

DISCUSSION DOCUMENT

VICH Anthelmintics Guidelines Revision and Identification of Information Gaps

1. Introduction

The VICH Anthelmintics guidelines were recommended for consultation at Step 7 of the VICH process at various time points in November 1999 (VICH GL7, General Recommendations; VICH GL12, Bovine; VICH GL13, Ovine; VICH GL14, Caprine) or June 2001 (VICH GL15, Equine; VICH GL16, Porcine; VICH GL19, Canine; VICH GL20, Feline; VICH GL21, Poultry) by the VICH Steering Committee.

In the years since these finalized documents have been in effect, areas of incomplete information and/or new scientific knowledge have been identified. We have determined that revision of the guidelines will make them more informative and help with consistency across sponsors and regulatory authorities.

Since the time the guidelines were written, more scientific knowledge of the development of antiparasitic resistance in gastrointestinal (GI) nematodes; specifically in cattle, small ruminants, and equines, has come to light. There is a need to address this growing worldwide problem with proactive revision of the effectiveness evaluation for certain species of target animals and parasite species in the appropriate VICH guidelines. There are also growing concerns about potential anthelmintic resistance developing in canine heartworm disease.

In addition to revising the existing guidelines for anthelmintic drugs, there is a need to either expand their scope or develop new documents to address effectiveness standards for other parasites of great interest to veterinary medicine (e.g., ectoparasites) and combination antiparasitic drugs with highly overlapping indications, which is an important consideration in terms of the control of antiparasitic resistance of GI nematodes of cattle, small ruminants, and equines.

The international consensus on how to incorporate the current knowledge of veterinary parasitology would help both sponsors and regulatory agencies to advance development of new effective and safe antiparasitic products and control resistance to these important drugs.

2. Problem

Japan, the European Union (EU), and the United States (US) have developed an Effectiveness of Anthelmintics General Recommendations Guideline (VICH GL7) and eight species specific VICH guidelines as stated above. In the years since they were published in final it has become apparent that there are areas in the guidelines that are silent or not informative and/or specific enough on a number of issues related to study design, methodology, and the basis of study conclusions. Additionally, there has been much discussion and increasing awareness of the emerging global problem of antiparasitic resistance. Many veterinary and parasitological professional organizations, such as the World Association for the Advancement of Veterinary Parasitology (WAAVP), The American Association of Veterinary Parasitologists (AAVP), American Association of Bovine Practitioners (AABP), The American Consortium for Small Ruminant Parasite Control (ACSRPC), and the American Association of Equine Practitioners (AAEP) have featured this topic as part of their agendas for the annual meetings. The recommendation for the use of standardized methods to detect and mitigate parasite resistance is critical to the preservation of the

VICH/IN/12/012

Draft 1

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effectiveness of anthelmintic drugs in cattle, small ruminants, and equines across the world. In an effort to establish a consistent means to determine effectiveness for ectoparasiticides and combination anthelmintic drugs with highly overlapping indications in cattle, small ruminants, and equines; global harmonization of the effectiveness requirements are necessary.

Revision of the existing guidelines and creation of additional guidelines will unify the global veterinary community's understanding of the basic principles upon which effectiveness determinations are based.

3. Impact on Public Health, Animal Health, and Animal Welfare

3.1 Animal Welfare: The revised harmonized anthelmintic guidelines and new guidelines would provide additional information on certain aspects of study design that, if followed, could minimize the number of studies that need to be conducted, thereby reducing the number of animals that need to be used in the demonstration of effectiveness of antiparasitic drug products.

3.2 Animal Health: The revised harmonized anthelmintic guidelines and new antiparasitic guidelines would also enable member countries to recommend comparable methods for evaluating effectiveness and make sharing of data possible. This may decrease the regulatory burden for drug sponsors and encourage development of new drug products to ensure successful parasite control.

In a global environment, the development of antiparasitic resistance within one country can affect the safety and effectiveness of products in surrounding countries. Therefore, to minimize the risk of a dwindling effective therapeutic arsenal, we need to ensure that effectiveness criteria be revised accordingly to face the challenges of today.

