28 January 2022
EMA/CVMP/IWP/618327/2021
Immunologicals Working Party (IWP)

Overview of comments received on the draft guideline on clinical trials with immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/260956/2021)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this guideline which originates in a common initiative by regulatory authorities and industry on increasing the availability of veterinary vaccines. A workshop dedicated to this topic was held 2017 at the EMA premises in London and as an important element, it was discussed whether the authorisation requirements for veterinary vaccines in the EU are proportionate to the benefits and risks of these products. As part of the workshop, the EMA undertook a review of all applications for centrally authorised IVMPs and concluded that field efficacy trials "appeared to be of limited value from an efficacy perspective and are only generally supportive to the claims". This analysis was considered useful to assist with establishing criteria by which omission of field trials may be justified. As a major outcome the availability of veterinary vaccines initiative ultimately led to a more flexible legislation (Annex II) explicitly allowing for field efficacy trials not to be needed in all situations where claims made in the SPC were justified by laboratory efficacy trials. In contrast to this approach, the draft Guideline seems to be written in a way that will certainly increase the requirements for laboratory efficacy trials, but also for field efficacy trials (when conducted) and even field safety trials. The document defines further requirements for designing and performing field studies, adding to or changing the existing guidance. The increased requirements introduced in this draft guideline in the case of omission of clinical efficacy studies will	The guideline is not intended to increase the requirements for laboratory or clinical efficacy trials. No particular requirements are in this guideline concerning the design or execution of laboratory efficacy studies in general. However, in accordance with the text in the Annex II to Regulation (EC) 2019/6 as well as with the outcome of the discussions with industry, the omission of clinical efficacy data is possible only when adequate data is acquired from pre-clinical studies. As a logical consequence, in some cases more emphasis may be put on particular aspects of pre-clinical studies (for instance, there relevance of the laboratory challenge model) in order to complete the data package and support the claims. Since clinical efficacy trials will only be required when the data from pre-clinical studies is not adequate to support the claims, the data derived from clinical efficacy trials must be reliable. Otherwise, it would not be possible to assess the risk-benefit balance of the product. Thus the guidance on particular requirements (for instance the inclusion of controls) may be somewhat more prescriptive than before, which is intended to improve predictability. The variability of veterinary vaccines and their fields of use is however taken into account throughout the guideline and the option to justify alternative designs and/or data gaps is included.

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	make it difficult to actually omit the clinical efficacy studies as introduced in the new regulation (Commission Delegated Regulation (EU) 2021/805 of 8 March 2021). Overall, as written, the draft guideline is not in line with the original intention to facilitate the availability of veterinary vaccines. AnimalhealthEurope would like make appeal to the CVMP to revisit the current draft keeping the spirit of the availability of veterinary vaccines initiative in mind. Finally, we also agree with the CVMP that the principles of 3Rs need to be respected. Practices such as vaccinating animals in the field with subsequent transfer and challenge under laboratory conditions or the request to include non-vaccinated placebo controls for demonstrating field challenge in comparator studies are, however, difficult to see in this context.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Executive summary			
42	1	**Comment:** Typographical error. The correct reference to the existing guideline (as per the document and concept paper) is EMEA/CVMP/852/99-FINAL	**Accepted.**
1. Introduction			
46-47	1	**Comment:** The phrase "large scale" may be interpreted as requiring several thousands of animals, whereas far fewer animals typically suffice. The EU legislation (Annex II) does not use this expression. For clarity, we would suggest replacing with alternative wording. **Proposed change**: "Clinical safety trials should be performed in order to verify results of pre-clinical safety studies, under field conditions and on a large**r** scale **than the corresponding pre-clinical safety studies**"	**Accepted.**
50-51	1	**Comment:** It is critical that the exact wording of the EU legislation is used. **Proposed change:** "~~clinical efficacy trials may not be required in those cases when pre-clinical studies fully support the claims made in the summary of product characteristics.~~ **When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required**"	**Accepted**.

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3.	**Legal basis and relevant guidelines**		
71-21	1	**Comment:** Reference to the Guideline on statistical principles for clinical trials for pharmaceutical products is concerning and not relevant. As the title says, this guideline was not developed for vaccines, but for pharmaceuticals, and proper considerations should be made before referencing it in the context of the field trial guidance for IVMP. It should either be removed (preferred option) or alternatively clearly restricted to non-inferiority trials (when such trials are conducted). If not, it is expected that Assessors may use the statistical guideline not only for non-inferiority but also for other topics as a "by-default" guideline for field efficacy trials, which would lead to counter-productive situations. **Proposed change:** Please remove reference to the Guideline on statistical principles for clinical trials for pharmaceutical products.	**Accepted.**
4. **4. 1**	**Requirements to provide field data** **Introduction**		
92	1	**Comment:** As mentioned above, it is critical that the wording of the EU legislation is followed. "May" should be replaced by "can". Furthermore, the current Annex II states in section IIIb4A: "In general, pre-clinical studies shall be supported by trials carried out in field conditions. When pre-clinical studies fully support the claims made in the summary of product characteristics, trials	**Accepted.** The word "may" was replaced by "can". The exact text of the annex II is quoted in section 4.1.

