24 June 2022
EMA/CVMP/EWP/552708/2018
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on the 'Guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector-borne diseases in dogs and cats' (EMA/CVMP/EWP/278031/2015)

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

Stakeholder no.	Name of organisation or individual
1	D. Otranto
2	European Veterinary Parasitology College (EVPC)
3	Federation of Veterinarians of Europe (FVE) Federation of Companion Animal Veterinary Associations (FECAVA)
4	Cruelty Free International
5	EGGVP – European Group for Generic Veterinary Products
6	AnimalhealthEurope

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	Thank you very much for providing us with the draft of the 'Guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector-borne diseases in dogs and cats'. We find it very much consistent with the content of the WAAVP guidelines that we are currently drafting. We will make sure our paper will take your work into account, and cite it when needed.	Thank you for the comments. Please find responses to the specific comments in the section below.
2	General comment regarding title and conclusion: It does not (very rarely) assess the prevention of a vector borne disease, but the reduction of the risk of transmission of vector borne pathogens. We rarely see clinical signs (i.e. disease) and in fact assess transmission of a pathogen through serology (antibodies, antigens), PCR, direct exam (blood smears, biopsies…).	Thank you for the comment. The title of the guideline has been amended accordingly. Please also find responses to the specific comments in the section below.
3	FVE and FECAVA welcome this guideline providing recommendations for the design and conduct of studies to support the efficacy of VMPs for the prevention of transmission of vector-borne pathogens (VBPs) in dogs and cats, which can be transferred by blood-feeding arthropods. We also welcome that the guideline establishes criteria for the demonstration of efficacy of a VMP in order to be granted a claim for the reduction of the risk of transmission of VBPs. […] We welcome the guideline giving a scientific up to date standard todays products need to comply with. It is important to make the high standard of products licensed in consideration of this guideline. Often veterinary practitioners Europe	Thank you for the comments. Please find responses to the specific comments in the section below.

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	are confronted with this. Owners have bought flea and tick products in a supermarket. These products, often not licensed as VMP are in competition with the properly and more recently licensed products which have been authorised in the last 10 years and have a proven efficacy up to latest standards. Owners have difficulty making this distinction.	
4	Cruelty Free International welcomes the opportunity to comment on the proposed new guideline, which aims to provide guidance on how to support an indication for a veterinary medicinal product (VMP) for the reduction of the risk of transmission of canine and feline vector borne pathogens (VBPs) transferred by blood-feeding arthropods. The guideline seems to be focused on VMPs that are already authorised for the treatment of tick and flea infestations in dogs and cats with a new claim for the reduction of the risk of vector-borne disease transmission. While we appreciate that the repellent, insecticidal and/or acaricidal efficacy of a VMP demonstrated against a vector (as described in the *'Guideline for the testing and evaluation of efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats', EMEA/CVMP/EWP/005/2000-Rev-3.*) may not be directly linked to the efficacy of a VMP in reducing the risks of VBDs (e.g. in some cases the vector may still have the ability to transmit the pathogen causing the VBD before it is killed), we are concerned about the requirement for additional laboratory and field tests in animals with the sole purpose of supporting a new claim for an existing VMP. Instead of defaulting to new tests in animals, the guideline should first recommend that existing data on the VMPs (many of which will	Thank you for the comments. Please find responses to the specific comments in the section below.