Ultimately, protecting the effectiveness of existing anthelmintic products and development of new effective antiparasitic drugs is critical for animal health and wellbeing through minimizing the damaging effects of parasitic infections.

3.3 Impact on Public Health: The revised harmonized anthelmintic guidelines and creation of new guidelines will help to minimize parasites in our companion animals and will help to control zoonotic parasites that are a threat to human health. Control of parasites in food animals is vital to protect and ensure a safe and nutritious food supply.

4. Anticipated Benefit

The benefits that will be obtained through the revision of the current of harmonized VICH Anthelmintic guidelines and creation of new ones are in keeping with the stated VICH objectives to:

- *Establish and implement harmonized regulatory requirements for veterinary medicinal products in the VICH Regions, which meet high quality, safety and efficacy standards while minimizing the use of test animals and the costs of product development and ensuring consistent interpretation of data requirements between sponsors and across different regulatory agencies.*

Considerations for addressing the development of antiparasitic resistance will:

- *Bring about a constructive dialogue between regulatory authorities and industry to provide technical guidance enabling response to the significant emerging global issue of antiparasitic resistance that impacts regulatory requirements within the VICH regions.*
- *Ensure that the newly approved anthelmintic drugs withstand or help minimize the biological pressure of resistance development.*

Creating new guidelines or additional sections to existing guidelines will:

- *Facilitate the efficient development and approval of drugs such as ectoparasiticides for both food and companion animals and combinations of anthelmintics with highly overlapping indications.*

5. Discussion

A. PROPOSED TOPICS FOR REVISION OF EXISTING GUIDELINES

1. ***Use of arithmetic instead of geometric means [Section A 4.2, GL7]:*** The current guidelines recommend the use of geometric means to calculate percent efficacy. The rationale given for the use of the geometric means is that log-transformed parasite counts or egg-counts tend to follow a normal distribution more closely than do non-transformed parasite counts. The resulting conclusion is that the geometric mean is therefore a more appropriate estimate of central tendency and has less potential for misinterpretation. The risk of continuing to use the geometric mean for cattle, small ruminant, and equine GI nematodes is a potential to overestimate the efficacy of drugs and thus approve drugs that in reality do not provide an acceptable level of efficacy for the labelled parasite species. This is particularly concerning in light of the development of antiparasitic resistance.

Contrary to an earlier expert position on using arithmetic means, recent published literature indicates that the use of arithmetic means is appropriate for efficacy calculations for parasite data, which is often skewed (a small proportion of the study population can harbor a large population of the parasites) (Dobson 2009¹; Alexander 2012²).

2. ***Adequacy of infection [Section A 4.5, GL7]:*** At present, the guidelines remain silent in regard to the adequacy of infection for cestodes, feline heartworm, and *Dirofilaria immitis* microfilaria. It is necessary to update the guidelines so that the regulatory requirements become standardized in these categories. Some cestodes (such as *Dipylidium caninum*) have the potential to be zoonotic. In order to protect both veterinary and public health and ensure the validity of the experimental model, an adequate infection should be defined. With regard to feline heartworm, the pathology of the disease in cats necessitates a deviation from the published VICH GL20, Effectiveness of Anthelmintics: Specific Recommendations for Feline (section 4.3), which states: “Generally, the minimal number of nematodes in feline considered to be adequate is in the range of 5 to 20.” This range is not representative of the

¹ Dobson SJ et al. Geometric means provide a biased efficacy result when conducting a fecal egg count reduction test (FECRT). *Veterinary Parasitology*, 2009. 161(1-2).

² Alexander N. Review: analysis of parasite and other skewed counts. *Tropical Medicine and International Health*, 2012. 17(6): 684-693.

number of worms seen in feline heartworm disease. Incorporating updates to the VICH guidelines for these subjects will improve our ability to determine the effectiveness of investigational products.

