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: GL7 Efficacy of Anthelmintics: General Recommendations

VICH EWG: ANTHELMINTICS

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)
5	American Sheep Industry Association (ASI) through FDA
6	People for the Ethical Treatment of Animals (PETA) through FDA
7	International Council on Animal Protection in Pharmaceutical Programs (ICAPPP) through EMA
8	Anonymous through UK

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. The pre-requisites for obtaining an acceptable efficacy have been made clear and the inclusion of the decision tree and the worked examples do help with understanding, however it does feel like the overall requirements have been increased from the previous guidance document.	We respectfully disagree that the overall requirements have increased. The number and types of studies to support efficacy of anthelmintic products has not changed. The interpretation of the dose confirmation studies is different, and there are some different recommendations and/or clarifications regarding study design.
1-2	When investigating efficacy against adult stages, could additional clarification be added to confirm what should be done if faecal egg counts (pre-treatment) do not show positive counts, i.e. failure to show patency, should this animal be removed from study? To proceed with one or more animals in this category would result in negative outcome.	Section B.2 (Dose Confirmation Studies) states that "A sufficient number of infected animals should be examined before treatment to ensure that at least 6 (= recommended) adequately infected animals for the parasite or life stage of a parasite are present at the start of the trial ..." Because adequate infections of adult stages (based on worm counts) cannot be fully confirmed before treatment in dose confirmation studies, infection status is evaluated through the use of methods such as fecal egg or larval counts. Protocols for dose determination, dose confirmation, and field studies should have inclusion/exclusion criteria for enrolling animals in a study that include parasitological criteria that are appropriate for the objectives of the study. No changes were made to the GLs because this topic (assessing adequate infections prior to enrollment/treatment) was not discussed as part of the EWG charge.

1-3	It may be beneficial to consider the 3Rs principle in drafting the guideline and to encourage the use of alternative methods to supplement *in-vivo* studies in host animals or the use of alternative study designs. It may not be necessary to perform two studies per claim if no significant findings are reasonably anticipated or other types of data are available to support the claim.	The VICH Task Force did consider alternative methods and determined that at the time of their discussion, there was insufficient evidence in place for broad recommendation of alternative methods in a GL. The number of studies per claim was outside of the scope of the EWG charge. The introduction section of GL7 states the following to address the possible use of alternative methods: "By their nature, guidelines address most, but not all possible eventualities. Each case has to be considered on its' merits, and if in a particular circumstance an alternative approach is deemed more fitting, a reasoned argument for the deviation should be prepared, and if possible, discussed with appropriate authorities before work is initiated."
2-1	The introductory chapters overlap greatly with the WAAVP guideline on the same topic (Geurden et al., 2022; doi: 10.1016/j.vetpar.2022.109698. Epub 2022 Mar 14). This and other scientific literature (citations, list of references) is missing throughout the document, which should be remedied.	The EWG agreed to add the following statement to the introduction section of GL7: "It is also important to note that technical procedures to be followed in the studies are not the aim of this guideline. We recommend that sponsors refer to the pertinent procedures described in detail in other published documents e.g. World association for the advancement of veterinary parasitology (WAAVP) guidelines and updated versions as they are published." The full citation below is included in a footnote: "Geurden, T., Smith, E. R., Vercruysse, J., Yazwinski, T., Settje, T., & Nielsen, M. K. (2022). World association for the advancement of veterinary parasitology (WAAVP) guideline for the evaluation of the efficacy of anthelmintics in food-producing and companion animals: general guidelines. Veterinary parasitology, 304, 109698."

3-1	In most species-specific guidelines adequacy of infection is now described at the animal level whereas previously mean counts were referenced. ACVM generally support this change, however using 2% aliquots, a minimum count of two worms is required to confirm adequacy of infection (=100 nematodes). Given the sampling error (Poisson distribution) there is a high (40%) probably that adequately infected animal (infection of 100 worms) will not register an adequate count. Flexibility (e.g., repeated sampling, larger aliquots, appropriate statistical models) needs to be promulgated.	This change did not reflect an actual change in practice because EWG members agreed that in general, adequacy of infection had historically been interpreted on an individual animal basis. In addition, in GL7 Section 4.5, Adequacy of Infection, the EWG added the following text, which was intended to reflect some flexibility: "The adequacy of infection in at least 6 individual animals, as defined in each of the species-specific guidelines, is intended to provide a guideline for when adequacy of infection should be considered acceptable without additional justification. However, if a study fails to meet the pre-defined adequacy of infection levels, investigators should consider the scientific validity of the model and investigate and discuss the reason for failing to meet expected infection levels in the study. Final conclusions regarding adequacy of infection will be made as part of the final report based on statistical analysis, historical data, literature review, or expert testimony. Justification for including the study to support efficacy should also be included as part of the submission file, as described above." Additionally, aliquot size used to determine parasite burdens should be carefully considered as part of the design of the study with an aim of accurately capturing infection levels for the parasite species under investigation and confirming adequate infection levels when they exist.
3-2	No requirements have been included for fixed dose combination anthelmintics. Does VICH plan to include efficacy requirements for this product class?	Requirements for fixed dose combination anthelmintics was expressly considered outside of the scope of the EWG charge.