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	have lengthy marketing histories) be considered in a weight-of-approach to support a new indication. For example, as briefly mentioned in the draft guideline (lines 113-115), data on the speed of kill/repellent effect of a VMP against specific dog/cat ectoparasites should be available in all cases where claims are made for speed of kill of less than 24 or 48 hours for fleas and ticks, respectively (as described in EMEA/CVMP/EWP/005/2000-Rev-3). This data should be considered in relation to the transmission time of a VBP from the vector to host i.e. if the speed of kill is faster than the transmission time of a VBP then infection is impossible and further animal tests should not be necessary. Furthermore, the guideline does not appear to describe the requirements for new VMPs with acaricidal/insecticidal/repellent effect claims AND reduction of transmission of VBP claims. Would it be sufficient to conduct a single laboratory study and a single field study per target species to support both indications?	The comment is noted. As explained in section 4 of the guideline, as a general rule, the efficacy (of a new claim) has to be demonstrated under laboratory and field conditions. Exceptions may be acceptable, if appropriately justified. However, as explained in this section 4, "*to evaluate the suitability of a claim for the reduction of the risk of transmission of VBPs, the speed of kill/repellent effect of the VMP against the ectoparasites from the dog or cat in relation to the transmission time of a VBP from the vector to host is considered to be important information, but not sufficient to justify such claims by itself*." Each new claim should be demonstrated appropriately.
5	EGGVP thanks EMA and the EWP for this guideline outlining the requirements for laboratory and field studies to demonstrate the efficacy of VMPs for the prevention of transmission of vector borne diseases in dogs and cats. There are no major comments as per requirements set; however, EGGVP recommends including appropriate reference and definition of the number of animals required to conduct study/ies so as to make this guideline of real value.	Thank you for the comments. Please find responses to the specific comments in the section below. The comment is noted. However, it is not considered necessary to indicate such information in this guideline since it should be read in conjunction with other guidelines where this information is included.
6	AnimalhealthEurope welcomes the opportunity to comment on the draft guideline.	Thank you for the comments. Please find responses to the specific comments in the section below.

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	Throughout the guideline efforts should be to ensure that a clear distinction is drawn between the minimum information required and those additional items that would be "nice to know". In line with the various specific comments made below a need is seen for additional clarification, particularly on minimum requirements for laboratory and/or field studies, around the use of positive and negative controls and thresholds for laboratory and field studies where available. Additionally, the difficulties in including control groups should be acknowledged in the document.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
4-6	3	Comment: In line 45 and 75/76 it is specified that the guideline applies to VBPs transferred by blood-feeding arthropods. To other parasites, which might be vector-borne are not in scope. This should be expressed in the title.	Not accepted. It is not considered necessary to amend the title in this regard; the explanations provided within the text are considered sufficient.
4-6	6	Comment: Line 45 and 75/76 specify that GL (only) applies to VBPs transferred by blood-feeding arthropods (this means that some VBDs, e.g. Thelaziosis are not in scope?). Proposed change: please consider the inclusion of this specification into the title of the GL.	Not accepted. It is not considered necessary to amend the title in this regard; the explanations provided within the text are considered sufficient.
11	2	Comment: Keywords : to add the following : « repellency » or « repellent effect » and « arthropods ».	Accepted.
46	3	Comment: In line 90 it is stated that laboratory **and (or)** field studies may be required. This is correct, as for example a field study might not be feasible for pathogens with a low incidence or a lab study might not be possible of no suitable model is available. Proposed change:	Not accepted. The original wording ("*laboratory and field studies*") is considered correct to avoid a misunderstanding (to note, the wording has been amended to "*pre-clinical studies and clinical trials*" in line with the terminology provided by Regulation (EU) 2019/6). This section is a summary in which the content of this guideline is described (not the

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		The text should be changed into "requirements for laboratory **and/or** field studies"	requirements themselves). In other sections the requirements are explained in detail. Generally, the efficacy should be demonstrated under laboratory conditions **and** confirmed under field conditions. Exceptions may be acceptable, if appropriately justified, as it is described in other sections of the guideline.
46	6	Comment: Line 90 (correctly) states that laboratory AND/OR field studies may be required (because, e.g. field studies may not be feasible for pathogens with relatively low incidence rates, lab studies may not be feasible if no appropriate model is available….) Proposed change: Please change the text to "requirements for laboratory and/or field studies".	Not accepted. Please see the comment above.
47-49	2	Comment: To reformulate this sentence. This is not correct to talk about a disease transmission. The causative agent is transmitted which can or cannot induce the disease in the recipient host. The prevention of transmission is determined by the repellent efficacy of the product preventing the arthropod to bite and therefore to transmit. A product with a great killing efficacy, can be implicated in the reduction of risk of transmission: it may have transmitted the agent to the bitten treated host, but won't be implicated in further transmission.	Accepted. All references to "*prevention of transmission of vector-borne diseases*" have been removed from the guideline. The text in lines 47-49 has been deleted.