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		carried out in field conditions are not required." Demonstration in the field should be done only on the claims that are not fully supported preclinically. **Proposed change:** "For efficacy, the requirement for provision of field data is less strict and the performance of clinical efficacy studies **for a specific claim** ~~may~~ **can** be omitted if adequate evidence of efficacy, supporting **this** claim~~s~~, can be derived from the pre-clinical efficacy studies."	**Accepted**
4. 2	**Criteria for the omission of clinical efficacy data**		
4.2	1	**Comment:** In section 4.2. another criterion considering the existence of a specific Ph. Eur. Monograph with detailed requirements for laboratory studies for a vaccine/disease should be added. **Proposed change:** Please Add the following paragraph at the end of section 4.2.: "**d) If a specific Ph. Eur. monograph exists for a vaccine/disease, and efficacy was demonstrated in pre-clinical studies following the requirements of the monograph, the performance of clinical efficacy studies can be omitted for the claims detailed in the monograph.**"	**Not Accepted.** Ph. Eur. monographs generally do not detail claims (just 'immunogenicity', based on a number of parameters). It is considered that clear and comprehensive criteria are listed in the GL.
99-109	1	**Comment:** This paragraph is very detailed and may raise the expectations from Assessors to request very demanding and potentially unrealistic requirements.	

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		- It is sufficient to describe the laboratory model of infection as relevant instead of using the terminology "highly relevant" which does not add further information.	**Accepted.**
		- The comparability of the laboratory model to the naturally occurring disease is very stringent as it is described. It is extremely hard to develop a laboratory challenge model which reproduces precisely the type and even more, the frequency of clinical signs observed under field conditions. Monitoring the distribution and/or shedding is not always relevant, as it depends on the type of disease and claims targeted. Also, in many cases, the distribution (*i.e.* dissemination) of the challenge organism is not extensively investigated, as the focus of field efficacy studies is, and should only be, on the expected sites of distribution in the body (*e.g.* lungs in case of *Mycoplasma hyopneumoniae* challenge).	**Not accepted.** The comparability of laboratory models to the naturally occurring disease is considered very important. The list of parameters is therefore extensive, in an effort to provide clarity and predictability to the applicants. Nevertheless, as stated in the last sentence : "If any of the requirements cannot be met, a robust scientific justification must be provided that assures the challenge model is still relevant."
		- To ensure occurrence of clinical signs, the route of infection for the model may be different from the natural disease but resulting in the same pathogenic mechanism and inducing the same severe clinical picture.	The last sentence is considered to also cover this aspect: "If any of the requirements cannot be met, a robust scientific justification must be provided that assures the challenge model is still relevant. "A sentence (as proposed) has been added to the end of the section that is intended to cover this aspect as well: "Where a specific Ph. Eur. monograph exists for a vaccine/disease, and efficacy was demonstrated in pre-

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		Specific Ph. Eur. Monographs (*e.g*. Ph. Eur. 870,450) require seronegative animals for the immunogenicity studies which are challenged not in the natural route and are considered as relevant to demonstrate the efficacy of the vaccine without field trials. - Animals used in laboratory (pre-clinical) studies are usually animals from dedicated breedings (single breed), for example for companion animals (*e.g*. dogs, cats, horses), at minimum age (according to general and/or specific monographs). Therefore, the request to include animals 'relevant for the intended population' (health status, age, breed) is not aligned with the design of laboratory trials and implies to multiply studies to have a representative panel of animals, which is not aligned with the 3R principles. - It should be sufficient (with no need for justifications) to use seronegative animals, of the minimum age recommended for vaccination on the expected label. The wording should be softened accordingly. If not, this opens the door for questions and additional generation of unnecessary data.	clinical studies following the requirements of the monograph, the performance of clinical efficacy studies can be omitted for the claims derived from the parameters detailed in the monograph". It is emphasised that the term 'relevant' is used, rather than 'representative'. Hence, in those situations where the breed is not relevant, the applicant should be able to provide a justification (see comment above). If the breed is however expected to have an effect on efficacy (i.e. SPF -layer type-birds vs. broilers) then the applicant is expected to provide efficacy data relevant to the intended use. The 3R principle is not intended to minimise animal studies to the extent where no useful/necessary results are obtained. Under the current regulation, efficacy data are expected to be generated in seronegative animals and in MD+/seropositive animals. If under the NVR laboratory studies are performed in seronegative/SPF animals as well as in the intended target (MDA+, seropositive etc.) OR when appropriate justification is provided (for the absence of such data), no clinical efficacy trials would be required concerning this aspect. This is considered to be clear from the proposed text and does not increase requirements compared to the current situation.

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		- The existence of a specific Ph. Eur. monograph should be taken into account to judge the relevance of the laboratory model. **Proposed change:** "a) A ~~highly~~ relevant laboratory model of infection was used, and results of the pre-clinical efficacy studies fully support the efficacy claims. The laboratory model **when possible** induces a disease that is comparable to the naturally occurring disease, ~~Comparability is evident~~ **for example with respect to** type and frequency of clinical signs, overall disease severity**,** ~~and~~ distribution **of the organism(s) in the target organs** and/or shedding ~~of the organism(s)~~. **Preferably,** the route of infection for the model **should be, when possible** similar to the natural infection route. A relevant strain or isolate of the pathogen is used; **for example,** relevance **may** ~~can~~ be deduced from data on the timing of isolation, location or origin of isolation and data on strain variability and cross protection. Animals used in these studies are relevant for the intended target population~~, with respect to health status and maternal immunity, age, category and/or breed~~. **By default, it is acceptable to use seronegative animals of the minimum age targeted for vaccination. If seronegative animals cannot be used, this should be appropriately justified. If clear evidence is found for breed-related**	A sentence concerning specific Ph. Eur. monographs was added to section 4.2 and is considered to cover this aspect.