3-3	Minimum efficacy threshold- With anthelmintic resistance at the forefront of the minds of regulators worldwide, the onus is on regulatory agencies to authorise anthelmintics with the highest possible efficacy against suspectable parasites. Therefore, a 95% efficacy threshold would seem to be more sustainable in terms of mitigating parasite resistance. Lower efficacy can still be considered on a parasite /host species basis. ACVM support the additional requirement for calculation of arithmetic mean reduction. We believe this is a more appropriate measure of central tendency compared to the geometric mean. The GM can hide potentially important biological differences in between-animal anthelmintic pharmacokinetics. We urge the VICH to consider using non-transformed data, as the primary method to calculate the measure of central tendency used in efficacy calculations. As efficacy is of interest and not mob burden, a recommendation to screen parasitised animals, e.g., using FEC, should be included. This would help confirm infection status prior to commencing a trial and increase the likelihood that infections are adequate. This could reduce animal wastage.	There are 3 points:1) The EWG discussed the possibility of raising the efficacy threshold and did not agree on this point. 2)The EWG position is that the choice of the best measure of central tendency may not always be straightforward, and in the context of the revision of the anthelmintic guidelines the EWG could not conclude firmly on which mean should be used to calculate percent efficacy. As part of the work for the EWG, FDA reviewed data from a substantial number of internal parasite datasets from food and companion animal dose confirmation studies submitted to the Agency which suggested that in many cases, comparisons using transformed data is useful for the initial calculation of efficacy. The updated guidelines add the use of the arithmetic mean, provide a harmonized method for how and when to use geometric and arithmetic means in the calculation and evaluation of percent efficacy, and provides for a secondary assessment based on the biological considerations mentioned by ACVM. 3) The EWG agrees that screening animals prior to conducting a study is recommended in many cases; however, adding this to the current GL was not within the scope of the EWG. ACVM is encouraged to consult other resources, such as the guidelines published by WAAVP for additional technical details for the design of these studies.
4-1	Calculation of percent efficacy In light of increasing antiparasitic resistance, the proposed method of using geometric mean and arithmetic mean as outline in Section 4.2 of VICH GL7 seems like a more appropriate method for estimating the efficacy of anthelmintic drugs. This method is likely to have less potential for misinterpretation. The risk of relying fully on the geometric mean for cattle, small ruminant, and equine gastro-intestinal nematodes can be high as it has the potential to overestimate efficacy resulting in having anthelmintics in the market that would not be providing an acceptable level of efficacy for the claimed parasite species.	Thank you for your feedback.
5-1	No revisions requested.	The EWG thanks ASI for their comments.

Commenters 6, 7, 8, and one in Japan	Major concerns expressed included: **PETA (text excerpted from the letter verbatim)** In general, the draft guidelines on effectiveness of anthelmintics do not include opportunities to reduce and replace the use of animals in testing, a stated goal of the FDA.1,2 Many of the identified tests in the draft guidelines do not take into account the painful nature of the studies and consider strategies to avoid or mitigate such suffering. Withholding treatment of infested animals is detrimental to their health and welfare and, ethically, should not be permissible. Options other than a negative/placebo control are available and used in other areas. For example, the FDA can permit the use of the critical test in additional scenarios or use controls described in human drug guidelines. These controls include 1) active treatment concurrent controls where the test drug is compared with a drug with known efficacy, 2) dose-comparison concurrent control where two doses of a drug are compared, or 3) historical control where test drug results are compared with historic test data or the documented history of the condition. The use of naturally infested animals in field studies provide data more indicative of real-world efficacy and provide a better comprehensive assessment of the performance of a product compared to studies on animals in laboratories. The use of naturally infested animals ensures that parasite strains that animals will be exposed to are accounted for, real-world variables are considered, and adverse events are better identified. Further, the FDA should consider requiring dose confirmation studies only for the dose limiting parasite for all species, which may be able to be identified using in vitro methods. For example, survival curves have been calculated for different doses of acaricide formulations using artificial membrane systems, indicating a possible strategy to identify dose limiting parasites in this area. The guidelines on effectiveness of anthelmintics should clearly state that developers may use the most relevant, modern techniques for dose determination. In vitro and in silico dose determination techniques are available, and the guideline should acknowledge these by describing them alongside the current description of in vivo study design or by eliminating the specification of any dose determination methods such that developers select an optimal method rather than defaulting to the in vivo method. An example of this approach is given by US Environmental Protection Agency guideline OCSPP 810.3300: The Efficacy of Topically Applied Pet Products Against Certain Invertebrate Pests (2021), in which dose determination methods are not specified.	VICH strongly supports the principles to reduce animal studies wherever possible (as stated in the introduction to Guideline 7). We agree that provision of strategies to minimize the need for repeated studies, including ensuring quality/acceptable data would be helpful; however, this may vary between regulatory jurisdictions (e.g., how and when to communicate with the regulatory authority), and be outside of the scope of this VICH GL. There are other VICH Guidelines which address study conduct standards (eg, VICH GL9, or GCPs, which are now specifically cited within the revised guidelines). Animal welfare is one of the key principles of VICH GL9. Determining effectiveness for anthelmintics has unique challenges, considering that for most internal parasites, there is currently no in vivo way to confirm the worm burden quantitatively in an individual animal or within a herd of animals. The EWG is aware of research into alternative methods for determining effectiveness of anthelmintics (e.g., capsule endoscopy in dogs); however, none of these methods are sufficiently validated to be able to include them in a guideline at this time. Other alternatives to untreated controls mentioned (critical tests, active concurrent controls, dose-comparison concurrent control where two doses of a drug are compared) can be considered according to the current VICH GLs if they are scientifically valid for a given species of animal and target parasite. The criteria for adequate infections in control animals do not require that animals are showing clinical signs of the parasitism, particularly any clinical signs that would be detrimental to the welfare of the animals during the study. These studies include provisions to monitor the

