16 September 2024
EMA/260063/2024

Overview of comments received on Guideline on live recombinant vector vaccines for veterinary use (EMA/CVMP/IWP/390313/2023)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	Access VetMed

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on the revision of this guideline. As this guideline is there to complement many existing texts applicable to the development and registration of the live recombinant vector vaccines, it is important that it does not unnecessarily paraphrase or repeat from the existing requirements, but only adding explanations where the text might need clarification or further explanation.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
47	1	**Comment:** it is useful in the scope of this guideline, to emphasise that this guideline is not a repetition of what is already well defined and fully applicable for live recombinant vector vaccines, in the European Pharmacopoeia, the Annex II of the Veterinary Regulation and other CVMP guidelines. This is stated already in line 51, for the environmental risk assessment guideline. **Proposed change:** The objective of this guideline is to define what should be presented in the quality, safety and efficacy part of the application taking into account the particular properties of live recombinant vector vaccines in the target and non-target species, including the natural host of the parental organism (where relevant). **This guideline only refers to the safety and efficacy requirements as set in other already-published documents (see paragraph 3), when it is needed to bring clarification or additional explanations to those, considering the specificities of live recombinant vector vaccines.**	Agreed to include a sentence, for clarification: "Standard requirements for vaccines are set out in other relevant documents (see section 3) and are not repeated in this guideline."
51-53	1	**Comment:** The reference of the Note for Guidance (EMEA/CVMP/074/95) should be replaced by the one specifically dedicated to Annexes II and IIIa of Directive 2001/18. Or added in a compromise situation. **Proposed changes:** This guideline does not repeat the requirements for environmental risk assessment, already developed in the ~~Note for~~ Guidance on environmental risk assessment for ~~immunological~~ veterinary medicinal products **consisting of or containing genetically modified organisms (GMOs) (March 2017)**.	Not accepted. Whilst the principles outlined in the cited document are still valid, most of the references in the document are not applicable to the current veterinary legislation, so the document cannot be referred to in the guideline.
78-79	1	**Comment:** See our comments under lines 202-206. **Proposed changes**: In addition, Ph. Eur. chapters 5.2.6 and 5.2.7, monograph 0062 and relevant individual monographs should be taken into account **(when those individual monographs describe in their**	Not agreed, the general Ph. Eur. monograph 0062 is being updated to clarify that vaccines such as recombinant or nucleic acid-based

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		definition a recombinant vector), as well as all other relevant EU and VICH guidelines.	vaccines are in the scope of the Ph. Eur. Unless otherwise justified, live vector vaccines are expected to comply with the relevant (live) vaccine monograph. No change in the current text is considered necessary.
90	1	**Comment:** It is common that after obtaining the final construct, it undergoes into a selection/purification and/or amplification process and/or attenuation passages to obtain a homogenous genetic population and sufficient stock. This latter is regarded as the master seed and should be reflected as is in the new version of the guideline. **Proposed changes:** In this context, the final construct **after possible selection, purification and/or amplification and/or attenuation passages** is regarded as master seed.	Agreed to include a sentence for clarification: "...after the necessary selection, purification, amplification and/or attenuation passages..."
96	1	**Comment:** Plasmids are not necessarily required. **Proposed Change:** A full description of the starting organisms and plasmids**, if any,** should be provided.	Agreed.
101-105	2	Comment: According to Regulation 2021/805, section IIIb.2c., paragraph (6), certificates of analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification. For starting materials used for construction exemption should be possible and it should be clearly noted.	No certificates of analysis are requested in this guidance. The description of what is required is considered sufficiently clear. No change.
106-107	1	**Comment:** To the knowledge of AnimalhealthEurope, plasmid DNA is usually very stable after isolation. Moreover, if the plasmid used to construct the vector has been well described/characterised, as indicated in lines 101-105, the analyses for plasmid DNA (in)stability seems to be superfluous. **Proposed change:** Please delete the requirement.	Not accepted. Plasmids can be instable during the production (leading to 'impurity' in the plasmid harvest), this can subsequently lead to 'impure' vector preparations. It is clear from the description in the GL that this is