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		susceptibility, then the breed should be relevant from an EU standpoint. If any of the requirements cannot be met, ~~a robust~~ scientific justification must be provided that assures the challenge model is still relevant. **If the laboratory model complies with the challenge model described in a specific Ph. Eur. monograph, the challenge model is considered relevant."**	
111		**Comment:** In a guideline there is no reason to emphasise obvious procedures as all claim-supporting studies should be relevant and from well executed studies. **Proposed change:** "b) The intended method of administration of the vaccine can be ~~fully~~ mimicked under laboratory conditions."	**Accepted.**
114-115	1	**Comment:** If specific, non-standard routes of administration were used during the laboratory efficacy studies, and criteria a) and c) are fulfilled, there is no need to test it again in a field trial. **Proposed change:** "Nevertheless, IVMPs intended for mass administration (e.g. via drinking water) or specific non-standard routes of administration (e.g. alternative injection sites like the lip, inhalers, nose spray or eye drop) **not tested in laboratory studies** may need supportive data from clinical studies to ensure that under field conditions of use proper administration is achieved…"	**Not accepted.** This point concerns particular situations that cannot be tested in the laboratory: for example, application via automated drinking water systems. For non-standard application routes, it is considered important that application by users in the field should not affect efficacy. As indicated, in general this should not be a problem for comparability and in most other cases it could be included as a parameter in a clinical safety study.

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117-120	1	**Comment:** The requirements under this paragraph appear to go beyond the current regulatory requirements, especially when the legislation reduces the need for field efficacy trials. In addition, this proposal is raising 3Rs questions (*e.g.* demonstrating a correlate of protection requires a lot of animals). All in all the intent of this paragraph to run field efficacy trials in the peculiar case of mass-administration or using non-standard routes of administration, is to ensure that proper administration can be achieved under field conditions, simply showing that the animals show an immune response to vaccination should be sufficient (for example, a serological response, without the need to show that the serological response is relevant for protection). This would support relevant "vaccine take" in the field conditions and address the point. **Proposed change:** " Where satisfactory efficacy has been documented in the context of pre-clinical studies, data on the effectiveness of particular administration methods or mass administration under conditions of field use may also be acquired ~~by using correlates of protection or by laboratory challenge of animals taken from clinical safety studies~~ **showing that animals vaccinated under field conditions develop an immune response (for example, a serological response) to vaccination**."	**Accepted.** The proposed sentence was further amended to include other than immunological methods to show vaccine 'take' (i.e. for coccidiosis vaccines, poxvirus) "…evidence of the effectiveness of particular administration methods or mass administration under conditions of field use may also be acquired by showing that animals vaccinated under field conditions develop an appropriate immune response to vaccination (for example, a serological response) or have appropriate vaccine 'take'.
121-122	1	**Comment:** With the requirements described in chapter 4.3 high quality of pre-clinical study is already	

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		ensured, adding "High quality with respect to design and execution" does not bring further information and may be considered redundant. We also suggest clarifying that biologically-relevant outcomes (such as reduction of viremia and shedding), not only clinically-relevant outcomes (such as reduction of clinical signs), can be considered too. Moreover, the evaluation of efficacy in pre-clinical studies may not always require statistical analysis (as per specific requirements, only clinical criteria may be included for example). For example, when a specific Ph. Eur. Monograph is followed. **Proposed change:** "c) ~~The~~ **P~~p~~**re-clinical efficacy studies are of ~~high quality with respect to design and execution and vaccine effects that are both~~ clinically **and/or biologically** relevant **and/or** statistically significant**, depending on the disease and specific legal requirements**~~, have been observed~~."	It is not clear what is meant with 'the requirements described in section 4.3.' Nevertheless, it is considered a requirement for omission of clinical efficacy data that the pre-clinical data is of high quality. While in the presence of clinical efficacy data there can be additional support for results of pre-clinical studies, this is no longer possible if clinical efficacy trials are omitted. Hence, the quality of the pre-clinical trials must be sufficient by itself to allow assessment of the benefit-risk balance. **Partially accepted.** The design and execution of pre-clinical studies is such that the results are sufficiently reliable to allow assessment of the benefit-risk balance of the vaccine. The observed vaccine effects are clinically and/or biologically relevant and normally statistically significant, depending on the indication and/or specific legal requirements.
4. 3		**Situations when clinical efficacy data is considered necessary**	
124-125	1	**Comment:** As many parameters can be investigated under laboratory conditions, even those which have epidemiological effect (*e.g.* virus shedding), exemptions should be permitted. **Proposed change:** "In the following situations, clinical efficacy data is considered necessary for	**Partly Accepted.** This is a list of situations where clinical efficacy data is generally considered necessary: the proposed phrase is considered to reduce the predictability that this guidance is trying to achieve. "Clinical efficacy data is generally considered necessary for immunological veterinary medicinal products…"