	The FDA should include a section in the guidelines on effectiveness of anthelmintics on strategies to reduce the use of animals. Strategies would include, for example, steps to reduce the need to repeat studies, tips to ensure regulatory acceptance of data, and computational and in vitro strategies that can be used to inform studies or in efficacy assessments. In addition, this section should include strategies to address animal suffering. Suffering results not only from painful parasitic infections but also isolation for social species and caging that does not permit species typical behaviors. **ICAPP (text excerpted from comments verbatim – additional comments under each bullet were similar to those from PETA, except the request for a workshop):** In general, we are disappointed that the draft guidelines do not include any significant improvements in terms of minimising the use of test animals, a stated objective of the VICH.1 We are also disappointed that the guidelines fail to acknowledge opportunities where relevant non-animal methods may be used to reduce or replace animal use throughout different stages of the evaluation (e.g. dose confirmation). We therefore request that the VICH considers the following suggestions: 1. Addition of a new sub-section that promotes the 3Rs principles and prioritises strategies that reduce or replace animal use. 2. Inclusion of options to avoid the need for an untreated control group. 3. Accommodating the use of non-animal methods for dose determination. 4. Prioritisation of the use of natural infections over induced infections. 5. Conduct of an international workshop to share best practices and identify further opportunities to replace, reduce and refine animal tests. **Anonymous:** would recommend to change wording on the requirements to conduct dose confirmation studies under field conditions. According to the current wording, such studies require natural infections (considered under field conditions) and finally worm counts in the intestine, thus euthanasia. This is ethically not acceptable at least in pets; propose to adapt an option only, where no challenge model in purpose bred animals is feasible/available. New methods of assessing the worm burden should be encouraged and possible, wherever justifiable, to avoid terminal studies.	health and welfare of animals and allow for removal of animals if welfare is compromised. The EWG agrees that natural infections in field studies provide valuable information regarding the effectiveness and field safety of the product. However, given that the only current way to determine worm burden in an animal is to euthanize it and count the worms, this is generally inappropriate and/or unethical for field studies, which typically enroll a larger number of animals (as compared to dose confirmation studies), and often recruits client-owned animals (at least for most companion animal studies). Therefore, the current method to assess effectiveness is to use a smaller number of animals to confirm that the product is effectively eliminating the parasite (and by what estimated percentage); and performance in the field is measured by the only available in vivo methods, which are not well correlated to worm burden (e.g., fecal egg counts). The availability of ethically sourced, naturally infected dogs and cats for use in these small terminal studies is becoming difficult; therefore, the EWG considers that induced infections are a suitable replacement, given that field studies should provide suitable supportive evidence. These guidelines are focused on testing for anthelmintic products; principles for ectoparasites may not be applicable. For Dose Determination Studies, the number and types of studies were not considered within the current EWG charge. However, the draft guideline (and the previous one) states, “Some regulatory authorities may waive the requirement for a dose determination study where alternative data are presented to support the intended dosage.” This allows some flexibility regarding dose determination studies already. Conducting an international workshop is outside of the scope and purview of the current VICH EWG.

	Organization from Japan: These comments were not translated into English for the EWG; however, the substance was similar to the other commenters in this group, and the EWG believes the response addresses the comments.	

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….

