25 July 2025
EMA/CVMP/EWP/479402/2019
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on the guideline for the demonstration of efficacy for veterinary medicinal products containing anticoccidial substances (EMA/CVMP/EWP/755916/2016) – Revision 1 (first version)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Veterinary Parasitology College (EVPC)
2	Federation of Veterinarians of Europe (FVE)
3	Cruelty Free International
4	French Agency for Food, Environmental and Occupational Health & Safety (ANSES)
5	AnimalhealthEurope
6	European Group for Generic Veterinary Products (EGGVP)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Maybe best to use italics for the coccidia species.	Thank you for your comments. Italics are now used for the coccidia species throughout the text.
2	FVE welcomes this revised guideline and especially as it extends to other species such as ruminants, dogs and cats, pigs and rabbits. We want to underline the importance in test animals to monitor visual evidence of clinical sign effects, performance characteristics, product quality where relevant, haematology and routine blood chemistry and for other parameters likely to be related to the biological properties of the active substance. See also FVE position paper on coccidiostats: https://www.fve.org/publications/fve-position-paper-on-coccidiostats-or-anticoccidials/	Thank you for your comments.
3	Cruelty Free International understands the need to update this guideline to include general data requirements for a wider range of target species affected by coccidiosis. While we appreciate the efforts that have been made to include reference to the EU Directive 2010/63 (on the protection of animals for scientific purposes) and consideration of the 3R principles (of refinement, reduction and replacement) throughout the draft guideline, there are still a number of areas that we feel would benefit from a workshop to determine if further improvements can be made in relation to the 3Rs.	Thank you for your comments. We welcome further improvements in relation to 3Rs. Where possible, adjustments to the text have been made.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	These include: • Use of in vitro assays for screening and efficacy testing • Possibilities to reduce the number of studies (dose determination, etc.) using combined studies or in vitro assays We request that serious consideration is made to the conduct of a workshop with manufacturers of these products. The workshop would determine, 1. The protocols manufacturers are already using and if there are any that are better in terms of the 3Rs than others (i.e. sharing best practice) and 2. To determine if further improvements could be made without affecting the rigor of the studies. **Use of in vitro assays for screening and efficacy testing** We are disappointed with the lack of guidance on the use of in vitro and/or other non-animal methods that can be used to reduce (and eventually replace) the use of animals required to demonstrate the efficacy of veterinary medicinal products (VMPs) for the prevention/reduction of coccidiosis. According to the World Association for the Advancement of Veterinary Parasitology (WAAVP)'s recently published 'guideline for evaluating the efficacy of anticoccidials in mammals', "*there is a growing body of new methods of in vitro cultivation systems for mammalian coccidia which can be used for pre-clinical drug screening and efficacy testing in cases of suspected resistance*" (Joachim et al. 2018). The guideline highlights the many shortcomings of the existing animal tests e.g. high costs, large	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	number of animals required, ethical issues (i.e. animal welfare) and high risk of contamination of propagated strains by accidental infections. The authors also stress the importance of developing alternative test systems, especially for the propagation and amplification of coccidia. Several in vitro systems are then described: • The combination of cell culture and quantitative PCR (cc-qPCR) in "a very sensitive method" to assess in vitro efficacy of drugs against *Cryptosporidium Parvum*, which is already being used by many laboratories. • Various cultivation systems, including cell culture (e.g. porcine intestinal cells) and embryonated egg inoculation for the propagation of various stages of *Cystoisospora suis*. • Use of in foetal primary cells to complete the whole life cycle of some bovine *Eimeria* spp. in vitro. • In vitro cultivation of *Eimeria ovinoidalis* to the sexual stages, which could be applied for in vitro drug screening assays. Other recent publications include; the development of an in vitro model (using bovine colonic epithelial cells, BCEC) to evaluate anticoccidial efficacy in ruminant hosts that could be used in the initial assessment of new anticoccidial drugs or bioactive substances (Odden et al. 2019) and the use of a reproduction inhibition assay (RIA) to assess the sensitivity of *Eimeria tenella* strains toward polyether ionophores (a well-known class of anticoccidial drugs) (Thabet et al. 2017). The authors of the latter publication state: "*we*	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	