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47-49 and 59-60	3	Comment: Next to repellent effects, parasiticides can have a "non-feeding" or even "killing" effect. Should this be covered by the guidelines as well?	Accepted. The relevant text in the 'Introduction' section has been amended for further clarification.
47-49	6	Comment: This draft guideline only addresses the reduction of the risk of transmission of VBPs by killing or repellent effect against the vector prior to the transmission of the VBPs. However, an important aspect would also be the "anti-feeding" properties of a VMP. Proposed change: Prevention of transmission of vector-borne disease in the context of this guideline means the reduction of the risk of transmission of VBPs by killing, **anti-feeding** or repellent effect against the vector prior to the transmission of the VBPs.	Partly accepted. The relevant text in the 'Introduction' section has been amended for further clarification.
52	2	Comment: To add "hematophagous" before arthropods.	Partly accepted. "*Blood-feeding*" has been added before "*arthropods*" to ensure text integrity and consistency.
54	2	Comment: To reformulate with "which can lead to disease".	Accepted.
59-60	6	Comment: Proposed change: please add: "…**killing the vector before transmission occurs**".	Accepted.

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60	1	Comment: My only suggestion to the current version is to include a sentence (e.g. line 60 and or line 115) about the relationship between the protection of VBPs and the prevention of pathogen transmission, which mainly relies on the pathogen transmission time (see also Otranto D. Arthropod-borne pathogens of dogs and cats: From pathways and times of transmission to disease control. Vet Parasitol. 2018 Feb 15;251:68-77).	Accepted. As suggested, a sentence addressing these aspects has been added in the 'Introduction' section.
62	3	There is one error in the introduction starting on line 62. It states that many ectoparasiticides are authorised as veterinary medicinal products across the EU for the treatment of flea and tick infestations and that they have been assessed in accordance with the guideline cited on line 64. This is factually incorrect. The only products which have been authorised in accordance with that guideline are products which have been authorised in the last 10 years since the guideline came into effect. There are still many products on the EU market which were authorised before that guideline came into effect.	Accepted. The text has been amended to take account of the comment.
73	6	Comment: Repellence may not be predictive of a risk reduction for transmission. Proposed change: Please consider adding: "**Also, the repellent efficacy of a drug does not allow direct**	Partly accepted. The text in former lines 70-73 has been reworded to take account of this comment: "*That is, a VMP that has achieved the required threshold for efficacy sufficient for an insecticidal/acaricidal and/or repellent claim may not be effective in reducing the risk of*

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		conclusions on the reduction of the risk of a transmission of a VBD."	*transmission of a VBP, as the vector may still have the ability to bite and, therefore, to transmit the pathogen causing the VBD before it is killed and/or repelled."*
67, 165, 205, 237	3	Comment: Refer to "***clinical** studies"* Proposed change: … how to design **clinical** studies for the…	Partly accepted. In accordance with the terminology and definitions provided by Regulation (EU) 2019/6, "*pre-clinical studies*" and "*clinical trials*" have been introduced throughout the document, as needed.
73	2	Comment: To add: "as the vector may still have the ability to bite and therefore to transmit the pathogen" …	Accepted.
91	6	Comment: The meaning here is unclear, "method" might refer to an applicator system, e.g. same active applied via spot on or spray, but really it seems route of administration is meant. Proposed change: Please consider changing "method" to "route".	Partly accepted. "Method" was modified to "route of administration and pharmaceutical form", since both can influence on the efficacy.
97	2	Comment: Add to the sentence between bracket "speed of kill".	Accepted.
104-105	3	Comment: Same comment as to line 46. Proposed change: "The efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven by appropriate	Not accepted. As a general rule, the efficacy has to be demonstrated under laboratory conditions and confirmed under field conditions. Exceptions could be accepted, that is, it would be possible to

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		clinical studies under laboratory **and/or** field conditions."	omit one type of study or the other if appropriately justified. Text has been amended for clarification.
104-105	6	Comment: The requirement *("Unless otherwise justified, the efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven by appropriate clinical studies under laboratory and field conditions.")* is not totally consistent with the other statements (line number 90: *"a claim for the reduction of the risk of transmission of VBPs needs to be demonstrated by laboratory and/or clinical field studies",* line number 145: "*Unless otherwise justified, at least one well-designed study under laboratory conditions covering the entire period of reduction of the risk of disease transmission is considered necessary for each claimed VBP*." and line number 234: "*Unless otherwise justified, field trials should be conducted and may constitute pivotal data where no valid laboratory transmission model is available*."). Proposed change: "The efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven by appropriate clinical studies under laboratory and**/or** field conditions."	Not accepted. Please see comment above. The various sections of the guideline have been aligned.