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		immunological veterinary medicinal products **unless relevant pre-clinical data are available:…**"	
126-127	1	**Comment:** The wording "or for which an epidemiological effect is obviously important (*e.g.* herd immunity)" may be interpreted in a way that every vaccine could require field efficacy data (as it could be argued that every vaccine may have an epidemiological effect, by introducing a selection pressure favouring the emergence of mutants), which is not the intent. We suggest, as foreseen in the legislation, to focus on the label claims. This would increase the predictability of assessment. It also needs to be considered that reduction in shedding may be seen as an epidemiological effect, a claim which may be sufficiently well demonstrated under laboratory conditions. **Proposed change:** "… that are claimed to have an epidemiological effect ~~or for which an epidemiological effect is obviously important~~ (e.g. **such as** herd immunity~~)~~."	**Accepted.**
128	1	**Comment:** We do not understand the rationale behind the need for specific "by-default" field efficacy trials for vaccines against vector-transmitted diseases. A very good illustration is the BTV vaccines, which were authorised at the time based on laboratory efficacy trials only. Still, to the best of our knowledge, those vaccines delivered appropriate efficacy when used in the field. Also, the wording on	**Accepted.**

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		the relevance of the model seems once again to raise the expectations very high ("to support that it fully replicates all relevant aspects of vector-mediated infection (for example, but not limited to: presence of saliva or other vector derived substances, low and/or repeated doses, intracutaneous application"). Fulfilling these requirements may lead to very demanding studies. As commented above, the lab challenge model should be relevant for the disease, in general terms. **Proposed change:** ~~" that are indicated against vector-transmitted diseases. An exception can be made if an appropriate laboratory model is used that employs challenge infection via a vector or that has robust scientific data to support that it fully replicates all relevant aspects of vector-mediated infection (for example, but not limited to: presence of saliva or other vector derived substances, low and/or repeated doses, intracutaneous application)."~~	
135-136	1	**Comment:** Performance parameters as listed in the proposal, can be measured in laboratory studies. If a pre-clinical study brings data to support such claim, the demonstration in the field is not needed. Any efficacy parameter should be included only in cases when measurement can only be achieved at a large scale due to the special characteristics of the disease (*e.g.* clinical manifestation of PCV infection of pigs: postweaning multisystemic wasting syndrome (PMWS)).	**Not accepted.** The relevance of performance parameters measured under laboratory conditions is questioned. It is considered that in the majority of cases/claims it is not possible to mimic field conditions to the extent that reliable data on performance could be derived from laboratory studies. This aspect was mentioned in the discussions with industry as being a valid reason to perform clinical efficacy trials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "- that are claimed to have an effect on performance parameters (e.g. weight gain, feed conversion, laying)**, when those could not be demonstrated under pre-clinical conditions** Or: **"...for which requested claims cannot be reproduced under pre-clinical conditions**"	
Section 4.4.	**Situations when clinical efficacy data may replace pre-clinical data**		
142-147	1	**Comment:** Similarly to the re-vaccination demonstration, a long-term duration of protection can also be supported by using an indicator of protection, not necessarily a challenge. This is aligned with section 7. of the guideline regarding animal welfare as well as Ph. Eur. 5.2.7 ("Claims related to duration of immunity are supported by evidence of protection. The test model described under Immunogenicity and/or Potency is not necessarily used to support claims regarding the duration of immunity afforded by a vaccine). **Proposed change:** "Bearing in mind that duration of protection after the basic vaccination scheme shall be justified in relation to the length of time for which animals are likely to be at risk, target animals should be vaccinated in the field and undergo thereafter a natural challenge in the field or an experimental challenge under laboratory conditions. **Alternatively, a suitable indicator of protection can also be used for the demonstration.**"	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
137-161	1	**Comment:** In line with chapter 4.3. an additional point may be added for cases when claims (such as effect on performance parameters) could be difficult to support by laboratory studies and can be replaced by clinical data from the field. **Proposed change:** Addition of a supplementary hyphen in section 4.4: "- **That are claimed to have an effect on performance parameters (e.g. weight gain, feed conversion, laying)**."	**Accepted.**
158	1	**Comment:** It should be clarified that the focus is on the organism(s) against which the vaccine is claimed to protect. **Proposed change:** "If clinical data should support the duration of immunity or the efficacy of the re-vaccination scheme, it shall be ensured that the vaccinated target animals are not exposed to intercurrent field infection **by the corresponding organism(s) targeted by the vaccine** (…)"	**Accepted.**
158	1	**Comment:** The possibility should be added to run clinical studies for assessing the influence of passively acquired maternally derived antibodies instead of conducting specific pre-clinical studies. This would be in line with the 3Rs principles. **Proposed change: "- where data assessing the influence of passively acquired maternally derived antibodies may be fully supported by**	**Accepted.**