believe that replacement of in vivo trials by RIA to construct meaningful sensitivity profiles is a realistic perspective". We strongly encourage the Committee for Medicinal Products for Veterinary Use (CVMP) to consider the conduct of a workshop to evaluate the available non-animal approaches for the testing of anticoccidial drugs and to identify areas that would benefit from the development of novel methods. In the meantime, because testing guidelines are not updated very frequently (the previous version of this guideline was published in 1995), it has become increasingly important to future-proof all new and revised guidelines to allow for flexibility as the science evolves. With the goals of minimising animal testing in mind, text should be added to the beginning of section 6 on 'efficacy studies' to provide guidance on the use of existing in vitro (or other non-animal) methods that can be used (e.g. screening assays, in vitro efficacy tests) to reduce the number of animals required to fulfil the data requirements for anticoccidial VMPs. **Opportunities to reduce the number of animal tests** The guideline recommends at least one dose determination study, at least two dose confirmation studies and at least one multicentre field trial in at least two different European geographical regions. It also requires pharmacodynamic (mode and mechanism of action) and pharmacokinetic (ADME properties) data, which could include tests in animals. We are concerned with the disproportionate number of animal tests being recommended in the draft guideline (e.g. it is not clear why TWO dose confirmation studies are needed). In the interest of	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	reducing unnecessary testing in animals, opportunities to combine some of these tests or waive them based on the results of previous tests, in vitro (using some of the methods described above) or existing data should be clearly mentioned throughout the guideline. This is in line with the EMA's ongoing commitment to support the implementation of the 3Rs principles (https://www.ema.europa.eu/en/human-regulatory/research-development/ethical-use-animals-medicine-testing) and the recent work of the joint CVMP/CHMP 3Rs Working Group to review and update EMA guidelines to implement best practice with regard to 3Rs in regulatory testing of medicinal products (https://www.ema.europa.eu/en/review-update-ema-guidelines-implement-best-practice-regard-3rs-replacement-reduction-refinement).	
4	These comments relate to the general and specific requirements for poultry.	Thank you for your comments.
5	AnimalhealthEurope welcomes the opportunity to comment on this draft guidance.	Thank you for your comments.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Several places	2	Proposed change: Change 'feed conversion' in 'feed conversion rate'. Change 'substance' in 'active substance'.	Accepted.
93	5	Comment: It might be worth defining which genera are belonging to the coccidia. Therefore, add the following sentence at the beginning of line 93. Proposed change: "The term coccidia will be used in the following for apicomplexan parasites belonging to the genera *Eimeria* and *Cystoisospora*."	Accepted.
95	5	Comment: Although the term "schizogony" has been used in publications, "merogony" may be more adapted to coccidia. Proposed change: replace schizogony with merogony	Accepted.
104-106	5	Comment: The sentence mostly focuses on food animals while the following includes cats and dogs. Proposed change: Replace sentence with: "Because coccidiosis is a relevant disease in many hosts requiring either prophylactic or therapeutic interventions, the scope of	Partly accepted. The respective sentence has been amended to provide general information relating to all target animal species concerned and now reads: '*As coccidiosis is a significant disease in many target animal species, the scope of the guideline, which historically only concerned chickens, turkeys and geese, has been extended*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the guideline has been extended from poultry to include other avian and mammalian target species."	*to include other avian and mammalian target animal species*.'
117	5	Comment: Although the general principles may also be applicable to other coccidia affecting the gastrointestinal tract (such as Cryptosporidia). *Cryptosporidium* are not coccidia, yet belongs to the class of gregarinae (see also Thompson et al., 2016. Food and waterborne Parasitology 4, 54-61). Proposed change: Change to although the general principles may also be applicable to **other apicomplexan parasites** affecting the gastrointestinal tract (such as *Cryptosporidium*)	Accepted.
134	4	Comment: Please note that the products used for the prevention of avian coccidiosis are coccidiocidal only because the lifecycle takes place only in epithelial cells which do not live for more than 48-72 hours.	Noted. In the context of a marketing authorisation application, the mode of action of the anticoccidial veterinary medicinal product should be described. Albeit currently there may only be coccidiocidal products, this does not mean that there cannot be any coccidiostatic products in the future.