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106-107	6	Comment: It is understood that an extrapolation from one VBP species to another VBP species is not acceptable. However, it has not been defined if an extrapolation from one vector subspecies to another vector subspecies is acceptable. *E.g*. when evidence is provided that the risk for transmission of *Borrelia burgdorferi sensu lato* by *Ixodes ricinus* ticks is reduced, would this allow extrapolating to *Ixodes scapularis*, if sufficiently justified? Proposed change: Pease clarify.	Accepted. A sentence addressing this aspect has been added in section '4. General consideration'.
108	2	Comment: In the context of VBP transmission, I think that the efficacy obtained in clinical studies should be confirmed by field studies in endemic areas for VBD such as leishmaniosis or dirofilariosis.	Accepted. Clarification has been included in section '6. Clinical trials'.
109	6	Comment: "or GLP Proposed change: Please amend the wording as follows: Good Clinical Practices (GCP) ~~or GLP~~.**, other standards such as GLP may be appropriate if justified**.	Partly accepted. Text has been amended for further clarification: "*Pre-clinical efficacy studies should follow the requirements for Good Clinical Practice (GCP) and/or Good Laboratory Practice (GLP), as appropriate (depending on the nature of the studies). In case GCP and/or GLP is not applied (e.g. absence of certified GLP status), traceability, accuracy, integrity and correctness of data should be ensured, and the use of such data in pivotal studies should be justified.*

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			Clinical trials shall be conducted in accordance with established principles of GCP. Deviations shall be justified".
111	6	Comment: The reference to CVMP GL not complete. Proposed change: EMA/**CVMP**/EWP/81976/2010	Accepted. The text was amended as proposed and moved to section '6. Clinical trials'.
112	6	Comment: For lab studies: shouldn't (where possible) increase of vector numbers for challenges be considered before increase of number of study animals (also given the 3Rs cited before)? Proposed change: Replace "study animals" by "vectors" and add "for laboratory studies".	Partly accepted. The text has been amended by adding "*vectors*" and moved to section '5.5. Information on the vector borne pathogen'.
117-118	6	Comment: What is meant by defined conditions? (Reduction of risk in a field study will not always have very defined conditions...) Proposed change: Please delete "..demonstrated under defined conditions and..."	Partly accepted. The text in former lines 117-118 has been reworded to read "*The reduction of the risk of transmission of canine and feline VBPs should be demonstrated under conditions representative of the field conditions*."

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127	3	Proposed change: … serological **tests**, antigen or **molecular detection-based assays for confirmation of infection (specific DNA ~~detection~~**)	Accepted.
136	6	Comment: The statement '*The evaluation of the claimed effect should be based on the absence/presence of the VBP in the final host animal, the antibody response of the final host animal, and/or the molecular detection of specific DNA of the VBP in the final host animal (with or without clinical signs of the disease), as appropriate for each VBP.*' seems to suggest it is mandatory to have absence/presence of pathogen AND antibody as a minimum, complemented with PCR if applicable or possible. Proposed change: We would advise to keep all options open and to leave it up to the applicant to define the efficacy parameters in the protocol, depending on which pathogen is targeted.	Accepted. The text has been amended accordingly.
138	2	Comment: The viability of the potentially transmitted VBP should also be assessed when possible according to the pathogen, for instance by culture (when feasible and pertinent).	Not accepted. The proof of the absence/presence of the VBP in the final host animal is sufficient. The proof of the viability of the potentially transmitted VBP is not considered necessary.

