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: GL19 Efficacy of Anthelmintics: specific recommendations for canines.

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	Pablo David Jimenez Castro through FDA (public docket)

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
1-1	Access VetMed welcomes the opportunity to comment on this draft guideline. Additional clarification on the required methodology (natural/induced infection) and on the adequacy of infection are welcomed and have addressed issues which are often raised during procedures.	Thank you for your comments. No revision requested.
2-1	This guideline lacks the appropriate scientific citations throughout, which should be remedied. The list of parasites information is given on varies, e.g. in Table 1 *Physaloptera* and other nematodes mentioned e.g. l. 199ff is not mentioned, nor are the tapeworms. Parasite names must be spelled out at first mentioning, and abbreviated later. The guideline should be adapted to show which helminths are under consideration, and if Table 1 is only for roundworms this should be mentioned (l. 125, Table header).	For the first point, the EWG intended to update references currently in the guideline if they were available by the time of final publication. This would include the updated WAAVP guideline for dogs and cats. 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. For the second point, the EWG agrees with only using the abbreviation after first spelling out the full parasite name. Finally, WAAVP is correct that not all parasites discussed in Section 4.4 (Label claims) are addressed in Section A.3, which provides the number of infective parasitic forms recommended for induced infections. Table 1 was outside the scope of the review of the EWG and does not only include roundworms. WAAVP's point is appreciated and the addition of other parasites to Table 1 should be considered in future revisions of the guideline.

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
75-76	2-2	Comment: The cited guideline is outdated. Proposed change (if any): Change citation to "World Association for the Advancement of Veterinary Parasitology (WAAVP): Second edition of guideline for evaluating the efficacy of anthelmintics for dogs and cats", Vet. Parasitol. 2022; 312, 109815; doi: 10.1016/j.vetpar.2022.109815.	Thank you for your comment. The EWG intended to update references if they were available by the time of final publication. This citation has been revised to reference the 2022 version of the WAAVP guideline.
81	2-3	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.
127-132 (Table 1)	2-4	Comment: The table lacks scientific citations. Proposed change (if any): Add relevant scientific citations.	This is a helpful suggestion; however, the EWG was not tasked with reviewing, updating, or providing clarification on Table 1. There were no citations for this table in the original GL and none were added as this was not part of the EWG mandate.
Section 4.1	3-1	For the following point. Can you please clarify if this requirement pertains to field effectiveness? “Effectiveness against helminths will be evaluated examining for the presence or absence of parasitic elements in faecal material or blood.”	This comment refers to Section 4.1, d. The EWG did not add this or update this language from the previous version of the GL; however, recognizes the question. The EWG added "In field studies," to the beginning of the sentence to improve clarity.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
166-172	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. 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.
179-180	2-6	Comment: 5 nematodes is 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 combined information from literature and from regulatory studies. 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.
180	2-7	Comment: "-For Dirofilaria…" seems incorrect. Proposed change (if any): delete hyphen.	The EWG deleted the dash mark in front of "For".

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
201	2-8	Comment: “C. vulpis” is erroneous. Proposed change (if any): Correct to “*T. vulpis*”.	For reference, we believe the comment refers to Section 4.4 Label claims, where *C. vulpis* is listed as an exception to the statement "approximately 7 days is a sufficient time period from the termination of treatment until the animals are necropsied." The EWG believes the original authors intended to refer to *C. vulpis (Crenosoma vulpis)*. Generally, 7-10 days has been sufficient for *T. vulpis,* and therefore it would not be considered an exception. It may be appropriate for the time to necropsy for *C. vulpis* to be longer than the specified 14 days; however, this was outside of the EWG charge. Therefore, no revision was made in response to this comment. Timing of necropsy could be considered in future revisions of the guideline.
208-211 (Table 2)	2-9	Comment: The table lacks scientific citations. Proposed change (if any): Add relevant scientific citations.	The EWG was not tasked with reviewing, updating, or providing clarification on Table 2. No edits were made to this table in the EWG revision except for minor formatting changes.
224-225	1-1	Comment: Good palatability is beneficial for the administration and compliance. It provides an alternative for the user (and the animal). Nevertheless, such studies would only be necessary if palatability will be claimed in the SPC. For the uniformity of the claim, it may be appropriate to refer to an appropriate guidance (EMA/CVMP/EWP/206024/2011-Rev.1). In the absence of palatability evaluation, the product can still be administered orally, either directly into the mouth or masked in small amount of food. Proposed change (if any): For oral formulations, palatability studies ~~should always be included in the evaluation of the effectiveness of the product~~ *are encouraged. Pending on the result, palatability can be claimed in the SPC.* [italicized font is proposed added text]	The EWG was not charged with revision of this topic; however, the EWG acknowledged that while the palatability of an orally administered product may directly influence the amount ingested by an animal and therefore may directly affect dosage and efficacy, specific palatability studies are not always required. Therefore, the EWG agreed to remove ‘always’ from the following sentence: "For oral formulations, palatability studies should ~~always~~ 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**
265	2-10	Comment: The microfilaricide or preventive evaluations for *D. immitis* have several specificities and should be better detailed. Proposed change (if any): Add the specificities to *D. immitis* in field studies.	Adding details regarding evaluations for *D. immitis* is out of scope for the EWG; therefore, no revision was made.
Not specified	4-1	The efficacy threshold to achieve for a Heartworm preventive should not be 100%, we have already published data addressing this issue. Please refer to Vidrashankar et al., 2017	Determining effectiveness for products intended for prevention of heartworm is outside the scope of the current EWG charge, although revisions may be considered in the future.