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			exceptional, but it should still be excluded (i.e. based on the vector backbone, size of insert). No change.
116	1	**Comment:** Please **c**hange possible to relevant	Agreed.
118	1	**Comment:** Markers are not necessarily required**.** **Proposed Change:** a detailed description of markers**, if any,** which are present should be provided.	Not accepted. The sentence already starts with "If applicable." No change.
120-122	1	**Comment:** As the safety of the vector is supposed to be confirmed as acceptable through all the safety studies, the wording here may be superfluous. **Proposed Change:** Please delete the paragraph: ~~Details of the integration of plasmid DNA into the vector should be presented and should address the impact of the gene insert on the expression of the neighbour genes in the vector, whenever possible. The effect of gene deletion on the biological properties of the live vector should be investigated.~~	Not accepted. Knowledge of the host and the impact that the insertion of genes of interest is considered important. Basic knowledge provides a scientific support for safety and efficacy that is then confirmed in laboratory studies that are generally at (very) small scale. No change.
123-124	1	**Comment:** please add insertion for added clarity **Proposed Change:** This should include at least the sequencing of the regions flanking the insertion sites and the **insertion** sites themselves.	Agreed.
135-137	1	**Comment:** It is common to observe a limited number of mutations during the production process which may nevertheless be demonstrated to be safe in the target species. Therefore, the sentence should be broadened. **Proposed changes:** It should be demonstrated as part of validation of the production process that the recombinant vector vaccine is stable throughout the manufacturing process to the finished product and that the integrated sequences have not undergone any rearrangements or **significant** mutations.	Agreed.

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140-141	1	**Comment:** Please reword to improve understanding **Proposed Change:** The applicant should provide techniques that ~~allow~~ **demonstrate that** differentiation between the parent strains of the vector and the **recombinant** vector vaccine **is possible**.	Not agreed. The current sentence is considered clear with regard to expectations.
150 - 153	2	Comment: Guidance on how to conduct such safety studies would be welcome.	Comment noted.
155	1	**Comment:** Please reword to improve clarity. **Proposed Change:** Transmission from vaccinated target animals to non-vaccinated **animals of the target species**.	Agreed.
164-165	1	**Comment:** As compared to the previous version of the guideline (EMA/CVMP/004/04-Final), GMO has been replaced by "vector" leading to possible misunderstanding. "Vector" should be replaced by "recombinant vector", as recombination may impact the transmission property. **Proposed change:** If transmission of the **recombinant** vector to animals or humans may occur, the conditions for use should be described in detail and suitable information provided in the SPC.	Agreed.
170	1	**Comment:** Please add parent vector to improve clarity. **Proposed Change:** The applicant should investigate possible changes of tissue tropism by comparing the behaviour of the **parent** vector and the recombinant vector vaccine.	Agreed.
172-173	1	**Comment:** Please reword to clarify that the detection system for the recombinant vector should be suitable for the purpose of the study. **Proposed Change:** A sensitive, validated detection system for the recombinant vector vaccine should be ~~available~~**used in the study**.	The sentence is identical to the existing guidance, there is no intention to change its meaning/scope in this version.
177-179	1	**Comment:** To be consistent with changes proposed in section 4.1. Quality, the following change is proposed in section 4.2.1.3. Increase in virulence. **Proposed change:** Vectors must be non-pathogenic or low pathogenic to a level that will ensure that the resulting recombinant vector vaccine is safe for	Accepted.

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		the intended target species. It has to be demonstrated that the insertion of foreign gene(s) does not lead to an increase in virulence**, otherwise attenuation passages may be carried out**.	
179 - 181	1	**Comment:** There seems to be an inconsistency on the data requirements on the reversion to virulence between this draft guideline and Guideline on data requirements for vaccine platform technology master files (vPTMF) EMA/CVMP/IWP/286631/2021. In the current draft Guideline on live recombinant vector vaccines for veterinary use, it states that "When appropriate data on genetic and phenotypic stability is available, there is no need for reversion to virulence studies using subsequent passages of the vector vaccine." (line 179 – line 181). However, special requirements for live vaccines such as reversion to virulence studies should be performed according to the "Guideline on data requirements for vaccine platform technology master files". **Proposed change:** Please harmonise	Noted. The Guideline on data requirements for vaccine platform technology master files" will be revised and aligned.
179-181	1	**Comment:** The last sentence of section 4.2.1.3 is unclear. To get appropriate data on genetic and phenotypic in vivo stability, passages of the vector vaccine in animals should be conducted to get the "in vivo passaged vector vaccine" to be analysed. So, at least a part of increase in virulence study should be conducted (passages in animals). It is assumed that the last sentence is referring to a specific study to evaluate the safety of the "in vivo passaged recombinant vector vaccine" (e.g. test for residual pathogenicity in Marek's disease vaccine monograph) and that it can be omitted if appropriate data on genetic and phenotypic in vivo stability are available. If this assumption is correct, the sentence could be revised as proposed below. **Proposed change:** When appropriate data on genetic and phenotypic **in vivo** stability is available, there is no need **to conduct specific studies** ~~for reversion to virulence studies~~ **to evaluate the safety of the recombinant vector vaccine obtained after** ~~using~~ subsequent **in vivo** passages.	Not accepted. Vector vaccines must be derived from non-virulent parent vectors. If these strains are genetically stable, there is no 'reversion' to virulence (as the parent strain was not virulent). It must be clear from the data package that the insertion of the genes has not changed the virulence or the genetic stability of the parent vector. If this is the case, there is no need for reversion to virulence studies performed in accordance with Ph. Eur. 5.2.6.