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145-150	6	Comment: The proposed lab studies with infected vectors can only be done where infection models exist. Proposed change: Please consider adding a list of VBDs for which such studies are possible? Acknowledge that they may not be possible, e.g., for Leishmania?	Not accepted. Adding a list of VBDs for which laboratory studies are possible is not considered appropriate, as the GL should be kept open for the future. The applicants should define and justify the efficacy parameters in the study protocol according to scientific knowledge.
149-150; 208-209; 262	4	*"A rescue protocol needs to be defined for all animals that have become infected".* *"Appropriate measures should be applied to reduce any negative impact on animal welfare (e.g. appropriate exit clauses and rescue protocols; see 5.1.)".* *"A rescue protocol needs to be defined for all animals that have become infected".* Comment: For both laboratory and field trials, the draft guideline recommends the use of 'exit clauses' and 'rescue protocols' to "*reduce any negative impact on animal welfare*" for animals that have been infected with a vector-borne disease. More effort should be made in the guideline to define and clearly describe the measures that should be taken to avoid unnecessary suffering to the animals involved (Can animals always be treated? What would the treatment period involve? Can they be re-homed? Are they re-used? Are some of them killed? Are humane endpoints used?).	Partly accepted. The guideline should be kept more general and open for the future. The applicants should define appropriate measures to reduce any negative impact on animal welfare (e.g. appropriate withdrawal criteria and rescue protocols) in the study protocol according to scientific knowledge and legislation on the protection of animals. Text was slightly amended for further clarification. A definition for "*rescue protocol*" has been added to the respective section, whilst "*exit clause*" is no longer mentioned in the guideline.

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		Proposed change: Provide more information and examples of 'rescue protocols' in section 5.1. of the guideline. It might also be helpful to include a definition of 'rescue protocols' and 'exit clauses' in the Definitions section at the end of the guideline.	
153, 214	3	Proposed change: …PCR-negative **hematology and routine blood chemistry)**	Partly accepted. Whilst reference to haematology can be accepted, reference to 'routine blood chemistry' is unclear, i.e. not clear how this might be used to demonstrate infection with a VBP. The text was amended to include "*absence of haematological evidence of VBPs*".
157	2	Comment: Add between brackets "e.g. for ticks and fleas"; for flying insects such as mosquitoes and sandflies, it is also usually recommended to check before the start of the study that all tested animals have the same ability to "attract" them.	Partly accepted. Reference to specific vectors has been removed from this paragraph. Appropriate information related to vectors is included in the introductory section.
160	5	Comment: clarification requested: does type of hair coat include length of hair (small, medium and long)?	Accepted. The sentence was reworded to read "*The origin, sex, age, body weight and type/length of hair coat of animals should be described*".

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174	2	Comment : Suggest to add that a control of their infection should be performed at least at the begging of the trial, or regularly during the trial.	Partly accepted. The text has been further clarified by adding the sentence "*The vectors should be adequately infected to ensure transmission of the VBP*".
181	6	Comment: It is unclear why the classical taxonomic information of a vector is insufficient to characterise the vector. Proposed change: **If necessary,** molecular barcoding or similar relevant data confirming the species classification.	Partly accepted. Considering the dynamic taxonomic changes (both at the level of pathogens and vectors) and discoveries of cryptic species on one side, and the easiness of applicability of DNA/RNA-based identification tools on the other side, merely taxonomic concept has almost become obsolete. Nevertheless, the concerned text has been amended to be more general: "[…] *Relevant data to confirm the species classification (e.g. molecular barcoding).*"
185	6	Comment: It is unclear what is expected to be provided as data to support '*The biology of the VBP in the vector and the host*.' Proposed change: Please remove the requirement or be more precise as to the data required.	Accepted. The text has been supplemented for further clarification.
187-188	6	Comment: Why is the morphological species classification not sufficient? Proposed change: please delete the requirement or make it optional.	Partly accepted. Considering the taxonomic changes (both at the level of pathogens and vectors) and discoveries of cryptic species on one side, and the easiness of applicability of DNA/RNA-based identification tools on the other side, merely taxonomic concept has almost become obsolete. Nevertheless, the

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			concerned text has been amended to be more general: "*Relevant data to confirm the species classification (e.g. molecular barcoding).*"
196	6	Comment: The proposal to put forward 4 weeks as cut off value between short term and long term seems to originate from the guideline on efficacy vs ticks and fleas. However, it would be advised to apply the requirements of 4 weeks (1 challenge at beginning of the efficacy period, one at the end) also to 1 month (some products have a 1month efficacy claim). Proposed change: Please modify the text to: '4 weeks **or 1 month**'.	Not accepted. Amendment is not considered necessary, the text is in line with the guideline EMEA/CVMP/EWP/005/2000-Rev.4.
201-203	6	Comment: To reflect field conditions in laboratory settings could be hard to achieve and it is unclear what is meant. *E.g.*, an animal may get ticks every day during tick season, and sandfly exposure may be for 8h rather than 1-2h. We do not see a need to adapt lab studies to such conditions as normally field studies will be required anyway and as a control group will be required for the lab studies, thus ensuring and demonstrating that the challenge is sufficient to lead to actual VBP transmission. Proposed change: Please delete the sentence "The experimental model…climatic conditions, etc."	Partly accepted. The text has been amended for further clarification of the situations where this option would be applicable: "*In exceptional and well-justified circumstances, e.g. in case the submission of field data is not possible, the experimental model should be designed to reflect field conditions in terms of challenges, duration of the challenge, number of bites (exposure) in the field, infection rate of the vector, climatic conditions, etc.*"

