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: GL15 Efficacy of Anthelmintics: specific recommendations for equines

VICH EWG: ANTHELMINTIC

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

Comment n°	Name - Country
1	Access VetMed through EMA
2	World Association for the Advancement of Veterinary Parasitology (WAAVP) through EMA
3	New Zealand's Agricultural Compounds and Veterinary Medicines (ACVM)
4	Animal Medicines Australia (AMA)

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
2-1	This guideline lacks the appropriate scientific citations throughout, which should be remedied.	The EWG intended to update references currently in the guideline if they are available by the time of final publication. This would include the updated WAAVP equine 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.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
76-78	2-2	Comment: The cited WAAVP guideline is not the latest one. Proposed change (if any): Change citation to "World Association for the Advancement of Veterinary Parasitology (WAAVP): Third edition of guideline for evaluating the efficacy of equine anthelmintics", Vet. Parasitol. 2022;303:109676. doi: 10.1016/j.vetpar.2022.109676.	Thank you for your comment. The EWG intended to update references if they were available by the time of publication. This citation has been revised to reference the 2022 version of the WAAVP 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 these 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.
123-126	2-3	Comment: These data lack scientific citations. Proposed change (if any): Add relevant scientific citations.	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.
92 and 204	1-1	Comment: Seems to be a potential for misinterpretation in which animals can be used /should not be used for terminal studies. In one place it advises against using young animals and later in the guidance document in proposes animals as young as 3 months. Proposed change: Suggest some clarification on the lower age limit for animals.	The EWG acknowledges the source of confusion. However, the GL specifically advises against use of young animals for *S. westeri*, which would require use of foals <3 months of age, so we do not think there is a direct conflict. Further, the mention of 3-12 month old animals in Section 6 is specifically referencing use of induced infections, which may need a different age range from horses with natural infections. Finally, revision to this text was outside of the scope of the current revisions.
126	2-4	Comment: There is no specification as to whether "Small strongyles" must include one or more species, whether a minimum number of different genera/species should be used or whether key genera/species must be included in such infection inocula. More information is required to specify the composition of such inocula. Proposed change (if any): Add information on composition of inocula for "Small strongyles".	This revision is outside the scope of the current EWG charge, and no revision was made. However, clarifications might be considered for future revision.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
155-159	2-5	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. Besides, if none of the studies could obtain at least 6 adequately infected animals in the control group, how can results be obtained by accumulating 12 animals? Does this mean a sufficient number of studies have to be done until the number of infected animals in the control groups add up to 12 (or more)? Proposed change (if any): Provide detailed information to answer the questions above. Besides, this part should be reworded to make clear what has to be done to achieve the number of animals required per group (maybe with example calculations).	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.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
169-170	2-6	Comment: 100 nematodes as a minimum number is too low to be considered an adequate infection. Proposed change (if any): Revise the number and/or include valid scientific citations to back up this number (see latest WAAVP guideline for evaluating the efficacy of equine anthelmintics, doi: 10.1016/j.vetpar.2022.109676).	This revision is outside the scope of the current EWG charge (there was no proposal to change the nematode numbers for adequate infection for horses) and no revision to the number for adequate infection was made. However, this recommendation is not in conflict with the WAAVP GLs, which specify that 10,000 is the threshold for all cyathostomes, and 100 is for any given species (see footnote "c" Table 2 page 4 of 2022 WAAVP guidelines for equine). In this case, we consider these per species, and therefore the 100 minimum remains consistent with WAAVP. Additionally, the EWG agreed to add a footnote in Section 4.3 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.
178	2-7	Comment: "distinction needs to be made" is poor grammar. Proposed change (if any): change to "distinction must be made".	The EWG respectfully disagrees that the proposed change makes an improvement to the grammar of the sentence. This is pre-existing text which was not revised by the EWG; however, the EWG added a comma to improve clarity: "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…"
179	2-8	Comment: Distinction must be made between the different life stages, but no timing for the different stages is provided. Proposed change (if any): provide a time frame for the different life cycle stages.	This revision is outside the scope of the current EWG charge, and no revision was made.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
181-184, 260	2-9	Comment: In relation to the comment on l. 126, "genus claim" and "mixed larval population" are not sufficiently detailed information on what is to be tested. Proposed change (if any): please provide detailed information	The EWG did not draft or revise this text, and revision is outside the scope of the current EWG charge. For reference, the statement in the GL is: "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." It may be beneficial to add clarity in a future revision.
189	2-10	Comment: What does 'animal relationship' mean? Proposed change (if any): please clarify	The statement under consideration is the following: "It is advisable to consider the weather and animal relationship with regard to effectiveness of topical formulations." 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 contact between animals that could impact the assessment of topical products? This section of the guideline was not within the scope of the EWG charge and no revisions were made.
199	2-11	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 proposed revision is outside the scope of the current EWG charge. However, the EWG believes there is an inappropriate comma in this sentence which could be removed to improve clarity. The "impact of coat length" is what should be assessed. This could be consideration of the coat length (summer vs. winter coats) in horses included in all studies conducted to support effectiveness. 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.
207	2-12	Comment: No age mentioned for *Strongyloides westeri* infections. Proposed change (if any): Define required age for *Strongyloides westeri* infections.	Age of animals for *S. westeri* is referenced earlier in the GL (see Section A.1). Although the EWG agrees that a clear definition (as in months of age) would be preferable, a revision to this section would be outside of the EWG charge.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
239	2-13	Comment: 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. Proposed change (if any): The term "effectiveness" should be replaced by "efficacy" for consistency throughout.	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.
246-248	2-14	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.

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 15 (GL15). 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 GL15 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 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**
262	2-15	Comment: The sentence "One using…" is incomplete, as it is missing a verb. Proposed change (if any): merge with the previous sentence, "…efficacy claims, one using…"	The EWG revised as, “Two basic study designs have been used to pursue persistent efficacy claims: one using a single challenge and another using multiple daily challenges following treatment.
279-282	2-16	Comment: ERP is not a tool but a metric or indicator. Proposed change (if any): Change wording accordingly.	The EWG agrees that "tool" is an imprecise descriptor of the ERP, and changed the statement to read, "ERP is a pasture contamination metric".
281	2-17	Comment: pasture contamination management tool, =repetition of Line 279 Proposed change (if any): Avoid repetition.	The second use of the word “a tool” was replaced with “used” to read: “It is used…”
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 only addition to the equine GL discussed as part of the EWG charge was addition of number of worms for adequate infections for *Anoplocephala perfoliata*, and therefore it was not considered necessary to create a table. If specific values for additional species were added in the future, the EWG agrees a table would be useful.