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

VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline: GL13 Efficacy of anthelmintics: specific recommendations for ovines.

VICH EWG: ANTHELMINTICS

Name & Country of individual, organisation, or VICH delegation that commented

Comment n°	**Name - Country**
1	Access Vet Med through EMA
2	World Association for the Advancement of Veterinary Parasitology (WWAVP) through EMA
3	New Zealand's Agricultural Compounds and Veterinary Medicines (ACVM)
4	Animal Medicines Australia (AMA)
5	American Sheep Industry (ASI) through FDA

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
1-1	Access VetMed welcomes the opportunity to comment on this guideline. As a general comment, we wonder if specification of dose-limiting parasites for each class of anthelmintic could be included in this document, as it is considered to be useful information.	This suggestion is not within the scope of the EWG charge, and no revisions were made to the guidance. In addition, it is important to note that although there is generally some overlap within anthelmintic classes, dose-limiting parasites may differ between specific drugs and/or formulations (ie. may be product specific). In addition, data to establish a dose limiting parasite is not available for many products. Specifying a dose-limiting parasite(s) for each anthelmintic class is not likely feasible.
2-1	This guideline lacks the appropriate scientific citations throughout, which should be remedied	The EWG intends to update references currently in the guideline if they are available by the time of final publication. This would include the updated WAAVP ruminant guideline. Because the EWG was tasked with updating only certain topics/sections in the guidelines, it would not be possible (and is out of scope for the EWG) to support all sections of the GLs with scientific citations.
5-1	Comments provided that were generally supportive, but noted the desire for other countries to become members of VICH and concerns with the lack of investment in the development of new drugs for sheep in the US	The EWG thanks the ASI for their comments.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
102	3-1	Section 2 -Use of Natural or Induced infections – housing. A requirement to house all animals for 2 weeks before treatment is included. Does VICH consider this is important for all studies in naturally infected animals e.g., for hypobiotic larvae. Does VICH have recommendations for animals' post treatment to prevent reinfection?	The specific sentence referenced with regard to housing of animals in dose confirmation studies is as follows: "In all cases, animals need to be housed (to preclude reinfection) for a minimum of 2 weeks before treatment." Although this topic was out of scope for the EWG, the EWG agrees that appropriate housing before and after treatment for the various study types (induced vs. natural) should be clarified. This should be considered in a future revision of the guideline.
109	2-2	Comment: According the WAAVP ruminant guideline, also natural infections can be used for persistent efficacy studies. Proposed change (if any): Please consider whether natural infection studies can be allowed for persistent efficacy studies.	The statement in question is from Section A.2: "Persistent efficacy studies should be conducted using induced infections with recent field isolates. " Similar statements also appear in GL12 (bovine), GL14 (caprine), and GL 15 (equine) although the comment from WAAVP was only provided for GL13 and GL14. Section B.4 (Persistent efficacy studies) currently describes the option for natural or induced challenge for protocols using multiple daily challenges; therefore, WAAVP has identified a potential internal contradiction within the guideline. The EWG charge included clarifying how the period of persistent effectiveness is determined; however, specifics regarding study designs for persistent efficacy studies were not within scope. The EWG agrees that persistent efficacy study design is an important topic that should be considered in future reviews of this guideline.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
119-122 (Table 1)	2-3	Comment: a) Infection doses are slightly different from those in the WAAVP ruminant guideline. Since the VICH guidelines often refer to the WAAVP guidelines for technical issues, it might be good to harmonise the numbers between both guidelines. b) The table lacks scientific citations. Proposed change (if any): a) Harmonise infection doses with the WAAVP ruminant guideline. b) Add relevant scientific citations.	The EWG appreciates the comment. However, Table 1 is outside the scope of the EWG charge and it was not reviewed or updated. In addition, the WAAVP ruminant guideline was not available for the EWG to review before this guideline was finalized. We suggest that a review of Table 1 is considered in future reviews of this guideline. See also Comment 2-1 regarding citations.
Section 4.3	4-1	The revised VICH GL13, GL14, GL15 and GL16 include recommended worm count for few parasites and a general statement such as minimum of 100 nematodes to be considered as an adequate infection. It does not however, have a clear table with recommended worm counts like that in VICH GL 12.	The AMA is correct. No table was created because a minimum of 100 worms was retained for all species except those for which lower counts may be expected (*Bunostomum* spp., *Oesophagostomum* spp., Trichuris spp., *Gaigeria pachyscelis* and *Dictyocaulus filaria*.). The EWG concluded that the current recommendations are appropriate for the purposes of harmonization with some flexibility.
122	1-2	Comment: Proposed change: Suggest that care would be needed when using infections from multiple parasitic species and conservative infection rate should be advised.	The EWG appreciates the comment. However, Table 1 is outside the scope of the EWG charge, and it was not reviewed or updated. The EWG agrees that the number of larvae used for a study will depend on a variety of factors including the age of the animals, whether one or multiple species are being inoculated, etc. These factors should be considered as part of protocol development.
122	1-3	Comment: Suggested infection rate for rumen fluke could be useful.	The EWG members agreed that while the addition of rumen fluke could be very helpful to some jurisdictions, there is limited experience and insufficient data to add rumen fluke to either Table 1 ("Number of Infective Stages to Produce Adequate Infections in Sheep for Anthelmintic Evaluation) or to Section 4.3 (Adequacy of Infection). This topic should be revisited when the guidelines are revised in the future.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
122	1-4	Comment: It is assumed that if multiple daily challenges are to be used than the total infective stages received by the animal will correspond to the contents of this table. Proposed change: Suggest clarifying	The EWG agrees that if multiple daily challenges are used (e.g. trickle challenges) lower numbers of larvae are used at each infection timepoint. For most induced infections in sheep, a single infection is used. As noted in a previous comment, the number of larvae used will depend on a number of factors and considered during protocol development. Table 1 is outside the scope of the EWG charge and no changes were made to the guideline at this time; however, this clarification could be considered for future revisions of this guideline.