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219	6	Comment: Threshold of 90% for any VBP appears very strict. Would a significant reduction be considered? There may be instances where these levels are difficult to be reached mainly under field conditions, e.g., bartonellosis, anaplasmosis, leishmaniosis, where other ways of infection are discussed (e.g., Latrofa et al. (2016) Parasit Vectors 9:269) and with limited possibilities of follow-up. The significant reduction may still be of relevance in control programs if no other alternative exists, e.g., current malaria vaccine provides 34% of protective efficacy (95% CI = 8-53%, p = 0.014). Proposed change: Please describe minimum conditions.	Not accepted. It is considered that the default 90% efficacy threshold is appropriate. If no other alternative exists, the applicants should explain and justify any deviation from the guideline requirements.
220	3	Proposed change: The recorded efficacy **end-points** should be …	Not accepted. The sentence has been amended and moved to section '4.1 General study design' for further clarification: "*Confidence intervals around the calculated efficacy (see sections 5.7 and 6.3) should be presented for completeness; it is not intended to compare their lower bounds to a minimum efficacy threshold.*"
220	6	Comment: We are not aware of requirements for confidence intervals for other claims where an efficacy limit around 90% is set.	Partly accepted. The reference to the confidence interval has been deleted from this section. However, a new paragraph has been

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		It is also unclear what the confidence interval would refer to (when the parameter for efficacy calculation is "% of infected animals per group", see line 288, would this mean that multiple field studies are required?). Also, in case of quantitative efficacy parameters, C.I. in a lab study setting could be rather broad – what does it signify? What are potential consequences regarding required animal numbers and animal welfare. Proposed change: Please delete the reference to confidence interval.	included in section '4.1 General study design' for clarification: "*Confidence intervals around the calculated efficacy (see sections 5.7 and 6.3) should be presented for completeness; it is not intended to compare their lower bounds to a minimum efficacy threshold*."
233	3	Comment: Perhaps worth indicating the number of clinical studies and a provision for the geographical distribution i.e. related to different EU regions.	Accepted. The minimum number of clinical trials to be conducted has been included and the text has been reworded for further clarification. Please see section '6. Clinical trials'.
234	6	Comment: Does this mean that in case where laboratory models exist field trials might be only supportive or possibly not required? Proposed change: please delete "…~~and may constitute pivotal data where no valid laboratory transmission model is available~~". As it does not add any relevant information.	Not accepted. By default, clinical trials should be conducted, however their omission could be accepted if appropriately justified, as stated in section '4. General consideration'. The text has been amended for further clarification: "*Unless otherwise justified, at least one clinical trial should be conducted. Clinical trials may also constitute pivotal data where no valid laboratory transmission model is available*." This explanation is considered appropriate.

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235, 237	6	Comment: For laboratory studies "at least one study" is requested (line 145). The way this is written it seems to imply multiple or at least multi-center. Proposed change: Please clarify minimum requirements.	Accepted. The minimum requirements have been introduced, as "*at least one clinical trial*". The text has been amended for further clarification.
237	2	Comment: Add after "different geographical locations", "and where the studied VBD is known to be endemic, when relevant".	Accepted. The text has been reworded for further clarification and to accommodate all the comments received on this matter.
237	5	Comment: "*The studies should be conducted in Europe in different geographical locations*". This requirement should be further detailed and explained i.e. recommend different geographical locations in Europe where studies can be conducted. Furthermore there may be an option to provide an appropriate justification for not conducting field trials (number?) in different geographical locations. This may apply in cases, such as absence of significant genetic variability in vectors and/or vector-borne pathogens. Proposed change: "The studies should be conducted in Europe in different geographical locations or an appropriate justification should be provided."	Accepted. The text has been amended for further clarification and to accommodate all the comments received on this matter.

