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: GL12 Efficacy of anthelmintics: specific recommendations for bovines.

VICH EWG: ANTHELMINTIC

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

Comment n°	Name - Country
1	Access Vet Med through EMA
2	WAAVP through EMA
3	ACVM

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.

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.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
122	1-2	Comment: Suggested infection rate for rumen fluke could be useful. Proposed change (if any):	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 cattle for anthelmintic evaluation) or to Section 4.3 (Adequacy of Infection). This topic should be revisited when the guidelines are revised in the future.
122	1-3	Comment: it is assumed that these numbers of infective stages relate to a single artificial infection, how do these numbers relate to multiple daily challenges and over several weeks? Proposed change: Can more information be provided as to how these numbers relate to persistent efficacy study design, e.g., if investigating a 21 day claim against *Ostertagia ostertagi*, then the proposed infection rate could be 21 daily challenges of 1000 L3.	The EWG appreciates the comment. However, both Table 1 and the topic of the use of multiple daily induced challenges for persistent efficacy studies were out of scope for the EWG revisions. These topics should be considered for future revision of the guidelines.
122	1-4	Comment: Very wide range of larvae is present for some parasites especially lungworm. Is this necessary? Upper levels quoted are likely to result in development of respiratory disease, possibly death. Proposed change: Reduce upper limit for lungworm if possible. Add footnote to suggest that for younger and/or naïve animals lower infection rates are recommended.	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.

SECTION ….			
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120-123 (Table 1)	2-2	Comment: a) 200,000 Strongyloides L3 is considered too high in new WAAVP guideline (under revision). b) The table lacks scientific citations. Proposed change (if any): a) Suggest lower number of Strongyloides L3. 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. We suggest that a review of Table 1 is considered in future reviews of this guideline.
131-132	2-3	Comment: How many animals in the medicated group(s)? Proposed change (if any): Detail minimum number of animal in both control and treated/medicated groups.	This comment refers to the following statement in Section 4.1, "a) Two dose confirmation studies conducted with a minimum of 6 adequately infected animals in the non-medicated control group in each study." The minimum number of animals in both control and treated groups is discussed in Section 4.2. Section 4.1 does not explicitly include a minimum number of adequately infected animals for the medicated group because adequacy of infection can only be determined at necropsy (post-treatment) based on information from the control group. There is an unstated but necessary assumption in the interpretation of dose confirmation studies that infection level in individual animals in the control group is similar between control and medicated animals at the start of the study (based on appropriate inclusion criteria). No revisions were made to the guideline in response to this comment.
149-151	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.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
163	2-5	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.	The minimum adequacy of infection numbers are based on both a review of the literature and information from regulatory studies. The EWG increased the minimum number of nematodes above 100 for some species as compared to the previous version of Guideline 12. The EWG added a footnote to the table in Section A. 4.3 explaining that the recommended minimum numbers are based on a review of published literature and data from dose titration and dose confirmation studies submitted for regulatory review. The WAAVP ruminant 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 VICH GL12.
166	2-6	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 agreed to add a footnote applying to the whole table 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.
163-180	2-7	Comment: The text is confusing and could be interpreted in the wrong way, because using the "generally, a minimum de 100 nematodes ..." but below were showed that other parasites could be expected lower counts. Proposed change (if any): The text should be clear as the text of lines 168 to 180 and 1. include Fasciola spp. and 2. consider the other species not listed as observation of "to others species a minimum of 100 nematodes or justified by the scientific literature should be described in the report".	The EWG revised Section 4.3 to consolidate the parasite species into a table with the addition of a minimum of 25 worms for *Trichuris* spp. The last sentence of the first paragraph in Section 4.3 (preceding the table) was revised to state: "The range of bovine helminths (adults) that has been considered adequate to grant a claim will vary according to the species. Recommended worm counts (in individual control animals) to be considered adequate for specific parasites include: Following the table, the following statement is included: "For other species, generally, a minimum of 100 nematodes in individual control animals is considered an adequate infection." The sentence "Lower counts are to be expected with *Bunostomum* spp, *Oesophagostomum* spp., *Trichuris* spp., and *Dictyocaulus* spp." was deleted because all parasites in this statement are included in the table.

SECTION ….			
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168-180	2-8	Comment: It is not clear whether these numbers are for mixed or mono-species infections. Proposed change (if any): Detail accordingly.	The adequate infection numbers apply to either mixed or mono infections. In the majority of cases, mixed infections are used to minimize the total number of studies needed. The EWG determined that no revision to the guideline was necessary.
187	1-5	Comment: 8 weeks would not be adequate to adult liver fluke. Also, overlaps with age range for late immature fluke quoted on line 196. Proposed change: Suggest as a minimum 10 weeks or preferred 12 weeks. This should ensure the patency of all fluke and would allow animals to be randomised into treated/untreated groups based on faecal egg count.	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.
189	2-9	Comment: Not entirely in agreement with WAAVP ruminant guideline Proposed change (if any): Harmonise numbers with 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 discrepancy. Revision of Section 4.4 was not within the scope of the EWG mandate and no changes are recommended 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.
202	2-10	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?

SECTION ….

Line No.	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
228	1-6	Comment: Proposed change: Suggest to include proposed treatment should not have any persistent activity.	"The statement referenced is in Section 6 (Animal Selection, Allocation, and Handling): "Animals not raised in a helminth-free environment should be treated with an approved anthelmintic, chemically not related to the test drug, to remove pre-existing infections followed by faecal examination to determine that the animals are helminth free." The EWG agreed to add the following sentence to GL12, 13, and 14: "Extended-release anthelmintics should not be used. If possible, treatment using anthelmintics with persistent activity should be avoided or the study schedule adjusted to prevent interference of the treatment with the establishment of induced infections."
246	1-7	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.
262	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. viviparus*, and revised the first sentence of the second paragraph in Section B.3. to read, "Effectiveness against adult nematodes can be assessed by the reduction of faecal egg counts (or larval counts for *D. viviparus*) and should be performed using samples from the same animal before and after treatment in both study groups (control and treated)."

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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. viviparus*) 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 ….			
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262-272	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, 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 above).
290	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 12 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 were not within scope. The EWG agrees this is an important topic that should be considered in future reviews of this guideline.