138	4	Comment: The term 'coccidian' is never used in English literature and should be replaced by "coccidia".	Partly accepted. '*Coccidian*' has been replaced by '*coccidia*' in the respective sentence. However, please note that the term '*coccidian*' can be used as an adjective as in the WAAVP guideline (2018) and other recent papers.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please replace throughout the document the term "coccidian" by "coccidia".	
140	4	Comment: Experimental infection *with Eimeria tenella* and *Eimeria necatrix* can cause high mortality if the infective dose is too high. It is recommended to determine adequately their pathogenicity in advance of pivotal studies. Proposed change: Please amend as follows: "3R principles should be followed through standardised methodology for infection and efficacy calculation ~~and by substituting~~ **to avoid** mortality and **use** ~~with~~ more humane endpoints (e.g. lesions scores in the case of chickens)."	Partly accepted. The sentence has been reworded as follows: '*3Rs principles should be followed through standardised methodology for infection and efficacy calculation, by avoiding mortality rate as primary endpoint and using other appropriate endpoints (e.g. lesions scores assessed in chickens euthanised prior to spontaneous death), where possible.*'
144-145	5	Comment: It would be useful if there is a recommendation of the type of rearing practice, like battery cage or floor pen for DDS & DCS. Proposed change: Please consider including recommendations.	Partly accepted. Not for dose determination and dose confirmation studies, but for clinical trials, under section 6.3, it is included that the age, sex and production type of the study animals should be representative for the target population. Please note that 'battery cage' has not been included as it will be banned in the EU by 2027.
146	5	Comment: Can this be in a CRO? The infection model will be very similar to field conditions.	Accepted. Clarification has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please clarify.	
156-159	5	Comment: Does it make sense to evaluate the MoA of a new anticoccidial drug in histological sections? Proposal to broaden the spectrum of available tools and techniques.	Accepted. The sentence has been amended to allow the use of other techniques.
162	2	Comment: Add incompatibility Proposed change: Potential interactions and incompatibility with feed additives	Accepted.
186	4	Comment: The pathogenicity of an infective isolate may vary among the same species so that it may be difficult to evaluate the representativeness of this isolate. The pathogenicity of the isolate should be evaluated to determine the adequate infective dose that can vary within the species. Proposed change: Please amend the text as follows : "The pathogenicity of the infective strains should be **evaluated depending upon the inoculated species** ~~representative of the respective coccidia species~~ (see host-species information in sections 8-10)."	Accepted. The respective sentence has been amended to read: '*The pathogenicity of the isolate should be evaluated to determine the adequate infective dose that depends upon the inoculated species and can vary within the species (see host-species information in sections 9-13).'*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
197	4	Comment: Oocysts can survive more than one year. Considering the difficulty of producing isolates, a 6 month-old oocyst isolate is considered acceptable. Proposed change: Replace "3 months" by "6 months" as follows: Freshly passaged isolates of sporulated oocysts, stored for a maximum period of ~~3~~ **6** months, should be used.	Partly accepted. The reference to 3 months of storage has been deleted. No other storage time has been included, considering that adequacy of infection has to be shown.
256-260	4	Comment: Naturally infected animals cannot be used in dose confirmation studies because animals will be sick at arrival and present lesions before the administration of treatment intended for the prevention of coccidiosis. Proposed change: Please delete 'or naturally" from the sentence: The study may be carried out in artificially ~~or naturally~~ infected animals.	Not accepted. The guideline is not applicable only for poultry and the possibility to carry out a dose confirmation study with naturally infected animals is not excluded.
263-265	4	Comment: Please note that no therapeutic claim is possible for the coccidiosis because only oocyst excretion can be reduced without any reduction of clinical signs if the VMP is administered during the outbreak.	Accepted. The respective sentence has been amended to remove reference to reduction of clinical signs.