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237	6	Comment: '*The studies should be conducted in Europe in different geographical locations'*. This requirement should not be set by default for all VBDs. In some cases, one location could be very representative or representative of a worst case scenario, *e.g*. for a hyper-endemic area or a high exposure to the vector borne disease. Additionally, for some VBPs (e.g. *Leishmania, Dirofilaria repens*) it may be difficult to conduct a field study in different geographical locations as these are prevalent in special areas only. Proposed change: Please modify the text as follows: "**Unless otherwise justified**, the studies should **preferably** be conducted in Europe in different geographical locations."	Accepted. The text has been amended for further clarification and to accommodate all the comments received on this matter.
238	6	Comment: This may be extremely difficult and potentially impossible to achieve for the vectors. What is the added value of this information when efficacy is evaluated against incidence in a control group? How would these data be taken into consideration in the overall claim evaluation? Proposed change: Please remove from the minimum requirements.	Partly accepted. The text has been amended to clarify that this information should be provided whenever possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
251	3	Comment: Please indicate the percentage for level of efficacy, 70 or 80% Proposed change: …. when an ~~**adequate level of**~~ **70-80 per cent** of efficacy is ~~**expected to be**~~ reached after product administration…	Not accepted. It is not considered necessary to indicate efficacy percentages in this sentence. However, the paragraph has been amended for further clarification.
253-255	6	Comment: In the opinion of AnimalhealthEurope a field study should reflect the intended use of the product in the field. In field studies products are administered to client-owned animals, *i.e*. according to weight bands. The use of the minimum recommended treatment dose does not reflect field conditions. Proposed change: **Field studies should be conducted with the final formulation intended for commercial use.** The chosen **dosing regimen** should be **based on** the **recommended clinical dose** and the established dosing interval.	Partially accepted. From an efficacy point of view, the worst-case scenario has to be demonstrated, that is the minimum dose (which is also representative of the recommended posology in normal conditions). The text has been reworded for further clarification.
256-257	6	Comment: If only a positive control group is included, and all groups are negative for transmission of VBDs at the end of a field study – what will be the proof that vectors carrying the VBPs have been present in the study period?	Accepted. Clarification on this matter has been added in section '6.3. Evaluation of efficacy'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please clarify.	
257-260	4	"*In those cases where laboratory data are not fully supportive of prevention or transmission, the inclusion of an untreated (negative) control group in the field study is considered necessary, to obtain information on the real transmission pressure".* Comment: In guideline EMEA/CVMP/EWP/005/2000-Rev-3, the use of an untreated control group in clinical field trials can be waived on animal welfare concerns. This waiver should also be included in this draft guideline. It is also not clear why a similar waiver could not apply to laboratory trials. Proposed change: In those cases where laboratory data are not fully supportive of prevention or transmission, the inclusion of an untreated (negative) control group in the field study is **recommended** ~~considered necessary,~~ to obtain information on the real transmission pressure. **If necessary, untreated control animals can be withdrawn from the study due to animal welfare reasons.**	Accepted. The text has been amended in line with the comment.
257-260	6	Comment: The large number of negatively controlled animals in a field study might be a concern of animal welfare and might be also a concern for the owners participating	Partially accepted. The text has been amended for further clarification of the fact that, in case of animal welfare concerns, animals should

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		in this study (ethical issue). This is also the case for highly pathogenic vector-borne diseases and for which there is no optimal treatment (*e.g.*: Leishmaniosis). Therefore, in these specific circumstances, the inclusion of a positive control group should be possible. This document may need to distinguish between field studies that use client owned animals and those that use laboratory animals. Proposed change: "In those cases where laboratory data are not fully supportive of prevention of transmission, the inclusion of an untreated (negative) control group in the field study is considered necessary **(besides highly pathogenic vector-borne diseases and for which there is no optimal treatment)**, to obtain information on the real transmission pressure."	be withdrawn from the study and a rescue protocol should be applied.
257-262	6	Comment: We would propose the inclusion of the option to obtain the incidence of a VBD in the specific region of study conduct (serology from a wide range of animals in this region). A field study then should prove that the incidence (by means of seroconversion) of the VBD in treated animals is well below the normal incidence in the region.	Not accepted. The comment is noted. However, it is preferred not to include such specific information since serological data may not be appropriate in all situations. General requirements for clinical studies are further explained in section '4.1. General consideration'.