Line No.	Comment N°	Comment received and rationale; proposed change	Outcome of consideration
68-70	2-2	Comment: The grammar is unclear. "bovine, ovine…" are adjectives, "swine", is not. The subject is missing for the first. Proposed change (if any): change to "..individual species guideline for bovine, ovine, caprine, equine, porcine, canine, feline, and poultry hosts."	EWG made minor revisions to the applicable sentence for readability. It now reads: "Additional guidance for individual species-specific recommendations is provided in VICH GL12 (bovine); VICH GL13 (ovine); VICH GL14 (caprine); VICH GL15 (equine); VICH GL16 (porcine); VICH GL19 (canine); VICH GL20 (feline); and VICH GL21 (chicken)."
87, 340	2-3	Comment: "its' "is wrong grammar. Proposed change (if any): change to "its".	The EWG corrected these typographical errors.
89	2-4	Deviations should always be discussed with appropriate authorities. Proposed change (if any): delete "if possible".	The "if possible" is included for those jurisdictions in which there isn't a good option for discussions prior to conduct of the work. This is also a section that was not revised per EWG charge. No revision was made.
110	2-5 1-4	Comment: no reference is given to guidelines on good clinical practice in clinical (veterinary) studies. Proposed change (if any): A reference to the existing VICH or other available GCP guidelines should be added.	The EWG added specific reference to VICH GL9, "Good Clinical Practice" where previously "Good Clinical Practice" was referenced.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
115	2-6	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 or at least for laboratory trials.	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.
118	1-5	Comment: With regard to larval claims, perhaps some guidance/preference could be provided with regard to acceptable study design preferences. Proposed change (if any): Suggest to add as footnote, that one acceptable means of investigating claims against larval stages is to treat animals at the specified stage of infection but wait until the parasite has reached adult stage prior to necropsy.	Some information regarding timing of treatment (and in some cases, timing of necropsy) is provided in the species-specific GLs relative to studies designed to evaluate effectiveness of a drug against larval stages. Additional technical details for specific parasites are available in scientific guidelines such as those from WAAVP. The EWG acknowledges that the GL7 does not provide much detail on the design of studies for larval claims; however, this was a topic that was not within the scope of the EWG charge. No revision was made.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
135	2-7	Comment: A 'drug efficacy profile ' is asked for when laboratory isolates are used. For every available drug class? Proposed change (if any): Please specify.	The comment from WAAVP refers to the following sentence in Section A.2., "The characterisation of each of the laboratory strains used in the investigations should be included in the final report i.e. source, acquisition date, location of isolation, maintenance procedure, drug sensitivity profile, number of passages (including anthelmintic exposure during passage), and expected establishment rates in the target host." As stated in the glossary, laboratory strains are isolated and characterized based on a particular property making it unique for a certain area of research. The level of characterization needed relative to drug susceptibility will depend on the purpose for which the laboratory strain is used. EWG agreed to add the italicized text in the following location: "The characterisation of each of the laboratory strains used in the investigations should be included in the final report i.e. source, acquisition date, location of isolation, maintenance procedure, drug susceptibility profile (*as applicable to the study objectives*), number of passages (including anthelmintic exposure during passage), and expected establishment rates in the target host.
135, 143, 146, 147, 534	2-8	Comment: Sensitivity and susceptibility are used as synonyms. Proposed change (if any): Use one or the other throughout the text for consistency.	The EWG edited to use “susceptibility” throughout for consistency.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
137-138	2-9	Comment: previous anthelmintic exposure should be described for field isolates. Why not a 'drug efficacy profile', as for lab isolates? In the next paragraph, this possibility is mentioned, but it is not required. For sheep gastrointestinal nematodes, fully susceptible field isolates are increasingly difficult to find. Proposed change (if any): Please harmonise between lab and field isolates.	The EWG agrees that there may be situations in which a drug sensitivity/susceptibility profile may be helpful or necessary for the selection of a field isolate before it is used in a study; however, this is not required. Isolates should be selected that represent the current status of infections in the field. In some cases, this may mean that it is appropriate to include an evaluation of the susceptibility/resistance of the isolate, but this is not an expected step for all field isolates. In addition, when such characterization is performed, and/or multiple isolates are isolated and characterized before the study, a discussion of how and why a particular field isolate is selected should be included in the final study report. The EWG added this information to GL7 to address concerns similar to those raised by WAAVP and to ensure transparency in the isolate selection process. However, the EWG also made a minor edit in the fourth paragraph of Section A.2, to remove, "and is not required" from the end of the first sentence because the phrase "in certain circumstances" already clarifies to the reader that characterization is not expected or necessary for all field isolates. The revised sentence reads as follows: "In certain circumstances, such as for studies using products containing a previously approved active ingredient or an active ingredient within the same class as a previously approved drug, characterisation of the field isolate prior to its use in a study may include an evaluation of the susceptibility/resistance of the isolate to previously approved drugs and/or the proposed drug product~~, but is not required~~.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
154-155	2-10	Comment: product equivalence involve same concentration of the active ingredient(s), apart from the other characteristics listed (same dose, etc.) Proposed change (if any): change to "… the same approved active ingredient(s), e.g. generic(s) when used at the same dose, at the same concentration, by the same route of administration…"	The VICH GL does not have the language quoted by WAAVP. This language comes from FDA CVM's GFI, which was historically different in this section, possibly due to differences in generic regulations in the United States versus other jurisdictions (the EWG is unsure of the reason for the differences from 20 years ago). However, because the CVM version of the Guideline is expected to be the same as the VICH version, except for minor changes required by law or guidance practices, the CVM representatives revised the wording in the current draft version of the CVM GFI to match the VICH GL as much as possible. No changes were made to the VICH GL in this section because it was not within the EWG charge.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
161-167	1-6	Comment: In case that the two products contain the same approved active ingredient(s) and are used at the same dose, by the same route of administration and in the same host, but differ in other ingredients, a blood level bioequivalence study is proposed. If it cannot be used, 2 dose confirmation or 2 persistence efficacy studies are proposed. Considering that both products contain the same active ingredients and their dosage will be the same, it may be sufficient to perform 1 dose confirmation or persistent efficacy study. In-vitro data and/or experimental or literature data on susceptibility of target parasites from different geographical regions (absence of regional differences in susceptibility) may serve as a surrogate for the second study. Such reduction in the number of studies would be in line with the 3Rs principle, most notably because of the terminal outcome of the in-vivo studies. Proposed change (if any): In either case for absorbed drugs that can be measured in the blood plasma, and for which a relationship with effectiveness can be correlated with pharmacokinetic parameters, a blood level bioequivalence study may be used. Alternatively and particularly where pharmacokinetic parameters cannot demonstrate a relationship with effectiveness, 2 dose confirmation studies using the dose-limiting parasite for therapeutic claims and/or 2 persistence efficacy studies per species claimed will be needed. One study may be sufficient, if appropriate in-vitro data or literature data are provided that demonstrate efficacy.	This section was not revised, as it was not within the scope of the EWG charge (see also comment to line 467-477).
181-182	2-11	Comment: A page brake was inserted after "described" Proposed change (if any): delete page break	The EWG attempted to remove inadvertent formatting issues. This was not a page break but an incorrectly placed “new paragraph” in the middle of text.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
190	2-12	Comment: "treated and control groups" is only applicable for controlled tests where a control group is included. Proposed change (if any): The text should be reworded to make clear that the data analysis is also applicable to critical tests.	The comment refers to the following sentence in Section 4.1: "If the results demonstrate significant statistical differences between the treated and control groups, then the next steps in the effectiveness evaluation should be performed as described in Section 4.2." Critical tests are not commonly used; therefore, the EWG did not have sufficient data to perform simulations and make data analysis and interpretation recommendations for critical tests. As stated in section A.2., "...the option to utilize critical tests should be supported with an explanation from the sponsor." This would include an explanation for the appropriate data analysis and effectiveness evaluation procedure. No revision was made.
Section 4	3-4	Section 4 - Recommendations for the Calculation of Effectiveness; Structurally it would be logical if this section followed the decision criteria presented in the appendix. i.e., adequacy of infection was the first point considered in the recommendations for calculation of product effectiveness.	The EWG agrees that the current organization of Section 4 does not match the decision criteria presented in the Appendix. The EWG agreed to move Section 4.3 (Number of Animals), Section 4.5 (Adequacy of Infection) and Section 4.6 (Aliquot Size) to the beginning of Section 4, making them Sections 4.1, 4.2, and 4.3 and then moving the other sections down accordingly. In addition, references to the appropriate sections in GL7 were updated throughout all the species-specific guidelines.
Section 4, cont'd	3-5	We need to consider if hypothesis testing is required? Given guidance recommends a minimum of 6 animals per group, a minimal parasite burden per control and the large effect size (i.e., 90% efficacy), any study meeting these criteria will show statistical significance. This could be easily substantiated based on simulation. Hence simple descriptive statistics would be adequate, reporting both arithmetic and Williams means. A measure of certainty around the mean parasite reduction would be useful (e.g., 95% CI).	Thank you for your comments. The EWG discussed both eliminating hypothesis testing and use of confidence intervals; however, ultimately the current proposal was the most universally agreed-upon method within the EWG.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
Not specified	3-6	If statistical models are to be used for hypothesis testing or generation of CIs, the proposed statistical models do not capture the variability associated with counting of the parasites in an aliquot (a Poisson process) nor the overdispersion associated with between animal variability (described by say the negative binomial or zero-inflated NB distributions). Also, as a zero count indicates no parasites were seen, but does not prove there were none, confidence/uncertainty intervals must reflect the biology. There are readily available methods to model these data that do not require transformation and have rational error structures.	We agree that the distribution of some parasites may be more precisely modelled based on better understanding of their biology and population dynamics. This guidance is developed to apply to all/most parasites, and therefore it would be challenging to specify models that may be appropriate for some but not for general purposes. We note that the first paragraph of Section 4.2 explains the basis for these general recommendations but does not specifically prohibit the use of other models as applicable for specific studies.
Section 4.1, lines 178-192	1-7	Comment: The expansion of this section is helpful, in that it describes incorporation of random effects into parametric mixed linear models, and therefore the use of least squares means in estimation of percent efficacy. Proposed change: N/A	No change requested. Thank you for the feedback.
Section 4.2	1-8	The considerable expansion of this section is beneficial from a harmonization perspective, in that it provides specific guidance for the interpretation of any discrepancies between percent efficacy calculations based on geometric versus arithmetic means.	No change requested. Thank you for the feedback.

Commenté [NB1]: Section 4.4 now!