266-268	3	*"For group-housed animals, each treatment should be replicated over several pens. Pen or individual animal weights should be recorded at appropriate time*	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
321-322 364-366		*points, and feed conversion calculated for the species where this is relevant".* *"In field studies or in group-housed animals, pooled samples or litter samples are allowed".* *"Where animals are housed in groups the design should take the between-group variation into account and the statistical model should take the pen effect into account".* Comment: While the use of group housing is mentioned throughout the guideline, nowhere does it explicitly state that the use of single housing should be avoided. Single housing is known to cause stress in social animals, which could confound experimental results. In fact, housing social species (e.g. dogs) on their own for prolonged periods is an example of a procedure that in itself can cause severe suffering under Annex VIII of the Directive 2010/63. Proposed change: We suggest that some text be added to the guideline (perhaps in the general section 6.4. on 'study animals') to discourage against the use of single housing: **The housing conditions should be selected in careful consideration of animal welfare aspects implying isolation (i.e. single housing) should be avoided as far as possible.**	The following sentence on 3Rs principles has been added in the legal basis section of the guideline, which is considered to address the concerns raised: '*In accordance with Annex II of Regulation (EU) 2019/6, all experiments on animals should be conducted taking into account the 3Rs principles (replacement, reduction and refinement) as laid down in Directive 2010/63/EU on protection of animals used for scientific purposes*.'

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In order to further reduce stress, enrichment of the environment should also be considered.	
267	2	Comment: Add ratio. Proposed change: …feed conversion **ratio** calculated…	Accepted. The wording has been amended to '*feed conversion rate*'.
273	4	Comment: The efficacy in poultry cannot be evaluated in the field unless there is a placebo group or sentinel animals because infection pressure is variable. Outbreaks of coccidiosis do not occur systematically and cannot be predicted from one batch to another batch. Proposed change: Please amend the section as field efficacy studies cannot be conducted in poultry. Field efficacy study should not be mandatory and should remain facultative.	Partly accepted. The use of a placebo group or sentinel animals has been included in the guideline. However, clinical trials remain obligatory in principle and can be possible in other target animal species (please note that the respective paragraph is not only about poultry). Omission of a type of study is always possible if properly justified (please refer to section 4, General considerations).
275	5	Comment: Does this refer to the EU or Europe?	This refers to the European Union. However, a non-EU European country could be considered representative for the EU area, if epidemiology and rearing practices are similar.
276	2	Comment: Add flock Proposed change: Sites and groups (e.g. farm, flocks, kennel) with a history	Partly accepted. The examples have been deleted and the type of site is left open.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
290	3	Comment: As stated in the 'general considerations' section, *"3R principles should be followed through standardised methodology for infection and efficacy calculation and by substituting mortality with more humane endpoints (e.g. lesions scores in the case of chickens)"*. This point should be re-iterated at the beginning of section 6.8. on 'endpoints and timing of efficacy assessment'. Proposed change: Add the following text to the very beginning of the section: **In accordance with the 3R principles, humane endpoints should be established for each species to reduce suffering. Mortality should not be used as an endpoint under any circumstances.**	Partly accepted. The following amended sentence has been included in section 4 General considerations: '*3Rs principles should be followed through standardised methodology for infection and efficacy calculation, by avoiding mortality rate as primary endpoint and using other appropriate endpoints (e.g. lesions scores assessed in chickens euthanised prior to spontaneous death), where possible*.' However, considering the severe nature of the disease caused by coccidia, mortality may be a highly relevant parameter and could still be included as primary endpoint.
297	4	Comment: The time of infection cannot be determined because infection occurs at variable times depending upon the animal batch, the persistency of oocyst in the building or the environmental contamination with oocyst (e.g. entry of materials, rodents, litter …). Proposed change: The timing of the assessment of an endpoint in relation to ~~both time of infection~~ the time **of appearance of clinical signs** and time of treatment should be explained.	Partly accepted. As the time of infection can be predicted in experimental conditions, the sentence has been slightly amended: '*The timing of the assessment of an endpoint in relation to time of administration(s), time of infection, and/or time of appearance of clinical signs should be explained*.'