147-149	2-4	Comment: "several studies… could be pooled to accumulate 12 animals". This statement is very loose and needs precise clarification regarding under which criteria data from different studies can be pooled. How many are "several studies? Therefore, how many could be pooled? What is the rationale for pooling said studies? Locality? Time? Testing official lab? As stated, it might be construed in different, wrong ways. Proposed change (if any): Provide detailed information to answer the questions above.	The EWG agrees that the description of pooling procedures in Section 4.2 is not clear and may be open to various interpretations. However, because this topic/section is not part of the EWG charge, no revision to the guidance were made. We suggest that this topic is considered for revision in the future.
150	2-5	Comment: Efficacy of the pooled studies should be > 90%. Proposed change (if any): Specify required anthelmintic efficacy for the pooled studies.	The EWG acknowledges that Section 4.2 (Number of Animals) does not specify the % efficacy required for pooled studies. However, this issue is addressed in Section A.4.6 of GL 7 (Pooling Data) which states, "The overall efficacy of the pooled studies should demonstrate efficacy of 90% or greater." No revisions were made to GL 13 in response to this comment.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
161-162	2-6	Comment: a) 100 nematodes as a minimum number is too low to be considered an adequate infection. b) Is this the same number for all species of Cooperia, Haemonchus, Teladorsagia/Ostertagia, Nematodirus, Trichostrongylus, etc.? Proposed change (if any): a) Revise the number and/or include valid scientific citations to back up this number. b) Add the minimum numbers for all parasite genera/species involved in this guideline and make it clear whether those numbers are for mixed or mono-species infections.	As currently written, 100 nematodes is the minimum number for all of the listed species (for each of 6 animals in the study) with the exceptions stated. It is important to consider that for these studies clinical parasitism is not required; and the minimums are established to provide for a valid model while not making it so burdensome that many more studies have to be conducted to meet the minimum adequacy requirement. Additionally, these minimum numbers for individual animals apply to both mixed and mono-species infections. At this time, the EWG agreed that no additional revisions were necessary; however, the numbers could be revisited in future guideline reviews. The EWG is aware that in some cases, sheep may carry higher worm burdens of some species without clinical signs.
164	2-7	Comment: a minimum of 20 adults of *Fasciola* spp. are considered adequate, but no citation is provided. Proposed change (if any): include scientific citations to back up this statement.	The minimum adequacy of infection numbers are based on combined information from literature and from regulatory studies. The EWG added a footnote applying to the whole section which states that "the recommended minimum numbers are based on a review of published literature and data from studies submitted for regulatory review". The EWG also acknowledges that providing citations could be beneficial and is consistent with good scientific practice; however, published information would not provide complete information in this situation because in most cases, experience from controlled regulatory studies were a primary factor in the determination of the minimum number.
167-181	2-8	Comment: The indicated days for the label claims differ slightly from those in the WAAVP ruminant guideline (Table 2). Since the VICH guidelines often refer to the WAAVP guidelines for technical issues, it might be good to harmonise the numbers between both guidelines. Proposed change (if any): Harmonise days p.i. for label claims with the WAAVP ruminant guideline.	The EWG appreciates WAAVP's comment; however, because the new ruminant WAAVP guideline has not yet published, the EWG cannot review the identified discrepancies. Revision of Section 4.4 was not within the scope of the EWG mandate and no changes are recommended (except for the change to the treatment times for *Fasciola* spp. below) at this time unless an important discrepancy is identified before the GL are finalized. Otherwise, this may be an issue that should be brought forward for review in the future.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
172	1-5	Comment: 8 weeks would not correlate to adult liver fluke in sheep Proposed change: Suggest to extend this to 10 or preferably 12 weeks to ensure that fluke have reached maturity and pre-treatment FEC can be used, if required, as part of the study design.	The EWG appreciates the comment from Access Vet Med and took the opportunity to revise the treatment times for *Fasciola* to align with its life cycle. For clarity the EWG recommends keeping all information on *Fasciola* together in the guideline and including the following treatment times for Fasciola in Section A.4.4. 1. Early immature stages: Treatment should be administered at 1 to 4 weeks post-infection when flukes will be migrating in the liver parenchyma. 2. Late immature stages: Treatment should be administered at 6 to 8 weeks post-infection when flukes are still immature but starting to enter the hepatic bile ducts. 3. Mature flukes: Treatment should be administered at 12 to 14 weeks post-infection when all forms are in the bile ducts and gall bladder.
187	2-9	Comment: What does 'animal relationship' mean? Proposed change (if any): Please clarify.	The comment from WAAVP refers to the following sentence in Section A.5 (Treatment Procedures): "It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations." This section of the guideline was not within the scope of the EWG charge and no revisions were made. This statement likely means consideration should be given to how animals are allowed to interact with one another in the study. For example, are they housed in a way that allows them to lick and engage in grooming behaviors after treatment?
197	2-10	Comment: How can 'coat length' be practically included in the evaluation of the effectiveness of the product? Proposed change (if any): Please clarify or remove.	The sentence referenced in this comment is as follows: "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." This section of GL 13 was not within the scope of the EWG mandate and was not reviewed or discussed but could be reconsidered in future revisions of the guideline. The EWG removed the comma after the parenthesis to improve sentence clarity: "the impact of weather (e.g., rainfall, UV light) and coat length should be included in the evaluation of the effectiveness of the product."