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
230, 233, 234, 250, 252, 266, 269	2-13	Comment: "pen" can also be any other group of animals, such as e.g. a litter. Proposed change (if any): Should be reworded e.g. as "a group of animals defined as experimental unit per protocol, e.g. a pen or litter" and "group averages" instead of "pen averages".	The EWG agrees with WAAVP that where the term "pen" is used, this could also refer to any other group of animals, such as e.g., a litter., even though in almost all cases, pen is an appropriate example. The EWG revised the GL in response to WAAVP's comment as follows: If the experimental unit is a group of animals (e.g., in a pen) rather than an individual animal, the initial calculation of efficacy should be performed by first computing the average for each experimental unit (arithmetic mean of parasite counts in the experimental unit); and then using these experimental unit averages in the analysis to derive the geometric means. In situations where each experimental unit includes the same number of animals, parasite count totals for each experimental unit may be used instead of experimental unit averages.
230-235	1-9	Comment: Situations in which the pen, rather than the individual animal, is the experimental unit are addressed, with the recommendation to calculate mean counts per pen. It should be noted that accounting for pen as the experimental unit is also possible in parametric models through the inclusion of pen as a random effect, although the guidance does not mention this as a possibility. However, using pen averages should achieve the same results as appropriately counting for pen directly in the model, and permits analysis via both parametric and nonparametric procedures. Proposed change: N/A	No change requested. Thank you for the feedback.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
268-301	1-10	Comment: The secondary approach describes a new, but seemingly reasonable, approach to resolve interpretation of conflicting results based on geometric versus arithmetic means. The approach sees treatment effectiveness in a favorable light, by using the animal (or pen) in the control group with the highest parasite burden as the reference. Full justification for selection of the 80% threshold for studies with 6 to 12 experimental units per group is provided. While this new approach may be unfamiliar to sponsors, the method is described in adequate detail and examples are provided. No threshold proportion is specified for the secondary approach when the number of experimental units per treatment group exceeds 12. Of note, for studies with these larger sample sizes, the Sponsor should justify the threshold they intend to use in advance, i.e. in the protocol. Importantly, the guidance acknowledges that new endpoints and analysis methods should be considered for implementation as they become generally acceptable in the veterinary parasitology field. Proposed change: N/A	No change requested. Thank you for the feedback.
276	2-14	Comment: Colon is missing after "follows" Proposed change (if any): insert colon to match format with the rest of the paragraph	The EWG corrected this typographical error.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
292-295	2-15	Too vague. Specify the proportion of animals that should have >90% reduction of worm or egg counts compared to control animal with highest counts, as was done for smaller group size.	The statement referenced by WAAVP is the following: "For studies with sample sizes greater than 12 animals/experimental units, the threshold proportion of animals/experimental units with at least a 90% reduction in parasite burden used to support effectiveness should be justified in the protocol." It is important to note that this secondary assessment applies only to dose confirmation studies and reductions in worm counts, and was not intended to apply to field studies or FEC. In addition, this assessment was developed based on an analysis of dose confirmation studies with 6 to 12 animals per treatment group. In these studies, adequacy of infection is defined as at least six adequately infected control animals. If more than 12 animals are used in dose confirmation studies, GL7 states that statistical methods of evaluating adequacy of infection may be needed in addition to the minimum requirement of six adequately infected animals. Because the secondary assessment starts with an evaluation of worm burdens in the control animals and assumes at least 6 adequately infected controls (and by assumption, animals in the treated group pre-treatment), a determination of a threshold value for larger dose confirmation studies would need to be determined on a case-by-case basis. The use of greater than 12 animals per treatment group is generally discouraged and is a relatively uncommon occurrence. There was no agreement in the EWG on the most appropriate solution to the questions raised by WAAVP and the EWG recommended reconsidering this issue in future revisions of the guideline.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
297-299	2-16	Comment: There is not a single harmonised recommendation for calculating percentage efficacy for field studies. Proposed change (if any): A recommendation should be provided in the animal species-specific guidelines. Alternatively, recommendation to follow WAAVP specific guidelines (existing or updated ones) should be clearly indicated.	The EWG appreciates the desire for a single harmonized method of analysis for field study designs for each of the species-specific GLs. However, with recent and rapid advances in diagnostic techniques and research into advanced statistical methods, the EWG could not agree on a single method for the purpose of harmonization. The following statement was included in the guidelines to acknowledge the potential for considering new recommendations for field studies: "Furthermore, new endpoints and analysis methods for evaluating field effectiveness should be considered as they are developed and generally accepted by experts in veterinary parasitology." Please note that the species-specific GLs do point to WAAVP GLs at the beginning and methods recommended by WAAVP should be considered. This topic could be included for reconsideration for future revisions.
311	2-17	Comment: "Pooling data is allowed when certain criteria are taken into account". Proposed change (if any): Such criteria should be explained in detail and exemplified.	The EWG did not have charge to specifically re-evaluate/revise the section on pooling and the EWG acknowledges that the criteria described in this section could be improved. The only revision to this section is reference to 4.6, and the intent was not otherwise to change the meaning from the previously existing GL. We suggest this topic is considered for revision in the future.
338	2-18	Comment: a page break was inserted after "animals," Proposed change (if any): delete page break.	There is no page break; however, there was an in appropriate new paragraph under Section 4.5 (page 7) that was removed.
343	2-19	Comment: the plural of minimum is minima not minimums. Proposed change (if any): change to correct term.	The EWG agreed to revise the sentence as follows "Multiple infections are acceptable, however, each helminth species must reach an acceptable minimum infection.
349	2-20	Comment: How is adequacy of infection defined in field studies? Proposed change (if any): add 'egg count distributions' for field studies.	The topic of "adequacy of infection" for field studies was not considered to be under the EWG charge. Therefore, this revision is declined.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
Section 4.5, Lines 343-350	1-11	Comment: The issue of parasite species in which low worm counts are expected is addressed, with the recommendation to specify a definition of adequate infection in advance, i.e. in the protocol. This will require that the Sponsor determine and justify species-specific definitions of adequate infection before conducting the study. The guidance also explains that employing a study design which increases the number of animals per treatment group in order to achieve 6 adequately infected animals per group is not sufficient to demonstrate adequate infection. Instead, adequacy of infection should be determined via statistical assessment of worm count distributions. It would be helpful if guidance on appropriate methods was given here (the previous version of the guidance described a particular method as a possibility). Proposed change (if any): Suggest including statistical test (from previous version) as a means of investigating adequacy of infection	The EWG discussed the statistical method included in the previous version and determined that it was not used on a regular basis and could be removed from the guideline. Simulations were performed and the results of these simulations and utility of this method were published. (see Zhao, X, et al. Revisiting the adequacy of infection criteria recommended in VICH GL7 for anthelmintic effectiveness studies: Retrospective simulations. Jan 2021. Vet Parasit. (289)https://doi.org/10.1016/j.vetpar.2020.109324). The EWG was not tasked with creating a new statistical method and believes this would be out of the scope of the current charge. A minor revision was made to the last sentence in the second paragraph of Section A.4.2 as follows: “In such cases, ~~a statistical method of evaluating adequacy of infection,~~ an additional justification (e.g., a statistical method based on worm count distributions) may be needed in addition to the minimum requirement of six adequately infected animals as outlined in the relevant species-specific guidelines."
357-359	1-12	Comment: The guidance clarifies that conclusions regarding adequacy of infection will be based not just on statistical analysis, but also based on historical data, literature review and expert testimony.	No change requested.
364	2-21	Comment: "Smaller aliquot size" is not correct. Proposed change (if any): change to either "A smaller aliquot size" or "Smaller aliquot sizes".	The EWG edited this to read “A smaller aliquot size…”.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
Section 5	3-7	Section 5- Standards of Effectiveness Information regarding treatment to prevent pasture contamination has been removed from both the general and some species-specific guidelines e.g., ovine and bovine. This is an important consideration for anthelmintic treatment in pastoral based farming systems. Can this please be reinstated.	The information that was removed is the strike through text in the following sentence: "However, there are regional differences where the epizootiology of certain parasitic infections may require higher minimal effectiveness, ~~especially when the aim for drug effectiveness is focused specifically on preventing pasture contamination.~~ " This was removed primarily due to changing management recommendations relative to resistance (drugs should not be relied upon solely for parasite control, but as part of a comprehensive pasture management plan), and the "aim" "focused specifically on preventing pasture contamination" could be misleading. However, the EWG acknowledges pasture contamination control could be used as part of an overall parasite management strategy in certain jurisdictions. The revision to the guideline does not preclude addressing these specific needs if appropriate.
376	2-22	Comment: "when the claimed parasites do not have any other effective treatment." appears incorrect. Proposed change (if any): Change to "When no other effective treatment against the parasite in question is not available".	The EWG edited the statement to: “Effectiveness below 90% may be adequate when no other effective treatment against the parasite in question is available.”