321	4	Comment:	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In poultry, rectal samples are very traumatic for birds. Furthermore, this method is not adequate for the isolation of coccidia species remaining in the caeca (*E. tenella* et *E. necatrix* in chicken, *E. adenoeides* in turkey, *E. grenieri* in guinea fowl. Proposed change: Please add '**if possible'** at the end of following sentence: Faecal samples for oocyst counts should be taken daily, **if possible.**	Pooled samples or litter samples may only be used for checking the presence of the parasite and are not relevant for correlation with the level of infection. Individual samples are necessary for quantification of oocysts and proper statistical analysis of the data. In section 5.5.6.2 Oocyst counts it is now stated: *'For dose determination and dose confirmation studies, individual faecal samples (e.g. by rectal sampling) are generally necessary for oocysts quantification. In certain circumstances such as in group-housed animals, pooled samples or litter samples can be used for the detection of oocysts, but not for quantification of oocysts, unless the method is validated.'*
327	4	Comment: OPG-time curve (AUC) of the daily mean per group is not an adequate endpoint for poultry as the concentration of oocysts is different depending upon the consistency of the faeces (more diluted in liquid faeces while dry droppings may also contain large amounts of oocysts which do not represent the total amount of oocysts). Proposed change: Please mention that clinical signs including the bodyweight loss should be the primary endpoint instead of the OPG-time curve (secondary endpoint).	Accepted. Species-specific information is included in the respective sections of this guideline.
332	5	Comment: Sentence should be divided for clarity.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "… shedding period are pivotal. Otherwise, it may inflate the number of statistical comparisons."	
340	4	Comment: Due to the fluctuation of OPG counts over the time, a 90% reduction of oocyste shedding is too low. A 100-fold reduction should be preferred. Proposed change: The efficacy in reducing oocyst shedding should ~~be at least 90%~~ a 100-fold reduction (e.g. avian species).	Not accepted. Increasing the efficacy requirements is not considered justified.
351	3	*"Due to the 3R principles, mortality should not be the primary endpoint in the study".* Comment: This implies that mortality could be used as a secondary endpoint. Proposed change: Due to the 3R principles, mortality should not be the ~~primary~~ endpoint in the study **under any circumstances and should be avoided as much as possible.**	Partly accepted. In the general considerations section it has been added that using mortality rate as primary endpoint should be avoided, where possible. However, considering the nature of the disease caused by coccidia, mortality may be a highly relevant parameter and can be an important endpoint in efficacy studies.
353	2	Comment: Add feed conservation rate. Proposed change: …water intake **and feed conservation rate** may be more …	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
385-386	4	Comment: Some recommendations regarding the evaluation of the immune response should be given in the guideline. Proposed change: For example: In order to show the suppression of the immunity response, a challenge trial with animals previously treated compared with naïve infected birds should be conducted.	Not accepted. The proposal to perform a challenge trial would increase the requirements, which is not considered justified.
390-393	5	Comment**:** Section 4.5 is not the appropriate section of the SPC as this section should include relative contra-indications to ensure the safe use of the product. Warnings to ensure the effective use of the veterinary medicinal product should be in section 4.4 'Special warning for each target species', similar to that which has been developed for the SPC guidance on anthelmintics (EMEA/CVMP/EWP/170208/2005). Also as resistance prevalence, mechanisms and detection are evolving matters and, as there are many factors that contribute to the selection of resistant coccidian, there should be sufficient flexibility and generalisation should be avoided. I would therefore propose to delete the sentence. Proposed change: Please delete the section.	Partly accepted. The recommendation to include the respective warnings in the SPC is maintained, but these should indeed be included in section 3.4 Special warnings, as the effective use of the VMP is concerned, rather than the safe use. The guideline has been amended accordingly.
394-395	4	Comment:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is not understood why and how a VMP might interfere with the efficacy of the product such as 'coccidiostats' and 'histomonostats'. Proposed change: Amend this recommendation: « This VMP should not be used together with feed additives/or other veterinary medicinal products that might interfere with the efficacy of the product~~, like 'coccidiostats' and 'histomonostats'.~~	The sentence has been reworded to improve clarity: *'This veterinary medicinal product should not be used together with feed additives or other veterinary medicinal products containing coccidiostats or histomonostats.'*
399	4	Comment: Strains instead of "stains". Proposed change: Please replace "stains" by "strains".	Partly accepted. 'Stains' has been replaced with 'species'.
402	4	Comment: Birds do not urinate but produce 'urates' mixed with the droppings. Proposed change: Please correct as follows: Data should be provided on the excretion of the anticoccidial active substance or its metabolites **in droppings** ~~via faeces or urine~~, which may contaminate the litter or the floor, as such contamination may result in a risk of increased (re)uptake by treated and/or untreated animals.	Accepted.