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257 and following	6	Comment: It is stated that in field studies 'a control group (positive or negative) should be included.' Proposed change: The efficacy formula on lines 264 is only applicable to studies with an untreated control group. This should be made clear in the text.	Accepted. The structure of section '6.3 Evaluation of efficacy' has been amended accordingly.
263	6	Comment: Section 6.3 is mostly appropriate for a negatively controlled study (reduction of risk, protection %). Proposed Change: Please distinguish the 2 options: 1. vs a negative control group 2. vs a positive control group	Accepted. The structure of section '6.3 Evaluation of efficacy' has been amended accordingly.
269	2	Comment: "incidience" instead of "incidence".	Accepted.
269	5	Proposed change: Please correct spelling of incidence from incidience at two places.	Accepted.
269	6	Comment: Typo (incidience)	Accepted.
269, 284, 288	6	Comment: Both formulas and consequent efficacy requirement are only applicable to studies using a negative control	Accepted. The structure of section '6.3 Evaluation of efficacy' has been amended accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		group (while line 257 mentions possibility of negative or positive control). Proposed change: Please add information that formulas are only applicable to negatively controlled studies.	
272	6	Comment: Cats are missing in this sentence. Proposed change: To overcome problems with dogs **or cats** lost to follow-up during field studies (e.g. death, withdrawal, etc.), and to account for potential differences in time spans during which the animals were included in the study; the incidence density rate (IDR) could be used.	Partially accepted. Reference to "*animals*" instead of "*dogs*" has been included.
282, 306	5	Proposed change: Please amend word "completed" to "completely".	Accepted.
289, 290	6	Comment: This just applies to negatively controlled studies. Proposed change: Please add the respective information.	Accepted. The structure of section '6.3 Evaluation of efficacy' has been amended accordingly.
290	6	Comment: The positive control for a field study should be a product "with recognised efficacy in the indication concerned". Does this mean recognised in scientific literature or approved for the indication? If the latter,	Accepted. The text has been amended accordingly.

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		approved for what indication: ectoparasiticide or prevention of VBD transmission? Proposed change: Please review the statement for clarification. Also, the sentence could or should include "if available" because it is possible that a product with recognised efficacy is not available.	
291	3	Proposed change: … efficacy in the **clinical** indication concerned…	Not accepted. The text has been amended for clarification.
299	6	Comment: For products that demonstrate >90% "risk reduction" is a rather weak wording… However, see comment on line 219. Also, the time period of efficacy determined in studies should result in a "minimum duration" not in an "up to" duration. Proposed change: Please replace "up to" by "at least".	Partly accepted. It is considered that the default 90% efficacy threshold should be met, therefore the wording is considered appropriate. The suggestion to replace "*up to*" by "*at least*" has not been accepted; however, "*up to*" has been deleted.
305-306	2	Comment: Suggest to rephrase a bit and to change "completed" by "completely".	Accepted.
315-317	3	Comment: Please consider to include pharmacokinetic properties.	Not accepted. This guideline provides the guidance on how to support an indication for a VMP for the reduction of the risk of transmission of canine and feline VBPs transferred by blood-

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			feeding arthropods. The guideline should be read in conjunction with other guidelines.
319	2	Comment: Suggest to add between brackets after "living organisms" "usually hematophagous arthropods".	Partly accepted. The wording "*usually blood-feeding arthropods*" has been added to ensure text integrity and consistency.
322	2	Comment: Suggest to add between brackets after "passive carrier" "mechanical vector".	Accepted.
333	6	Comment: More recent references might also be considered, e.g. - Otranto (2018) Vet Parasitol 251:68-77 - Richards et al. (2017) Environments 4:37-50)	Partly accepted. Otranto (2018) reference has been included.
338	6	Comment: versus "EMA/CVMP/EWP/325284/2011-Rev.1"	Accepted.
339	6	Comment: Why is there a reference to the PK GL, nowhere mentioned in the text and does not seem to be relevant? Proposed change: Please delete.	Accepted. The reference to the pharmacokinetic guideline has been deleted.
341	6	Comment: "**EMEA**/CVMP/EWP/81976/2010"	Accepted.

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354	6	Comment: "CVMP/VICH/595/1998**-FINAL**"	Not accepted. Addition not considered necessary. The currently applicable version of any guideline should be used.