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
384-385	1-13	Comment: Two dose confirmation studies are requested if species claim are to be made for immature species (in case there is more than one species in that genus). It may be beneficial to emphasize that this requirement is related to immature stages. Like in other cases, one study may be sufficient, if adequate alternative (e. g. in-vitro study or scientific literature) data are provided. Proposed change (if any): If species claims are to be made for immature stages, then the presence of each should be confirmed including two dose confirmation studies for each parasite. An in-vitro data or literature data of appropriate quality can be used in place of one of the confirmation studies, if they can demonstrate similar susceptibility of parasites (efficacy) from various geographic locations or an absence of clinically relevant differences in susceptibility	This section was not revised, as it was not within the scope of the EWG charge. The potential use of *in vitro* methods could be proposed for future EWG discussion.
389	2-23	Comment: “new parasite” is not accurate. The document seems to refer to other parasites not currently addressed, and not new host-parasite relationships, which is what the wording “new parasite mean. Proposed change (if any): Replace "new" with "other".	This comment relates to Section 7, "Approach to new indications". The purpose of this section is framed by the title of this section focusing on new "indications". The adjective "new" is intended to modify "parasite indications", not "parasite", and is further clarified by the phrase within the parentheses "not currently addressed in VICH Guidelines". Therefore, the EWG respectfully disagrees that a revision is necessary.
392	2-24	Comment: Why should the number of studies for 'new' parasites be different? Proposed change (if any): Stick to a minimum of 2 dose determination and 2 dose confirmation studies.	The intent of this section is to provide a list of information for sponsors to consider. New indications may not have quite as clear a roadmap as for those which are already established. However, the intent is not to change the requirements for new indications; rather provide a comprehensive list of information that should be provided to the regulatory authority when seeking approval. A revision to this section is not necessary.
397	2-25	Comment: "may include" is not correct. Proposed change (if any): correct to “should include”.	The EWG agreed with the proposed change.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
410	2-26	Comment: "implication for study design": wrong grammar Proposed change (if any): change to "implications for the study design".	The published draft states "implications for study design"; "the" implies a single study but may in fact affect multiple studies. The EWG declines addition of "the" to avoid confusion.
418	2-27	Comment: The number of dose determination studies is not specified. Proposed change (if any): specify the number of dose determination studies required.	Specifying the number of dose determination studies that should be performed for a given product is outside the scope of the EWG revision.
433	2-28	Comment: a comma after "made" is wrong grammar. Proposed change (if any): delete comma.	The EWG agreed with the proposed revision.
436	2-29	Comment: The sentence "When only one parasite species…" is not necessary, this can be concluded from what is stated before. In addition, dirofilaria imittis should be written in italic font and, in line with the use of species names in other guidelines, be abbreviated to "D. immitis" after first mentioning. Proposed change (if any): delete sentence.	The editorial change of using italic font for consistency is acceptable; this is the first mention of the genus/species in the document, and therefore the full name is important on this line. The next mention is in the last paragraph of this section and can be abbreviated. Because this section is outside of the EWG scope for revisions, we did not consider removing the sentence.
440	2-30	Comment: "a group of untreated controls" appears inaccurate. Proposed change (if any): change to "an untreated control group" or "a group of untreated (control) animals".	The EWG made minor revisions to clarify the text in line 440 as follows: "One internationally accepted design includes a minimum of three groups of animals receiving different levels of anthelmintic treatment together with a group of untreated controls animals (e.g., 0, 0.5, 1 and 2x the anticipated dose)."