415	5	Comment: Timing of lesion scoring post challenge is very	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		important as even one single day will change the scores drastically. Proposed change : Please make sure that the "well-characterised disease models" accurately define the date of necropsy.	The following sentence has been added to the respective section: *'Furthermore, the timing of necropsy should be accurately defined in the study protocol, as timing of lesion scoring post infection can influence the scores considerably.'*
416	5	Comment: Quality of inoculum is critical. Complete removal of potassium dichromate, absence of any organic materials, reduced levels of other species contamination, etc. Proposed change: Please add sentence: "…group mean of 2 on a scale of 1 to 4). Of critical importance is the quality of the inoculum to minimize variability between studies. Adequacy of infection should be determined…"	Accepted. The following sentence has been added to the respective section: *'To minimise variability between studies, the quality of the inoculum is of critical importance.'*
421	5	Comment: One more group would be meaningful: Infected, positive control. Proposed change: Add additional group: infected, medicated (positive control).	Not accepted. The infected, medicated group is the IVP group. For laboratory studies, a positive control group (comparison with other anticoccidial) is not recommended.
431	5	Comment: "As a standardized lesion scoring system has been developed for chickens…" Suggestion is that a reference to this system be provided.	Not accepted. The lesion scoring system can be different for each *Eimeria* species. Furthermore, the standard might change from gross lesion scoring to microscopic scoring systems. That means there is not one standardised method to refer to, there are

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Add reference.	several, and, moreover, what is state of the art might be different in the near future.
449, 564	2	Comment: Add changes in Food Conversion Rate Proposed change: The nature of clinical signs in infected lambs or kids are comparable (e.g. diarrhoea, reduced body weight, reduced food conversion rate, …) irrespective	Accepted.
454	5	Comment : It might be worth adding a few details on the minimum study requirement of treated- and control-groups. Would the guideline recommend inclusion of a non-infected, treated group besides the infected, non-treated and the treated groups ?	Partly accepted. The inclusion of non-infected, treated animals might be important in determining target animal safety, which is out of the scope of this guideline. Nevertheless, a new section has been added to address the question regarding safety parameters to be included in the study protocol of efficacy studies.
458	6	Comment: please correct spelling from "live" to "life".	Accepted.
462	6	Comment: please delete repeat word "E. bovis".	Accepted.
479	1	Comments : Brackets to be corrected.	Accepted.
482	6	Comments : please abbreviate "p.i." to post-infection.	Accepted.
497-499	1	Comments: This is misleading. Suggested rewording: "animal	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be treated during the prepatent period of infection, i.e. 0-4 days post infection." Why is the application of the inoculum specified for rabbits but not for e.g. piglets? The rabbit part is very detailed given that there is basically no up-to-date scientific literature, and specific methods are mentioned unlike for e.g. pigs. For dogs an infection dose for the inoculum is given but the species of coccidia are not specified. It would make more sense to give spans of doses and recommend mixed infections with min/max relative amounts of the different species. The primary parameter for pigs, unlike for e.g. ruminants, is oocyst excretion. It should also be diarrhea as a co-primary parameter, otherwise the clinically relevant part of coccidiosis is neglected.	The respective sentence has been shortened to avoid any confusion: *'The timing of infection and treatment should be justified depending on the proposed claim and the dose regimen recommendations'*. Further details are not considered necessary at this point in time. Oocyst reduction (a surrogate endpoint) is considered an appropriate endpoint for dose determination and dose confirmation studies. For clinical trials diarrhoea (patient-oriented outcome measure) as co-primary endpoint is considered appropriate.
497-499	5	Comment: For consistency-reason we propose to move this section to "10.3.2 Experimental design". Proposed change: Please move this section.	Accepted. The paragraph has been shortened and moved to the Experimental design section (currently section 12.3.2).
501-504	5	Comment: It might be worth adding a few details on the minimum study requirement of treated- and control-groups. Would the guideline recommend inclusion of a	Not accepted. Inclusion of non-infected, treated animals might be important in determining target animal safety, which is out of the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		non-infected, treated group besides the infected, non-treated and the treated groups?	