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		clinical trials (e.g. no valid challenge model available, redundancy of laboratory and field study design)."	
Section 4.5. Deviations from the basic principles			
165-168	1	**Comment:** Clarity is lacking on how to justify that a disease occurs only rarely and sporadically (bibliography data may be scarce or country/region-dependent). This is the situation for several agents, especially in EU. The fact that more extensive pre-clinical studies may be required in those situations is clearly a hurdle against the omission of clinical efficacy trials, and contrary to the 3Rs and limited markets principles/requirements. It also remains unclear if in these cases additional requirements to specific Ph. Eur. monographs are set up. **Proposed change:** Please delete : "~~For instance, more extensive pre-clinical efficacy studies could be necessary~~"	**Accepted.** However, this does not exclude that more extensive pre-clinical studies could be necessary.
169-174	1	**Comment:** The point about the efficacy test on IVMPs against notifiable and/or exotic animal diseases for which vaccination is not allowed in the European Union is more relevant under section 4.2. Further concern is that the local agencies responsible for epidemiological issues are not necessarily the same as the agency responsible for the future MA procedure which makes the judgement on omission of clinical trials difficult.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "In cases of IVMPs against notifiable and/or exotic animal diseases for which vaccination is not allowed in the European Union, it may be difficult to find other suitable areas to carry out clinical trials, if required (in case the claims could not be established in pre-clinical trials). ~~Such cases are judged on an individual basis to determine If there is a~~ **In reference to** zoo-sanitary legal requirements ~~to restricts the efficacy and safety investigations to pre-clinical trials~~ **efficacy and safety clinical trials can be omitted**. Data from clinical trials conducted outside the EU, in particular when conducted according to Good Clinical Practice, may be considered in support of applications for such IVMPs."	**Not accepted.** For these diseases the normal 'rules' as set out in the previous sections apply. Thus, if the claims cannot be met using pre-clinical data alone (i.e. no valid challenge model available), then clinical trial data would be required. The exception is that for notifiable diseases, these data could be gathered outside the EU. Investigations may be restricted to pre-clinical data also for safety, to be judged on an individual basis.
Section 5. Section 5.1	**Assessment of efficacy under field conditions** Efficacy criteria		
183	1	**Comment:** It is often not possible to include all parameters for the disease concerned. **Proposed change:** "~~Justification shall be given for not including parameters that are known to be related to the disease concerned~~".	**Not accepted.** If it is not possible to include all parameters, this could be (part of) a justification. No change is proposed compared to current requirements, i.e. if only production parameters are recorded, a justification is normally provided and accepted.
185-187	1	**Comment:** Generally, clinical trials are conducted to support those parameters of the claim which are mostly evaluated as secondary parameters in the pre-clinical studies. For this reason, this paragraph is too restrictive.	**Not accepted.**

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		Furthermore, it is not unusual to use viremia and/or shedding as primary parameters (example of PCV2 and BTV vaccines). We suggest that the text is reworded accordingly. Also for consistency with section 4.3, feed conversion could be added in the examples of parameters related to production. **Proposed change:** "Primary efficacy criteria are generally derived from main disease parameters **such as** mortality, morbidity, clinical signs, **viremia, shedding** and/or lesions. Secondary criteria may for example include parameters related to production (e.g. weight gain, **feed conversion**, egg laying) or **other relevant** ~~infection~~ parameters ~~(e.g. shedding, viraemia)~~."	It is agreed that it is not unusual to use infection parameters as primary efficacy criteria, nevertheless primary efficacy criteria are generally derived from main disease parameters.
189-190	1	**Comment:** The definition of an indicator of protection should not be restricted to the immune response only, as there may be other parameters such as for example virus load in the blood. Moreover, other immunological parameters could also be used as representative of the immune response, being an alternative to situations where classical protective antibodies are not produced. **Proposed change:** "An indicator for protection ~~should be shown to~~ **may** play a substantial role in the immune response, **other parameters** relevant for protection of the target species against the disease concerned **may be possible when justified**."	**Not accepted.** The parameter mentioned as an example (virus load) is not an indicator of protection, but rather an efficacy criterion. Indicators of protection are not positive effects of vaccination but rather have a role in establishing these effects. Indeed, any measurable component of the immune response that can be correlated to efficacy and reasoned to have a role in protection could be used as such (not restricted to antibodies).
Section 5.2. Controls and study design			

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200-203	1	**Comment:** The purpose for the inclusion of controls depends on the disease and design of the study. Especially, for example in the situation of an animal disease that rarely occurs in the field and for which an indicator of protection is used, the controls would not serve the purpose as 'evidence that exposure to infection took place'. **Proposed change:** "It is necessary to define in the study protocol what purpose the control group serves. This **may** ~~shall~~ include: …"	**Accepted.**
207	1	**Comment:** Since statistically correct randomisation is not ensured in certain cases (*e.g.* at poultry farms where this shortcoming is compensated by the large number of the involved animals or vaccines for very young animals, such as suckling piglets), exceptions should be allowed. **Proposed change:** "- The animals of both groups have to be randomised according to the experimental unit, **unless justified**"	**Accepted.**
213-215	1	**Comment:** The sentence is difficult to interpret as it starts with negative statement using historical data and then follows with options when to use. **Proposed change:** "The use of historical data for control purposes is ~~rarely acceptable~~ **not encouraged** but…"	**Not accepted.** The wording is intentional and improves predictability. It is stressed again that clinical efficacy trials need only be performed if pre-clinical studies do not support all claims, hence clinical studies need to produce highly reliable data in support of these claims.