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
443-445	2-31	Comment: The text states "For each selected parasite, there should be at least 6 (= recommended) adequately infected control animals, but if there is any doubt about the level of infection then the number should be increased accordingly (see data analysis).". However, in the Chapter on Statistical analysis, 4.5., adequacy of infection, line 345-350 it states "If inadequate infections in a significant number of individual study animals are expected, increasing the number of animals in the study groups to achieve six adequately infected control animals should not, by itself, be considered an appropriate modification to the study design. In such cases, a statistical method of evaluating adequacy of infection, based on worm count distributions, may be needed in addition to the minimum requirement of six adequately infected animals as outlined in the relevant species-specific guidelines." This appears to be a contradiction. Proposed change (if any): Reword to make clear how low-level infections should be dealt with (pro-and retrospectively).	This sentence is under "dose determination studies"; which was not edited as part of the scope of the current revisions. However, the EWG did make revisions to Section 4.5 about adequacy of infection that could be perceived as contradictory to this statement. Section 4.5 states that "increasing the number of animals in the study groups to achieve six adequately infected control animals should not, by itself, be considered an appropriate modification to the study design. In such cases, a statistical method of evaluating adequacy of infection, based on worm count distributions, may be needed in addition to the minimum requirement of six adequately infected animals as outlined in the relevant species-specific guidelines." Therefore, the EWG revised the statement as follows: "For each selected parasite, there should be at least 6 (= recommended) adequately infected control animals~~, but if there is any doubt about the level of infection then the number should be increased accordingly~~."
448	2-32	Comment: Larval stages are usually the dose-limiting stage. Does this mean that they should always be included in dose determination studies? Proposed change (if any): Please clarify.	This revision would be outside of the scope of the EWG charge. [For reference, this is under Dose Determination studies and appears to refer to the following: This phase of the testing should be conducted using adult parasites unless there is information that larvae of a particular parasite could be a dose-limiting stage or the proposed product claim is only targeting a specific parasite at the larval stage (e.g. *Dirofilaria immitis*).]
449	2-33	Comment: "Dirofilaria immitis" should be abbreviated to "D. immitis" and written in italic font. Proposed change (if any):	The EWG agreed to this change.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
464	1-14	Comment: General study design for inhibited stages are unclear. Proposed change (if any): Suggest footnote to briefly describe acceptable study design for these stages.	This revision would be outside of the scope of the EWG charge.
464	2-34	Comment: The sentence "Against inhibited stages only natural infections are recommended." does not make sense. Proposed change (if any): Should be rephrased to "To evaluate efficacy against inhibited stages, only the use of natural infections is recommended", or “Only natural infections are recommended for evaluatiing efficacy against inhibited stages”.	The sentence "Against inhibited stages only natural infections are recommended." was revised to read, “Only natural infections are recommended for evaluating efficacy against inhibited stages”.
467	1-15	Comment: For generic products could 2 dose confirmation studies against a recognised dose limiting parasite be accepted. Proposed change (if any): Suggest including reference to dose limiting parasites for generic drugs.	Generics are referenced in Section A.3 - Product Equivalence. Specifying the number of studies for generic products is outside of the scope of the EWG charge, therefore no changes were made.
456 vs 487	2-35	Comment: “Studies should be conducted" vs. "studies shall be conducted"- there is no justification for using two different expressions. Proposed change (if any): reword for uniform phrasing.	For consistency, the EWG revised the few instances of "must" and "shall" to "should" in GL7 and in the corresponding places in the species-specific guidelines. This change is consistent with the introduction of GL7 which states, "The guidelines should not consist of rigid stipulations, but should make clear recommendations on the minimal standards needed. By their nature, guidelines address most, but not all possible eventualities."

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
467-477	1-16	Comment: Two studies per individual claim are required due to possible variations in susceptibility of helminth strains in animals raised in disparate regions and climates and under respective husbandry conditions. Nevertheless, it may be desirable to limit the number of studies, if appropriate data (e. g. in-vitro tests, scientific literature) is provided. Such data would need to demonstrate an absence of differences in susceptibility of target parasites originated from different regions (where the product will be marketed). The reduction of studies would be in line with the 3Rs principle, most notably because of the terminal outcome of the in-vivo studies. Proposed change (if any): At least two controlled or, when appropriate, critical dose confirmation studies per individual claim are recommended (single or multiple infections). Two studies are the minimum needed to verify that efficacy can be achieved against various helminth strains in animals raised in disparate regions and climates and under respective husbandry conditions. At least one of the studies should be conducted in the geographic location where registration is being pursued and both studies should be conducted under conditions that are sufficiently representative of the various conditions under which the product will be authorised. In the event that in certain locations parasites are particularly rare then two trials from outside the location will be acceptable. A dose determination study can be used in place of one of the confirmation studies, if the final formulation was used and administered under label recommendations. An in-vitro data or literature data of appropriate quality can be used in place of one of the confirmation studies, if they can demonstrate similar susceptibility of parasites (efficacy) from various geographic locations or an absence of clinically relevant differences in susceptibility.	The number of dose confirmation studies required is outside of the EWG charge for the current revisions. In addition, the request for two studies is not only to provide information on different representative isolates, but to also provide independent substantiation for confirmation of efficacy.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
476	2-36	Comment: "studies, if" is wrong grammar. Proposed change (if any): delete comma.	The EWG agreed with this revision.
491	2-37	Comment: a page break was inserted after “a". Proposed change (if any): delete page break.	The EWG removed the extraneous “new paragraph” formatting.
492	2-38	Comment: what profile is meant here? Proposed change (if any): reword or explain.	This was the original text and the EWG did not draft it, nor were we charged with revising this section. We agree that this is not clear, but it is outside the scope of the current EWG to make this revision.
494	2-39	Comment: referring to the glossary is not applied throughout Proposed change (if any): uniformly refer to the glossary or delete here.	This was the original text and the EWG did not draft it, nor were we charged with revising this section. It is outside the scope of the current EWG to make this revision.
495	2-40	Comment: "local" as a noun is an inhabitant of a particular area or neighbourhood, so it is wrongly used here. Proposed change (if any): delete "local/"	The commenter refers to the following sentence: "To achieve the requested numbers, it is also acceptable to conduct multi-centre studies with sub-trials in each local/region." The EWG agrees to change "local/region" to "locality/region" to maintain consistency with the previous sentence.
503	2-41	Comment: Why should only broad spectrum anthelmintics have a persistent efficacy? Proposed change (if any): Remove 'broad spectrum'.	The EWG agrees with WAAVP and will remove "broad spectrum" in the sentence "~~Broad spectrum a~~Anti-parasitic compounds may show persistent effectiveness due to the presence of residual activity of either the parent compound, or the metabolites, in the treated animal."
511	2-42	Comment: "a minimum for a persistence claim" - something seems to be missing here. Proposed change (if any): change to "minimum requirements for a persistence claim.	The EWG agrees that the sentence is missing a noun. The sentence will be revised to state, "minimum requirements".