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
231 + 237	1-6	Comment: Can this be expanded upon for generic products? Proposed change: For generic products, suggest that the use of established dose limiting parasites could be acceptable.	A discussion of generic products is outside the scope of the current EWG mandate, and no revisions were made to the guideline.
247	2-11	Comment: a) Effectiveness and efficacy are used as synonyms. According to the EMA document "https://www.ema.europa.eu/en/documents/presentation/presentation-efficacy-effectiveness-models_en.pdf" these are two different things. The guidelines are always only concerned with efficacy, not with effectiveness. b) In the case of *D. viviparus* is not the Faecal egg counts, are the faecal larval counts Proposed change (if any): a) The term "effectiveness" should be replaced by "efficacy" for consistency throughout. b) Either correct to "faecal egg/larval counts" or add the sentence "Faecal larval counts should be performed for *D. viviparus*".	a) The EWG acknowledges the differences between effectiveness and efficacy identified by WAAVP and described in the EMA document. During review of the VICH GL, the EWG noted that the previously published guidelines did not use the terminology consistently in the text; and glossary definitions provided in the General Guideline (GL7) may not reflect current thinking. However, this topic was out of scope for the EWG. The EWG discussed the possibility of changing all terms to “efficacy” for consistency throughout the document and did not agree unanimously to this approach. The EWG agrees this topic should be considered in a future revision. Regarding comment b) the EWG agrees that fecal larval counts should be mentioned for field studies of *D. filaria*. The first sentence of the second paragraph in Section B.3. was revised to read, "Effectiveness against adult nematodes can be assessed by the reduction of faecal egg counts (or larval counts for D. filaria) and should be performed using samples from the same animal before and after treatment in both study groups (control and treated)."
253-255	2-12	Comment: Not clear if > 90% FECR is required between treated and control group AND between post- and pre-treatment FEC in the treated group (or whether the latter is only optional). Proposed change (if any): please clarify.	As noted in the EWG response to ACVM on the topic of field studies (below), flexibility on the size of, or even the need for, a control group may be appropriate depending on the drug product, claims, and objectives of the study. Because control groups are generally included in field studies submitted for regulatory purposes, the EWG concluded that the additional comparison may be performed in addition to the post-treatment comparison between the treated and control group. However, depending on the drug product, claims, and objectives of the study, flexibility on the need for a control group may be appropriate. The proposed changes to the field study section are listed in the response to the ACVM comment (row below).