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220-221	1	**Comment:** If a reference vaccine is available, a placebo may not be ethically acceptable for trials carried out in veterinary clinics. **Proposed change:** "It is recognised that in some circumstances (*e.g.* enzootic diseases, **trials in veterinary clinics**) inclusion of placebo/non-vaccinated controls may be difficult for reasons of animal welfare."	**Partly accepted.** The sentence is considered sufficiently clear with the reason being animal welfare. The sentence is adapted as follows: …. Even when the inclusion of ***negative*** controls is not possible... It is stressed again that clinical efficacy trials need only be performed if pre-clinical studies do not support all claims, hence clinical studies need to produce highly reliable data in support of these claims.
224-227	1	**Comment:** The text may be adapted to the wording of the Ph. Eur. Chapter 5.2.7. ("…single batch of product could be used to assess both safety and efficacy under field conditions. In these cases, a typical routine batch of intermediate titre or potency may be used…"). The expectation to use minimum titre/potency batches for clinical efficacy studies evaluating only efficacy and not safety may be tempered for cases where a comparator product is used as control group, as comparator products are by definition commercial batches thus "standard titre/potency" batches. Moreover, this GL should not be contradictory with other recommendations, in particular in case of combination/association, where "the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies." in the field studies (as per GL EMA/CVMP/IWP/594618/2010).	

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		Proposed change: "The batch(es) used ~~should~~ **may** be of standard or intermediate potency or titre whenever safety and efficacy measurements are combined in one clinical study. ~~Alternatively~~ **I~~i~~n case separate trials are performed to determine safety and efficacy in the field**, ~~it is expected that~~ **the use of minimum titre/potency batches** ~~would~~ **is also acceptable in the efficacy trials** ~~in order to maximise the information that can be derived from the studies~~. **When the IVMP is being compared with a comparator product, the use of a standard titre/potency batches is acceptable.**"	**Accepted.**
Section 5.3.	**Comparator product**		
232-233	1	**Comment:** The scope of the guideline on statistical principles does not include IVMPs. Because of this, Industry could not comment as to whether those principles were relevant (or realistic) for field studies conducted with IVMPs. Likewise, the relevant working party (IWP) may not have been involved in the drafting of such guidance at the time (the guideline only refers to EWP). All together, we believe that reference to this guideline is premature before further consideration is given to the impact for IVMPs. **Proposed change**: Please remove the reference to the Guideline.	**Not accepted.** It is considered the guidance may be of help. A sentence is added to stress that the scope of the GL does not include IVMPs and the suggestion is only to provide help to applicants.
234-237	1	**Comment:** Exposure to infection is extensively treated in the next chapter. We propose moving the first part of the sentence under chapter 5.2.2. (Exposure to infection) where it would fit better. As	If the beneficial effect of the vaccine has been fully demonstrated under laboratory conditions there is generally no longer a requirement to perform clinical efficacy trials.

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		this chapter details methods to demonstrate exposure, the second part is not needed, especially as the beneficial effect of the vaccine has already been demonstrated under laboratory conditions. **Proposed change:** ~~"When the IVMP under study is being compared with a comparator product, a group of non-vaccinated or placebo controls shall still be included whenever possible in order to verify field challenge. If this is not possible, sufficient evidence shall be presented that both products are having a demonstrable beneficial effect."~~	**Not accepted.** The sentence is not considered to be a repetition and is well placed in the section on comparator product.
5.2.2.	**Exposure to infection**		
239	1	**Comment:** The use of adverbs and adjectives such as "clear", "rarely" *etc*. do not add to the clarity. **Proposed change:**"~~Clear~~ **E**~~e~~vidence that the vaccinated animals…."	**Accepted.**
241-242	1	**Comment:** Considering the information already given in sections 4.1 to 4.5, the sentence stating the need for pre-clinical data should be removed. **Proposed change:** "…/…. ~~Observation of signs of disease is rarely sufficient by itself and clinical records shall be supported by pre-clinical data.~~ …"	**Accepted.**
244-246	1	**Comment:** Exposure to a specific pathogen in field trials is monitored through serological or other tests to detect the presence of the corresponding pathogen (virus isolation or PCR on blood samples, for example). Typically, this does not require statistical	Virus isolation is a direct measure of pathogen exposure and is mentioned as such in the text. Serological tests can be a supportive/additional parameter of exposure (i.e. seroconversion).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considerations. We do not understand the requirement for exactly the same test to be used as in pre-clinical study. It should be perfectly acceptable to use different methods for the different studies for monitoring exposure to infection, provided they are validated and fit for the purpose. Also very often, commercial, validated tests are used during clinical studies for serological measurements. We suggest rewording accordingly. **Proposed change**: "Regular serological **or other relevant** testing **(e.g. virus isolation or PCR on blood samples)** performed on a ~~statistically~~ number of animals **suitable for the purpose**, may be a supportive measure to demonstrate exposure to the relevant pathogen. The ~~serological~~ method(s) used shall be validated ~~and the same as used in the pre-clinical studies."~~	**Partly accepted.** This concerns in particular serological testing which can be used as a supportive parameter of exposure. Virus isolation/detection is a direct measurement of exposure. The test need not be the same as used in pre-clinical testing.
248	1	**Comment:** This requirement is not realistic for clinical studies conducted in a large-farm environment because the individual necropsy is not feasible considering the usual loss in avian flocks and aquaculture systems. Therefore, it would be preferable to apply the previous requirement laid down in EMEA/CVMP/852/99 4.1.4. with a slight change. **Proposed change:** "The causes of any deaths or unexpected signs of disease **related to the**	**Partly accepted.** Normally deaths should be investigated to some extent in order to determine whether or not they are related to the relevant disease/parameters. In poultry or finfish a justification may be provided for not investing all deaths (i.e. death rate normal for the phase of production). "The causes of any deaths or unexpected signs of disease shall be determined using appropriate methods, where possible, unless justified. It is expected that necropsy is performed in such cases. In avian and finfish industrial

