or Induced Infections, Definition of Laboratory and Field (Helminth) Strains*).

LABORATORY STRAIN*:* A sub-population of helminths isolated from the field, which has been characterized and segregated in the laboratory based on a particular property which makes it unique for research areas, such as resistance to certain antiparasitic compounds, and/or other characteristics such as establishment rates/infectivity or pathogenicity. Characterization should include the elements described in section A.2. *The Evaluation of Effectiveness Data, Use of Natural or Induced Infections, Definition of Laboratory and Field (Helminth) Strains*.

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

IV. Appendix 2. Effectiveness Decision Criteria for Dose Determination, Dose Confirmation, and Persistent Effectiveness Studies

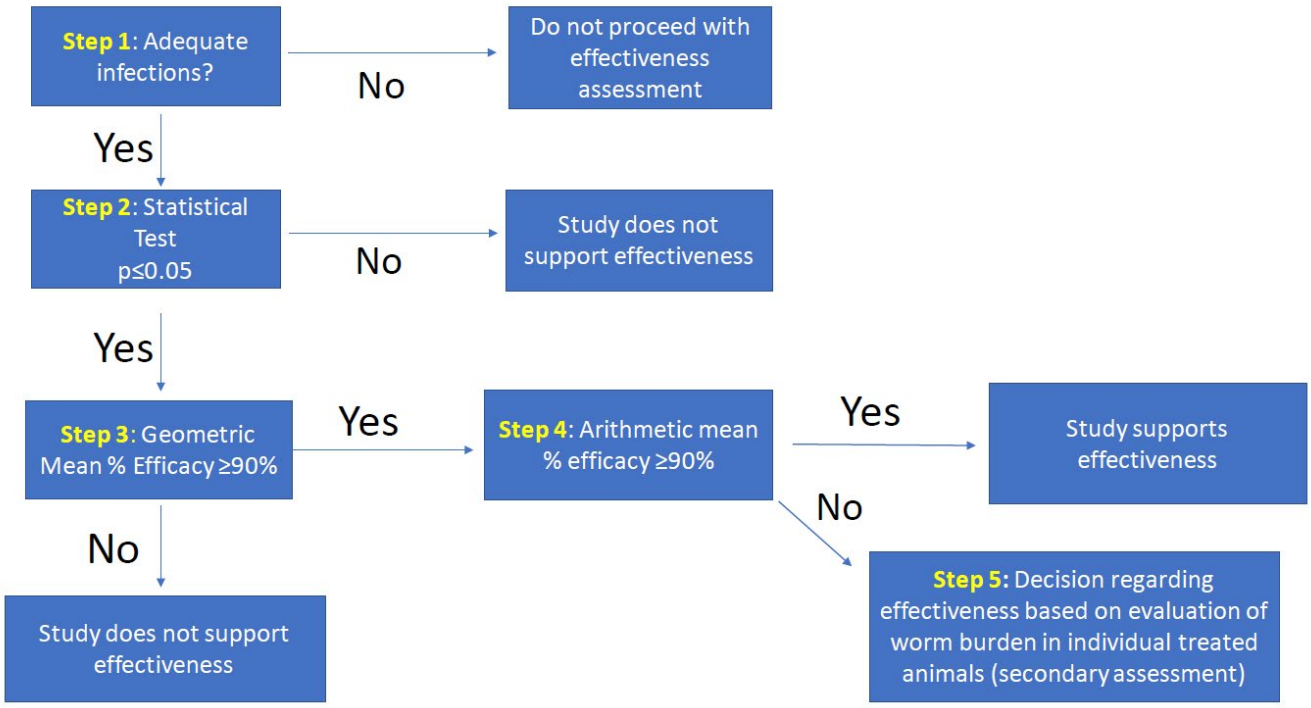
Step 1: Assess adequacy of infection. If adequate infections are confirmed in the control group, proceed to Step 2. If adequate infections are not confirmed, do not proceed.

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 % Effectiveness using Geometric Means. If % effectiveness is **≥ 90%** (GM), proceed to Step 4. If % effectiveness is < 90%, do not proceed, study does not support effectiveness.

Step 4: Calculate % Effectiveness using Arithmetic Means. If % effectiveness is **≥ 90%** (AM), the study supports effectiveness. If % effectiveness 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. See Section A.4.5, Step C for details on this assessment, and examples in Tables 1-4 below.



Examples:

Table 1

Animal Number	Treated	Control
1	1,700	15,880
2	13,240	740
3	0	25,300
4	5,200	17,600
5	13,540	22,200
6	20	21,620

In this example, the experimental unit is the animal. The % effectiveness based on the GM (c = 1) is 95.1%. The % effectiveness based on the AM is 67.4%. The highest control animal is 25,300 worms. If this animal were to have 90% reduction in worm burden, the worm count would be 2,530; 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	2,900	8,250
2	1,700	7,950
3	1,400	9,360
4	400	15,250
5	2,700	15,800
6	600	6,000
7	350	28,000
8	350	5,800
9	300	8,700
10	2,300	17,270

In this example, the experimental unit is the animal. The % effectiveness based on the GM (c = 1) is 91.6%. The % effectiveness based on the AM is 89.4%. The highest control animal is 28,000 worms. If this animal were to have 90% reduction in worm burden, the worm count would be 2,800; 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 % effectiveness based on the GM (c = 1) is 92.0%. The % effectiveness 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 % effectiveness based on the GM (c = 1) is 90.0%. The % effectiveness 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.