3. **Clarification regarding the number of adequately infected control animals [Section A 4.3, GL7]:** - Adequacy of infection defines the level and distribution of infection of a particular parasite in a given host species. In doing so, adequacy of infection supports the model such that the results can be interpreted with statistical and biological confidence. The anthelmintic guidelines (general and species specific) state that an adequate infection is required in a minimum of six animals in the control group. The guidelines do not specify a maximum number of animals per group nor do they define adequacy of infection as a percentage of control animals. CVM has received protocol submissions with as many as 12-14 control animals. With such a large number of animals in the control group, the biological confidence of the model is weakened if only six animals are required to have an adequate infection.
4. **Use of Natural or Induced Infections, Definition of Laboratory and Field (Helminth) Strains; Age of Isolates [Section A 2, GL7]:** For some strains, using isolates that are 10 years old may not be appropriately representative of the current field situation in light of anthelmintic resistance. This is especially important for nematodes of cattle, small ruminants, and equines, and potentially for heartworms in dogs or cats or both.
5. **Dose Confirmation Studies [Section B 2, GL7]:** CVM would like to discuss whether other regulatory authorities would approve an indication without at least one study conducted in their country, and if so, what would be the appropriate circumstances to allow for that. The guidelines should provide information on the number of studies, facilities, investigators, and sources of isolates in the situation where the parasite is rare.
6. **Raising the Minimum Efficacy Threshold to 95% [Section A 4.1, GL7]:** There is good evidence around the world that antiparasitic resistance is established or developing in cattle, small ruminants, and equines. The use of a higher efficacy standard for dose confirmation studies in these species may enable selection of drugs with a potentially decreased vulnerability to the development of resistance (the higher the efficacy, the lower the prevalence of resistant worms).
7. **Persistent Effectiveness Studies [Section B 4, GL7]:** To obtain an indication for a persistent effect period, the current guidelines state that a persistence claim should include two trials (with worm counts) each with a non-treated and treated group. These guidelines should be updated to reflect additional criteria that should be met.
8. **Adequate Infection in Control Animals [VICH GL 16 & 21 (specific recommendations for porcine and poultry, respectively)]:** These guidelines currently state that a minimum of six adequately infected animals must be in each of the non-medicated and control groups. These recommendations do not take into account that such studies in these species are often designed using pens of multiple animals housed together, with a total animal number that is normally much higher than in studies in other species.

B. PROPOSED TOPICS FOR ADDITION TO EXISTING GUIDELINES

1. **Approach to New Indications (not a newly discovered species):** CVM is receiving requests to consider parasite indications not currently addressed by VICH Guidelines (e.g. *Baylisascaris procyonis*,

Dirofilaria immitis microfilariae). Because this is not addressed in the VICH Guideline, there is no harmonization on the appropriate manner to consider indications for these species or life stages.

2. **Recommendations for Calculation of Effectiveness [Section A4, GL7]:** CVM would like to explore if there are ways to obtain a robust level of data generated from the controlled dose confirmation study when it is not possible to get animals with an adequate level of infection. In companion animal target species it can be difficult to find adequate numbers of infected dogs and cats to conduct studies. CVM would like to explore if other variables could be measured besides worm counts.
 3. **Route of Inoculation for Specific Parasites:** VICH does not address the route of parasite inoculation and whether parenteral (subcutaneous) inoculation is appropriate. Further, the timing between inoculation and treatment and/or necropsy in those cases is also not addressed.
 4. **Blocking [Section A 6, GL12, Bovine]:** VICH suggests that blocking in replicates by weight, sex, age, and/or exposure to parasites may reduce trial variance. CVM is concerned that this description is too suggestive that blocking always be done. Blocking will result in the reduction of experimental error if blocks are constructed such that the units within a block resemble each other more than units in different blocks. However, in some cases, the use of blocking may be a statistically inefficient strategy.
 5. **Fecal Egg Count Reduction Test in field studies:** The fecal egg count reduction test (FECRT) is the current method of choice to monitor the effectiveness of an anthelmintic in grazing animals (cattle, small ruminants, and horses). The inclusion of this test as a primary endpoint in the clinical field study would not only provide a good pre-approval assessment of effectiveness, but would also provide baseline information for monitoring the development of resistance on marketed drugs for regulatory agencies, researchers, and field veterinarians.
 6. **Parasite Counting Issues:** VICH does not address specific recommendations on parasite counting. For dose confirmation studies, worm counts are the pivotal variable for determining effectiveness. However, with certain gastrointestinal nematodes, female parasites within a genus cannot be speciated, leading to situations of possible inaccurate worm counting. CVM recommends adding details to the current guidelines that outline how to distribute female worm counts within certain genres based on the biology of the parasite and the host species.
 7. **Resistance Indications:** The cattle, small ruminant, and equine guidelines should outline considerations for anthelmintics with resistance indications. This should include a description of ways to characterize resistant parasites and standardize methods used to evaluate resistance indications.
 8. **Development of model to replace worm count studies:** The current practice is for sponsors to perform necropsies on companion animals in order to perform worm counts. CVM would like to discuss whether other models can be adopted to obtain appropriate worm counts without the need to sacrifice animals.
- C. PROPOSED NEW GUIDELINES RELATED TO THE EFFECTIVENESS OF ANTIPARASITIC DRUGS