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		parameters being measured shall be determined ~~using appropriate methods, where possible~~ **unless justified**. It is expected that necropsy is performed in such cases. **In avian and finfish industrial production, standard procedures for diagnosis may be used to determine the cause of death.**"	production, standard procedures for diagnosis may be used to determine the cause of death."
251	1	**Comment:** We consider that the paragraph LL 244-237 with the respective comments taken into consideration are more appropriate placed here. **Proposed change:** Please add at the end of this chapter following LL 251 **"When the IVMP under study is being compared with a comparator product, a group of non-vaccinated or placebo controls shall still be included whenever possible in order to verify field challenge."**	**Not accepted.** The sentence is considered to be logically placed.
5.2.3.	**Intercurrent infections**		
253-256	1	**Comment:** It should be made clear that there is no "by-default" expectation to implement a (serological/virological/bacterial) monitoring of pathogens other than the ones under study (*i.e.,* targeted by the vaccine). Where needed, additional investigations are carried out. **Proposed change**: "Infections with agents other than those under study that may influence the parameters being measured may affect the outcome of the trial. Such an influence on the trial can be reduced considerably if vaccinated and control	**Not accepted.** It is not considered necessary in this case to state what is not required. *Post-mortem* investigations are addressed under 5.2.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		animals are investigated in parallel and if randomisation is applied for allocation to study groups. **It is not expected that a specific (serological/virological/bacterial) monitoring is put in place to detect the presence of other pathogens than the ones under study (i.e., targeted by the vaccine). However, where needed, additional investigations (such as post-mortem investigations) are carried out to confirm or exclude a specific diagnostic.** "	
5.2.4.	**Pre-existing antibodies**		
260-262	1	**Comment:** If the impact of MDA is addressed through a pre-clinical study, it should not be required to also address this impact in the clinical study. In certain cases, the individual MDA levels can be highly variable among flocks/herds and it is not possible to determine an exact titre which can be considered as normal. **Proposed change:** "If the indication or specific claims for the IVMP are related to efficacy in the presence of maternal antibodies against the vaccine agent(s) **and when the impact of MDA is not addressed in a preclinical-study,** the trial protocol shall include **a group of** animals with ~~titres of these~~ maternal antibodies **representative of those normally occurring in the field.**"	**Accepted.**
263-266	1	**Comment:** We suggest an alternative wording for clarity. Animals may have antibody levels at the time	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of vaccination which would make them not (or less) "susceptible to the infection", however, they could still be relevant for the purpose of the trial. **Proposed change**: "…ensuring that the animals are still **relevant for the purpose of the trial** ~~susceptible to the infection~~."	
267-268	1	**Comment:** There may be exceptions and justified reasons as to include animals previously vaccinated such as: - For trials conducted to support a "booster" effect (inactivated vaccine following primer with a live vaccine, in poultry for example) or simply to demonstrate the efficacy of the proposed regular booster regimen, the expectation is that the animals would already have been vaccinated with products containing the same active substances as the IVMP under study. - For use of the vaccine in multiparous sows/cows and for some diseases when vaccination is widespread vaccination after the stated duration of immunity should be considered acceptable **Proposed change**: "~~In all cases,~~ **C**clinical trials shall not be carried out in animals that have been vaccinated with products containing the same active substances as the IVMP under study. **Exceptions**	**Partly accepted.** In general, vaccination after the stated duration of immunity of an IVMP is not acceptable. A claimed DOI may not be the same as the actual DOI since the first depends on the duration of the study provided in the dossier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		such as cases when a booster effect is investigated or vaccination occurring after the stated duration of protection are acceptable."	
6. **6.1.**		**Clinical safety trials** **Parameters**	
277-281	1	**Comment:** Except for fish vaccines carcass quality is (very) rarely monitored as a parameter in field studies. We suggest specifying this here. Likewise, we suggest giving an example of "change in behaviour" as this category may be quite vague and difficult to address comprehensively. **Proposed change**: "Parameters used to determine systemic effects of vaccination may include allergic reactions, mortality, anorexia, pyrexia, changes in behaviour **(such as depression)**, weight gain, feed conversion, carcass quality **(for fish vaccines)**, milk/wool/fur production, egg production and hatchability of breeding eggs and male and female fertility. Additional or alternative parameters relevant for a specific pathogen may be used, where appropriate and justified.	**Accepted.**
282-283	1	**Comment:** The assessment of the behaviour of the vaccine agent(s) is already evaluated in pre-clinical studies. This behaviour should be assessed in clinical studies only if it is deemed necessary, but not systematically. These requirements are relevant especially for GMO, less so for any type of live vaccines.	**Partly accepted.** If deemed relevant based on results of preclinical studies, behaviour of live vaccines (either GMO or conventional) should be documented.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "In case of ~~live~~ vaccines **consisting of or containing GMOs**, the behaviour of the **corresponding** vaccine agent(s) in animal populations should be documented (*e.g.* spread, persistence in the environment) **if deemed necessary following results obtained in preclinical studies.**	