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
515	1-17	Comment: Could the use of dose limiting parasites not be considered for persistent efficacy claims? Proposed change (if any):	The use of dose limiting parasites in persistent efficacy studies in lieu of conducting 2 studies for each duration and parasite claim was not discussed within the EWG group (only certain elements of study design). Therefore, no change was made in response to this comment. This could be a topic considered for future revisions.
511-517	1-18	Comment: Similar comment applies as for dose confirmation studies. Proposed change (if any): As described for dose confirmation, a minimum for a persistence claim (for each duration and parasite claim) should include 2 trials (with worm counts) each with a non-treated and treated group. At least 6 animals (= recommended) per treatment group shall be adequately infected. The adequacy of the infection should be defined in the protocol phase. Persistence claims will only be granted on a species-by-species basis. Persistent efficacy claims should be granted for the longest period between treatment and the last challenge where effectiveness criteria are met and all preceding time points tested meet the criteria as well. An in-vitro data or literature data of appropriate quality can be used in place of one of the studies, if they can demonstrate similar susceptibility of parasites (efficacy) from various geographic locations or an absence of clinically relevant differences in susceptibility. Comment: For generics, local regulatory requirements are to be addressed in addition to demonstration of equivalence. Further advice on the issue (appropriate consideration of local regulatory requirements) should be provided or the sentence should be deleted. Proposed change (if any): ~~Local regulatory requirements should be addressed accordingly.~~	The number of persistent efficacy studies was not discussed within the EWG group (only certain elements of study design). Therefore, no change was made in response to this comment. This could be a topic for future revisions. Requirements for generic products is outside of the scope of the current EWG revision. Therefore, no revision was made. [For reference, this phrase is in the glossary under the definition for generic(s). Not in the same section as persistent efficacy studies.]

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
556	2-43	Comment: "A parasite that will be identified during dose determination studies that will identify the dosage of the drug" is wrong, the second part of the sentence is related to "studies" but as it is used in the subordinate part of the sentence it would refer to "A parasite", which makes no sense. Proposed change (if any): Rephrase	The EWG recognizes that this definition could be improved; however, updating this definition was not within the EWG charge. It should be considered for future revisions. [For reference, this refers to the definition of "dose-limiting parasite" in the glossary.]
562	2-44	Comment: as above, "efficacy" should not be replaced by "effectiveness" Proposed change (if any): use correct expression throughout.	The comment refers to the definition of Effectiveness in the Glossary. The word "effectiveness" was previously defined in the original GL. The EWG only updated the definition to include the additional considerations for effectiveness, and the charge did not include considerations such as reviewing the entire GL for whether "efficacy" or "effectiveness" is the most appropriate word choice for each scenario. Consideration for the use of “efficacy” or “effectiveness” throughout the entire document could be considered for future revisions. The EWG did not agree that “efficacy” should be applied universally throughout the document.
575	2-45	Comment: dosage does not equal concentration. Proposed change (if any): change to "…active ingredient(s), at the same concentration as the approved drug”.	The comment refers to the definition of “Generic(s)” in the Glossary. Requirements for generic products is outside of the scope of the current EWG revision. Therefore, no revision was made. This definition should be reconsidered in future reviews/revisions of the Guideline.

582 vs 587	2-46	Comment: Is a strain kept in the lab for >10 years without segregation a field isolate or a laboratory strain? Proposed change (if any): it should be stated clearly that segregation (e.g. selection for anthelmintic resistance) is not mandatory for a laboratory strain	As part of the revisions to the Guideline, the EWG removed the specification that a laboratory strain is at least 10 years old because laboratory strains, regardless of age, are defined by their level of characterization and segregation, making them unique for certain areas of research. By contrast, field isolates do not go through specific segregation and should be representative of current parasite infections in the field. An age limit of 10 years is given as a guide to what may be reasonably considered as "current". An isolate kept in a laboratory for over 10 years is unlikely to be useful for evaluation of drug efficacy unless it has been more fully characterized (and likely segregated). GL7 does not exclude the possibility that laboratory strains could be used for dose confirmation studies in certain circumstances; however, these uses should be fully justified *a priori* in accordance with the study objectives. No change was made to the guidelines in response to this first comment. With regard to the proposed change, the EWG agrees that a revision may be acceptable. Resistance is an example of a characteristic for which a laboratory strain may be selected/segregated; however, this is not required, and a laboratory strain may be segregated based on other characteristics (e.g., pathogenicity). The EWG agreed to a revision to the elements of characterization for laboratory isolates in Section A.2 (adding "as applicable to the study objectives" with reference to the drug susceptibility profile of the isolate). In addition, the EWG proposes the following revision to the definition of a laboratory strain to clarify that resistance is not the only property on which laboratory strains may be segregated: "LABORATORY STRAIN: A sub-population of helminths isolated from the field, which has been characterised and segregated in the laboratory. Segregation is based on a particular property making it unique for areas of research such as resistance to certain antiparasitic compounds, and/or other characteristics such as establishment rates/infectivity or pathogenicity. Characterisation should include the elements described in Section A.2."

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
594	2-47	Comment: "significant morbidity and clinical symptoms" should be the other way around to comply with the order of observations (individual followed by herd). Proposed change (if any):	The WAAVP comment is referring to the definition of rare parasite in the glossary. Updating the definition of "rare parasite" is not within the scope of the EWG charge. A review of all definitions could be considered during future revisions of this GL.
602	2-48	Comment: full stop is missing at the end of the explanation. Proposed change (if any): add full stop to align format with the other parts of the glossary.	The EWG agreed to add a period after the definition of VICH.