1. **Combinations of anthelmintics with overlapping indications:** Anthelmintic combinations are increasingly recommended for use to control parasite strains resistant to one or more drugs in the combination and/or to theoretically delay the development of anthelmintic resistance to all drugs in the combination. During a public meeting held by CVM on March 5 and 6, 2012, the scientific experts agreed that approved fixed combination products with overlapping spectrums of activity would be of benefit to grazing animal populations including horses, cattle, sheep, and goats because of the ability of certain drug combinations to slow the development of resistance. A harmonized guideline to address the development of such combinations would benefit cattle, small ruminant, and equine species worldwide by ensuring long-term effectiveness of new and existing antiparasitic drugs.
2. **Ectoparasites:** Guidelines for the evaluation of effectiveness of antiparasitic drugs to control fleas and ticks in dogs and cats; and mites, ticks, lice, and biting and nuisance flies, and myiasis-causing flies in ruminants are available from the World Association for the Advancement of Veterinary Parasitology. However, no harmonized guidelines are available. A harmonized guideline for ectoparasites would improve the efficiency of review of effectiveness globally.

6. Recommendations

All the issues identified here are common across the regulatory jurisdictions of the VICH countries. Therefore, CVM recommends that VICH establish an Expert Working Group (EWG) to elaborate harmonized guidelines utilizing the basic principles underlying the topics outlined above. The goals of the EWG would include:

A. REVISIONS OF THE EXISTING GUIDELINES TO

1. Include the use of arithmetic means for the calculation of the % efficacy for all studies (dose determination, dose confirmation, field studies, and persistent efficacy) and accept geometric means only in certain circumstances in the guidelines for cattle, small ruminants, and horses.
2. Create standardized definitions for adequacy of infection for specific parasite species and populations.
3. Clearly define the appropriate size of the control group relative to the number of adequately infected animals deemed necessary.
4. Reconsider the current maximum limits on the age of isolates where appropriate.
5. Clarify that two separate studies conducted in different locations, using different isolates, and conducted by different investigators are necessary for all parasite species regardless of rarity.
6. Raise the threshold for efficacy for cattle, small ruminant, and equine anthelmintics from 90% to 95%.
7. Review the requirements for persistent effectiveness claims and update them as necessary, especially with regard to equines. Criteria such as the number of adequately infected control animals, percent efficacy, statistical significance, and effectiveness at certain time points should be defined.

8. Re-examine the definition of minimum number of adequately infected animals in treated and control groups in effectiveness studies for porcine and poultry, taking into account study designs made of pens of multiple animals.

