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: GL16 Efficacy of Anthelmintics: Specific Recommendations for Porcines.

VICH EWG: ANTHELMINTICS

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

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

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
1-1	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 guideline for swine. 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	1-2	Comment: Citation of WAAVP guideline is incorrect. Proposed change (if any): Change citation to "World Association for the Advancement of Veterinary Parasitology (WAAVP): Second edition of guidelines for evaluating the efficacy of anthelmintics in swine", Vet. Parasitol. 2006;141:138-149.	The revision to update the formatting of the citation is accepted; however, the EWG intends to update the reference if a new version of the guideline is available by the time of publication.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
87	1-3	Comment: The statement that "Critical tests are generally considered not to be very reliable for porcine parasites" is not supported by the literature; this only relates to helminth infections not to parasites in general. Proposed change (if any): change "parasites" to "helminth parasites".	The topic of critical tests is outside the scope of the EWG charge; however, the EWG agreed with the editorial comment and the minor revision of "parasites" to "helminth parasites" was made to the guideline.
Section 4.3	3-1	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 (*A. suum*, *A. strongylina*, *P. sexalatus*, *S. dentatus*, *Metastrongylus* spp. and *Fasciola* spp..). EWG could consider specifying the minimum worm counts for these species; however, it may be difficult to harmonize across the jurisdictions, especially with limited data. Consistent with the other species specific guidelines, 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".
103	1-4	Comment: What is a "recent" field isolate? Proposed change (if any): add definition (here or in the glossary).	Field isolate is defined in GL7 and there is not a separate definition for a "recent field isolate." As stated in the glossary definition of field isolate from GL7, a field isolate is considered representative of current parasite infections in the field. Generally, it is isolated close to the time the study is conducted. The EWG acknowledges that the term "recent" is a relative term but cannot be more explicitly defined. No revision was made in response to this comment.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
118-119 (Table 1)	1-5	Comment: a) The table lacks scientific citations. b) *Oesophagostomum* spp.: is this number for one species or a mix of species? Same for *Metastrongylus* spp. Proposed change (if any): a) Add relevant scientific citations. b) clarify	Table 1 is outside the scope of the EWG charge and was not reviewed/discussed. There were no citations in the original guideline. The EWG cannot confirm the intent of the authors of the original version of GL16; however, we note that the upper limit for *Oesophagostomum* spp. in Table 1 is three times the upper limit listed in the 2006 version of the WAAVP GL for swine. Regardless, the number of infective stages to inoculate should be aimed at producing adequate infections at a species level. Adjustments to Table 1 (if needed) could be considered as part of future reviews/revisions to the guideline.
120	1-6	Comment: "a trickle infection with a low number of eggs" is not quite clear, first these are trickle infections (plural) and second, the total number of eggs (as the sum of the eggs administered in each of the trickle infections) should be 250-2500, this should be stated clearly. Proposed change (if any): change to "To maximize the establishment of adult worms, trickle infections with low numbers of eggs each (e.g. five times 50-500 eggs) is recommended."	This comment refers to the following footnote to Table 1 referring to establishing infections for *A. suum*: "* To maximize the establishment of adult worms a trickle infection with a low number of eggs is recommended." Although this proposed revision is outside the scope of the EWG charge, it is a relatively minor edit that will be useful to the users of the guideline. The EWG agrees to revise the footnote as follows: "To maximize the establishment of adult worms, trickle infections with low numbers of eggs each (e.g., five times 50-500 eggs) can be considered.
151-153	1-7	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 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	1-8	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.	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. At this time, the EWG agreed that no additional revisions were necessary; however, the numbers could be revisited in future guideline reviews. The updated WAAVP swine guideline was not available before final publication for the EWG to consider if any revisions were needed to the minimum adequacy of infection recommendations in GL16.
171	1-9	Comment: "Fasciola spp." are not listed in Table 1. It would be appropriate to list the helminths considered under this guideline. Proposed change (if any): Clarify.	Table 1 is outside the scope of the EWG charge and was not reviewed/discussed. The EWG agrees that the parasite species listed in Table 1 are not carried through the rest of the guideline consistently. This issue should be considered as a topic for revision in the future.
193	1-10	Comment: Genus names must be abbreviated after first mentioning. Proposed change (if any): Abbreviate "*Stephanurus*" to "*S.*"	The EWG agreed and the revision was made in the 4th paragraph of Section 4.4.
199	1-11	Comment: "in the sow milk" is wrong grammar and also not precise enough; *S. ransomi* larvae are excreted primarily with colostrum not milk. Proposed change (if any): Reword, either to "in the sows' colostrum/milk" or in "sows' colostrum/milk".	This is an acceptable revision. The EWG agrees to revise the sentence to state, "in the sows' colostrum/milk"
212	1-12	Comment: "Samples of medicated water or medicated feed should be collected to confirm drug concentration" should be changed to "Samples….concentrations". Proposed change (if any): correct	This sentence was likely written as "samples... drug concentration" because multiple samples may be taken to confirm a targeted concentration. No revision was made to the guideline.
213	1-13	Comment: "consumed to" is wrong grammar. Proposed change (if any): change to "consumed by".	This is an acceptable revision. The EWG agrees to revise “consumed to” to “consumed by” in the last sentence of Section 5.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
220	1-14	Comment: "If animals are housed in pens, the animals should be randomly assigned to each pen." Rearranged social groups of pigs are a serious welfare issue, and this practice should be refined or dropped. Proposed change (if any): Check and correct.	The statement from the draft guideline that is referenced by WAAVP is included in Section A.6 as follows: “If animals are housed in pens, the animals should be randomly assigned to each pen. The experimental units (animals or pens) should also be assigned randomly to each treatment group. Randomization to treatment group should be performed using an adequate method that should be described in the protocol and final report." The EWG agrees that the welfare of animals should be carefully considered in the design of studies. The random assignment of individual animals to experimental units (EUs) is desired, as it reduces the potential for systematic differences among EUs (e.g., if similar animals such as litter are clustered in an EU); however, there may be other methods besides strict randomization procedures to achieve this result. Regardless, typical strict randomization procedures should be used to assign EUs to treatment group. In addition, there are potential ways to minimize the stress of rearrangement of pigs, including providing sufficient time to acclimate to new social groups; and adequate pen space, feeder space, and/or environmental enrichment. However, this topic is out of scope of the EWG charge and the EWG members were not in agreement that a specific statement should be added to GL16. The general guideline (GL7) already states that all studies should be conducted according to principles of Good Clinical Practice (GCP). As stated in the GCP Guideline, adherence to the GCP standard provides assurance that the welfare of the study animals and the safety of the study personnel are ensured. This is accomplished by, among other things, having sponsors, clinical investigators, and other personnel that are appropriately qualified by knowledge, scientific training, and experience; and that fulfil their responsibilities as described in the GCP guideline. Regardless, this topic may be reconsidered in future revisions of the guideline. Finally, regarding the description of the randomization procedures, the EWG revised the following sentence to provide additional flexibility: "If animals are housed in pens, the animals should be randomly assigned to each pen." to read, "If animals are housed in pens, the animals are typically randomly assigned to each pen."