512-514	3	*"Secondary endpoints could include: histopathology, faecal scores, reduction of days with diarrhoea, reduction of the number of days with oocyst shedding, percentage of piglets with oocyst shedding, mortality rate caused by coccidiosis and bodyweight gain".* Comment: Mortality should not be recommended as a secondary endpoint for testing in pigs (or any other species). Proposed change: Secondary endpoints could include: histopathology, faecal scores, reduction of days with diarrhoea, reduction of the number of days with oocyst shedding, percentage of piglets with oocyst shedding~~, mortality rate caused by coccidiosis~~ and bodyweight gain.	Not accepted. Mortality should be recorded and taken into account in the statistically analysis (see also section 5.5.6.3).
568	2	Comment: Add rate Proposed change: Food conversion **rate** should also be calculated.	Accepted. '*Feed conversion rate*' is currently used throughout the guideline.
573	2	Comment: Please add general provisions for test animals. Proposed change: …deficient or difficult to maintain. **Test animals shall be monitored for visual evidence of clinical signs effects, performance characteristics, product**	Partly accepted. A new section (section 7) on safety parameters has been included in the guideline. This section reads: '*Safety of an anticoccidial should also be evaluated during pre-clinical efficacy studies and clinical trials, in particular when the margin of safety is narrow. Clinical parameters*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		quality where relevant, haematology and routine blood chemistry and for other parameters likely to be related to the biological properties of the active substance.	*likely to be related to the properties of the active substance need to be monitored during all efficacy studies.* *Clinical assessment with the aim to detect adverse events should be conducted before and after treatment and documented in the study report.'*
576	2	Proposed change: …(e.g. immunocompromised animals **proven by count of white blood cells).**	Not accepted. Diagnosing immunodeficiency is beyond the scope of this guideline. It is not considered relevant to include such information.
581	2	Comment: Anaemia confirmed by haematology. Proposed change: Anaemia confirmed by haematology.	Not accepted. Diagnosing anaemia is beyond the scope of this guideline. It is not considered relevant to include such information.
590-591	5	Comment: It would be helpful to find more details on the experimental design, e.g. when after infection to do the treatment, housing (mixed groups), etc.	Not accepted. No specific details are considered necessary and reference is made to the general recommendations.
605-607	5	Comment: Move "shedding of oocysts" to "clinical signs." Proposed change: "…thus withdrawal of the substance may lead to completion of the life cycle and possibly both the appearance of clinical signs **and shedding of oocysts** several days after medication is discontinued."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
611	1	The cited literature is quite random, and where are the WAAVP guidelines? They should be included.	Accepted. The WAAVP guidelines have been added to the list of references.
611	3	**References** Joachim et al. (2018). WAAVP guideline for evaluating the efficacy of anticoccidials in mammals (pigs, dogs, cattle, sheep). Veterinary Parasitology, 253: 102-119. Odden, A. et al. (2019). Preliminary studies on in vitro methods for the evaluation of anticoccidial efficacy/resistance in ruminants. Experimental Parasitology, 201: 34-41. Thabet, A. et al. (2017). Anticoccidial efficacy testing: In vitro Eimeria tenella assays as replacement for animal experiments. Veterinary Pathology, 233: 86-96.	Accepted. These have been added to the list of references.
632	1	There are numerous misspellings in the species list in the Annex, and for cattle only the pathogenic species are names whereas for small ruminants also non-pathogenic species are named, this must be consistent. If all species are to be mentioned then some of those are missing In sheep coccidia- *E crandalis* should be *E crandallis*. Also E ovin should be *E. ovina*	Accepted. Misspellings have been corrected: *E. crandallis* and *E. ovina.*
634	4	Comment: *Tyzzeria perniciosa* is the most pathogenic species for ducks in the field. It should be added in the table.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please add *Tyzzeria perniciosa* to the pathogenic species of ducks.	
634-635	5	Comment: I think that the *Eimeria* species *E. ovin* under "Sheep" is a fragment (copy-paste-error) Proposed change: Please delete *E. ovin*	Accepted. *E. ovin* has been corrected to *E. ovina.*