B. ADDITION OF NEW INFORMATION TO THE CURRENT GUIDELINES

1. Consider the most appropriate manner to approach new indications (not newly discovered species) and provide the points to consider in determining the validity of new indications and whether they should be permitted.
2. Explore options for other variables of effectiveness for companion animal species where it is hard to find an adequate number of infected animals to conduct terminal dose confirmation studies.
3. Decide whether route of inoculation of specific parasites is of significant priority to be included in the VICH guidelines. Infective stages, treatment times, and time to necropsy should all be considered along with the various routes of inoculation.
4. Blocking should be more clearly defined, as well as the situations where it is appropriate to block and where it is not.
5. Consider inclusion of FECRT as one of the methods for evaluating the effectiveness of anthelmintics for cattle, small ruminants, and equines in addition to the standard treated versus control group comparison for clinical field studies in ruminants and horses.
6. Parasite counting techniques should be addressed in more detail to provide guidance in situations where not all parasites can be speciated.
7. Determine whether resistance indications are appropriate given the current state of knowledge and, if appropriate, create a new section to existing guidelines for ruminants, small ruminants, and equines for how these indications should be pursued.
8. Consider alternative methods to necropsy for obtaining accurate worm counts and include them as a new section to existing guidelines for canine and feline target animals.

C. RECOMMENDATIONS FOR FUTURE VICH GUIDELINES

1. Develop a guideline for fixed combination anthelmintic products with overlapping indications for ruminants, small ruminants, and equines.
2. Develop a series of guidelines for ectoparasites of all species of animals. The priority for the development of ectoparasitic guidelines should be the creation of a general VICH ectoparasite guideline document, outlining the requirements for all ectoparasiticide drugs. This general document could provide a brief passage for all species. After the general guidelines are established, more specific documents could be created to address the specific issues relating to (1) fleas, (2) ticks, and (3) mites for small animals, and (1) lice, (2) mites, (3) ticks, and (4) flies for food-producing animals and equines.

7. Timetable and Milestones

Step 1	Establish the EWG	3 months
Step 2	The EWG decides which revisions, additions to existing guidelines, and new guidelines will be acceptable. A face-to-face meeting of the EWG will be convened to facilitate successful harmonization on the scientific issues. The EWG submits the guideline to the Secretariat with the signatures of all experts.	24 months
Step 3	The draft revised and new guidelines are submitted to the Steering Committee for approving their release for consultation.	6 months
Step 4	Once adopted by the SC, the draft revised and new guidelines are circulated to all interested parties for consultation, applying an appropriate consultation period (normally 6 months). The regulatory coordinators should inform VICH secretariat when the consultation process in their region is delayed.	6 months
Step 5	The comments received are directed to the EWG for consideration. At this step, the topic leader must be a representative of a regulatory authority. The EWG prepares a revised draft and submits it to the Secretariat with the signature of all experts. The signatures of industry experts are clearly separated from those of experts representing regulatory authorities.	6 months
Step 6	The revised draft revised and new guidelines are submitted to the SC for approval.	12 months
Step 7	Once approved by the SC, the final Guidelines and a proposed date for their implementation are circulated to the regulatory authorities represented in the SC.	
Step 8	The SC members report to the SC on the implementation of the Guidelines in their respective regions.	
Step 9	Monitoring, maintenance and review of Guidelines	Continuous with formalized review 3 years after implementation

8. Impact Assessment

Industry

1. The guidelines will provide clarity of the effectiveness standards for antiparasitic drug products.
2. The combination guideline will provide clarity of the requirements for anthelmintic drugs with overlapping indications.

VICH/IN/12/012

Draft 1

Dated 17/11/12

3. Unified requirements may lead to a reduction in number of studies needed to obtain global marketing. As a result, the numbers of test animals used should also decrease which results in an increase in animal welfare (3R principle).
4. Most importantly, these guidelines will allow for global consistency in evaluating effectiveness studies.

Regulators

1. Increase the clarity of the requirements in the countries, and therefore there will be less uncertainty expressed by Industry.
2. Lead to a consistent approach in interpretation and assessment by the competent authorities.
3. Decrease the number of submissions with studies that are inadequate for determining effectiveness of new antiparasitic drugs.