SECTION ….			
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131, 165-167, 220-221, 254, 310 vs. 213	1-15	Comment: the authors use "pen" throughout to describe a group of animals, but in l. 213 they use "group of animals". Proposed change (if any): use "pen" consistently	The EWG agreed this is an acceptable revision (change "group of animals" to "pen")
229	1-16	Comment: "helminth naive" does not match the style used in the rest of the text. Proposed change (if any): change to "helminth-naïve".	The EWG agreed to add hyphens to both “helminth-naïve” and “helminth-free” where they were not previously present. This resulted in two revisions to GL16. Hyphens were also added to GL12, 13, 14, and 15.
236	1-17	Comment: "A minimum 7 day acclimation" is poor grammar. Proposed change (if any): change to "A minimum acclimatisation period of 7 days" or to "Acclimatisation should be at least 7 days".	The EWG agreed to revise this sentence to state, "A minimum acclimatisation period of 7 days is recommended"; and to make this change to all other species-specific GLs where this statement is made. This same edit was made to GL12, 13, 14, and 15, and a similar edit made to GL21 (which specifies a 10 day acclimation period). The wording of GL19 and 20 was already slightly different and was not revised.
238	1-18	Comment: "monitored daily" for adverse reactions or "monitored at appropriate time points after treatment"? Proposed change (if any): clarify and change if necessary	The EWG agreed that the grammar in the sentence could be corrected without changing the meaning of the sentence. The sentence currently reads, "Animals should be monitored daily to determine adverse reactions". Good Clinical Practice states that protocols should describe procedures for "observing study animals with sufficient frequency to detect AEs"; and all of the species-specific GLs state that animals should be monitored daily. Therefore, the EWG revised the sentence to read, "Animals should be monitored daily for adverse reactions" For consistency, this change was also made to all other species-specific GLs (12, 13, 14, 15, 19, 20, and 21).
283	1-19	Comment: the sentence "One using..." is incomplete Proposed change (if any): Rephrase to "…efficacy claims, one using…"	The WAAVP reviewer is correct that the second sentence is incomplete. The EWG agreed to revise this sentence to be consistent with the other species-specific GLs (see GLs 12, 13, and 14), and merge the first and second sentences with a colon.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
265	1-20	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.
Not Specified	2-1	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 discussed that the FECR (fecal samples collected from the same animals pre and post) could provide valuable additional information, and added that it may be appropriate in some situations where significant individual animal variability is expected. However, the EWG did not agree to remove the comparison to control animals at this time. The current description of field study designs for swine provides for flexibility on this topic as it describes both options and then states, "The primary basis of the effectiveness determination should be defined in the protocol." Finally, the EWG agreed to add the following statement consistent with other species specific GLS, "Furthermore, additional endpoints for evaluating field efficacy should be considered as they are developed and generally accepted by experts in veterinary parasitology."