SECTION ….			
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Not specified	3-2	Most species-specific guidelines now specify a paired study design (i.e., faecal samples collected from the same animals pre and post treatment) which ACVM supports. However, the primary analysis recommended does not reflect this design. We would like VICH to recommend the primary measure of efficacy uses pre and post counts, without reference to controls. Using pre and post counts removes an important source of within-animal bias. Our experience with FECRT is that using a negative control to adjust for natural changes in FEC 10 -14 days post treatment is unnecessary in most situations, and the paired design proposed is most appropriate to estimate field efficacy. If negative controls are required for another purpose e.g., to support safety this can be stated, however the additional manipulation associated with collection of faecal samples can be omitted. This design also eliminates the need for a negative control group which aligns with the VICH commitment to promote the 3Rs. Note study designs seen in NZ may include repeated FECs in study animals over an extended period, in which case a negative control group may be appropriate to monitor parasite population dynamics.	The EWG recognized the scientific advancements related to the interpretation of FEC data and refinement of the associated field study designs for certain animal species. As a result, the EWG added the recommendation to consider the use of a calculation of FECR (fecal samples collected from the same animals pre and post) to the draft Guideline 12 (GL12). At this time, because the inclusion of a control group is justified for many regulatory studies, the EWG has not removed the reference to the treated versus control comparison from GL12 or the General Guideline 7 (GL7). However, depending on the drug product, claims, and objectives of the study, flexibility around the size of, or even the need for a control group may be appropriate. The General Guideline (GL7) states that controls should equal a minimum of 25% of the treated animal numbers in field studies, and that "request for additional (or fewer) studies, and/or animals (animal welfare considerations) by local regulatory authorities should be fully justified." This provides the applicant an opportunity to propose alternative designs for field studies. In addition, as methods for interpreting field study data evolve, this could be a topic for refinement in future revisions of the VICH guidelines. The EWG made minor revisions to the following section of the GL: "Efficacy against adult nematodes can be assessed by the reduction of faecal egg counts (or larval counts for *D. filaria*) 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. Unless otherwise justified, 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 from animals in the treated group may provide further information on field efficacy. Furthermore, additional endpoints for evaluating field efficacy should be considered as they are developed and generally accepted by experts in veterinary parasitology.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
268,269 and 276-280	2-13	Comment: This protocol is different from the protocol in the WAAVP ruminant guideline, where treatment days are staggered and the infections are all given the same day, to avoid variability in the infectivity of the larvae. Proposed change (if any): Suggest to adapt to WAAVP protocol.	The referenced statement is in Section B.4 ("Persistent Efficacy Studies") and reads as follows: "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." Earlier in Section B.4, GL 13 states, "Two basic study designs have been used to pursue persistent efficacy claims: one using a single challenge, another using multiple daily challenges following treatment.....A study design is recommended using multiple daily challenges, as this most closely mimics what occurs in nature." The EWG charge included clarifying how the period of persistent effectiveness is determined; however, specifics regarding appropriate study designs was not within scope. The EWG agrees this is an important topic that should be considered in future reviews of this guideline.