6.2.	**Controls and trial design**		
291-296	1	**Comment:** The requirements related to the vaccine batches used should not be different whether safety and efficacy are addressed in a combined or separate clinical trial. The safety of the maximum titre (at the least attenuated passage for live vaccines) is demonstrated through dedicated pre-clinical studies. As stated in Lines 85-87, *pre-clinical studies shall be supplemented with data from clinical trials, using batches representative of the manufacturing process described in the marketing authorisation application.* With the change in the legislation, there will be more cases where only field safety trials will be conducted. When only field safety trials are conducted, this should not automatically be seen as a requirement to conduct those trials with "worst-case" vaccine batches (such as least attenuated and/or maximum potency/titre). The latter requirements would require specific batches (such as large GMP batches) to be produced and add to the costs and may result in delays to start such studies. Consistent with the spirit of the legislation, as a general rule, it should be allowed to conduct field safety trials with either	**Accepted.** Sentences slightly amended for clarity. The batch(es) used in clinical safety studies or combined safety and efficacy studies may be of standard or intermediate potency. In case separate clinical safety trials are performed, batches used may contain the maximum titre of the vaccine agent(s) or batch potency to be stated on the label, if deemed necessary following results obtained in pre-clinical studies. For live vaccines, the vaccine agent(s) may be at the least attenuated passage level that will be present in a batch of the IVMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"standard" (commercial-like) batches or "worst-case" batches. Applicants should be able to justify either approach on a case-by-case basis. According to Annex II and Ph. Eur. 5.2.6. (safety of veterinary vaccines) the use of batches containing the maximum titre or potency is required for laboratory studies only. The text may also be adapted to the wording of the Ph. Eur. Chapter 5.2.6. ("…single batch of product could be used to assess both safety and efficacy under field conditions. In these cases, a typical routine batch of intermediate titre or potency may be used…"). Moreover, this GL should not be contradictory with other recommendations, in particular in case of combination/association, where "the use of standard batches is accepted, which allows the investigation of safety and efficacy in the same field studies." in the field studies (as per GL EMA/CVMP/IWP/594618/2010). **Proposed change**: "The batch(es) used ~~shall~~ **may** be of standard or intermediate potency or titre whenever safety and efficacy measurements are combined in one clinical study. In case separate clinical safety trials are performed, one dose of IVMP may contain a ~~commercial-like~~ **standard or intermediate titre or potency, or if deemed necessary following results obtained in pre-clinical studies alternatively a titre close to** ~~shall~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~not contain significantly less than~~ the maximum titre of the vaccine agent(s) or batch potency to be stated on the label. **In this specific situation and if deemed necessary f**~~F~~or live vaccines, the vaccine agent(s) may ~~shall~~ be at the least attenuated passage level that will be present in a batch of the IVMP~~, in order to maximise the information to be derived from the study~~."	
8. Analysis and interpretation			
307-308	1	**Comment:** See above. **Proposed change**: "A clinically **or biologically** relevant effect size should be described a priori."	**Accepted.**
311-313	1	**Comment:** Please refer to comments made above regarding the scope of this guidance. **Proposed change:** "~~Guidance on the calculation of sample size and the design on non-inferiority studies can be found in the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010).~~"	**Partly accepted.** Sentence adapted for clarity: While it is acknowledged that the scope of the guideline does not include IVMPs, guidance on the calculation of sample size and the design on non-inferiority studies as provided by the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010) may be helpful.
314-315	1	**Comment:** The reference is unclear as it does not match to the reference listed in section 3 (Position paper on indications for veterinary vaccines (EMEA/CVMP/042/97-Rev.1-FINAL). **Proposed change:** "The analysis of the data of clinical efficacy trials shall be related to the indication and specific claims made for the IVMP, and the parameters measured (refer to "~~indications and~~	**Accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~specific claims for immunological veterinary products~~" **EMEA/CVMP/042/97-Rev.1-FINAL**)".	
Definitions			
334	1	**Comment:** Clinical trials may investigate both safety and efficacy. **Proposed change**: "Clinical trial: A study which aims to examine under field conditions the safety **and/**or efficacy of an IVMP"	**Accepted.**
338	1	**Comment:** Some pre-clinical trials (for example, for inactivated vaccines with fixed antigen content) may investigate both safety and efficacy. **Proposed change**: "Pre-clinical study: A study not covered by the definition of clinical trial which aims to investigate the safety **and/**or efficacy of an IVMP."	**Accepted.**
340-346	1	**Comment**: The wording of the definition given for 'Indicator of protection' should be aligned with the ones on L. 150-157 (section 4.4) and on L. 188-191 (section 5.1). To avoid repetition, a refence to the definition section may be made under these sections 4.4 and 5.1. **Proposed change:** "An indicator for protection ~~should be shown to~~ **may** play a substantial role in the immune response, **other parameters** relevant for protection of the target species against the disease concerned **may be possible when justified**."	**Not accepted,** for reasons explained above.