SECTION ….			
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286	1-21	Comment: "in nature" is not adequate. Proposed change (if any): change to "under field conditions"	The EWG agreed that the revision from "in nature" to "under field conditions" is acceptable; and the same revision was made to GL12, 13, 14, and 15.
314	1-22	Comment: "the circumstances of the study" should be better defined. Proposed change (if any): add “circumstances for which the use of pens as experimental units may apply”.	The WAAVP comment relates to the following sentence in the definition of experimental unit in the glossary: "The experimental unit is the basic unit for the statistical analysis. The experimental unit may be the individual pig or the pen depending on the circumstances of the study." The circumstances of the study are points described in 1) and 2) following this statement. Therefore, for additional clarity the EWG revised the sentence to more clearly highlight the circumstances listed in this section: "The experimental unit is the basic unit for the statistical analysis. The experimental unit may be the individual pig or the pen depending on the circumstances of the study as follows:"
Section 4.3	2-2	Can VICH provide guidance regarding what % of infected animals per pen would represent adequate infection.	The EWG agreed that defining the number and percentage of animals in an individual experimental unit (e.g. pen) that would represent an adequate infection is an important point that will depend on the study design and the parasite under investigation. The EWG does not have a specific recommendation to offer for the guidance and suggests that this topic is revisited in future reviews of the guideline. See also Section 4.2 (Adequacy of Infection) of GL7.
Section 4.4	2-3	Please clarify that for adult claims, treatment should not be administered more than the specified number of days after infection for each species. Currently this is not clear.	Currently, in Section A.4.4, the GL provides the earliest treatment timepoint after infection for evaluation of efficacy against adult stage parasites. It is not clear what ACVM is recommending for revision. No revision was made in response to this comment.