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			Text changed in order to clarify: "If the parent strain used is known to be both non-pathogenic and genetically stable and when appropriate data on genetic and phenotypic stability of the resulting vector vaccine is available, there is no need for reversion to virulence studies using subsequent passages of the vector vaccine."
192	1	**Comment:** Stability in different climate conditions may not be necessary. **Proposed Change:** persistence of the product in the environment ~~at various climate conditions~~).	Partially agreed. Sentence changed to "...taking into account worst-case climatic conditions."
193-196	1	**Comment:** Directive 2001/18 does not explicitly say that a validated method should be provided, and that this method should be able to differentiate. Rather "information on monitoring of the GMO", this is different. **Proposed change:** **It should be possible to** ~~A validated method should be provided that is able to detect the vector vaccine in the field and to~~ differentiate ~~it~~**the vector vaccine** from the wild-type microorganism/antigen and/or inserted sequences (see also Directive 2001/18/EC, Annex IIIA, Part V.A.1), especially if diseases caused by the wild strains are subject to eradication and control programs.	Not accepted. The text has been updated to 'A validated method should be provided that is able to detect the recombinant vector vaccine in the field and to differentiate it from the wild-type microorganism/antigen and/or inserted sequences (…)'.
201	1	**Comment:** This sentence ("The requirements of Regulation (EU) 2019/6 Annex II, Section IIIb, Part 4 fully apply") closes the door to limited market vaccines, for example those consisting of a vector in a non-major species and addressing an unmet need. Was this intentional? **Proposed change:** Please consider revising to allow the application of the limited market concept.	Not accepted. The Regulation specifically states exemptions from the regulation in case of Art. 23 procedures, there is no need to address this exemption in this guideline. Other guidance is available on data requirements for those specific cases.

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201-202	2	Comment: The draft guideline states that *"The efficacy of **each of** the components of a vector vaccine shall be demonstrated."* Sometimes an individual component does not provide efficacy when used alone, but only in combination with another component(s). How will this be addressed? Clarification would be welcome.	If two components are required for immunity, this should be justified (and supported by data) in the dossier. Then it follows that the efficacy of both components can be considered demonstrated. No change required.
204-206	2	Comment: In most cases, the safety profile would not be significantly different Proposed change: *If the monograph requirements for immunogenicity cannot be met, the benefit-risk evaluation may still be positive if the safety of the vector vaccine is **comparable** to that of the live vaccine and depending on the level of protection shown.*	If the vector vaccine cannot meet the requirements of the relevant Ph. Eur. monograph (i.e. for the corresponding live vaccine), there must be an added benefit. This can for instance be found in the direct safety for the target animal, but also in the absence of recombination events (leading to new strains) or earlier induction of immunity (i.e. in the face of MDA or due to early use in otherwise too sensitive animals). Sentence changed as follows: "If monograph requirements for immunogenicity cannot be met, the benefit-risk evaluation may still be positive, depending on the level of protection shown and other advantages of the vector vaccine.
202-206	1	**Comment:** The following sentences (especially the one in italics) appear to be against the principles on how the European Pharmacopeia monographs are drafted and enforced: "The efficacy of each of the components of a vector	Not agreed. The Ph. Eur. general monograph 0062 is being updated and will specify that

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		vaccine shall be demonstrated. *Immunogenicity tests described in relevant Ph. Eur. monographs (i.e. for corresponding live vaccines) shall be performed and vector vaccines should comply with the requirements*. If monograph requirements for immunogenicity cannot be met, the benefit-risk evaluation may still be positive if the safety of the vector vaccine is superior to that of the live vaccine and depending on the level of protection shown." The EP Monographs for individual vaccines (such as those for live attenuated vaccines) are supposed to apply only for the corresponding vaccines (under "definition" in the EP Monograph). It is not an automatic expectation that a live recombinant vector would be as efficacious as the corresponding live attenuated vaccine(s). EP Monographs are drafted when there is at least one commercial vaccine authorized in at least one Member State. Asking "upfront" (without the relevant data at hand) that the respective live recombinant vaccines would need to comply with the corresponding live attenuated vaccines monographs may unnecessarily place barriers towards registration of those latter products, without any good reason. We also wish to refer to the similar comments we provided to EDQM on a similar discussion on the revised General Chapter 5.2.7 (see page 2 especially). To give a concrete example, there are different live recombinant vectors approved in EU against Marek and IBD in poultry. Still, the respective EP Monographs refer to those vaccines as being "a preparation of one or more suitable strains of the corresponding virus" *. Clearly, this wording does not include recombinant vectors. We would suggest that EDQM updates the relevant monographs, if necessary (id est, based upon assessment of available data), before the requirements are strengthened unnecessarily (and therefore possibly blocking innovation).	monograph requirements for individual vaccines are applicable to vector vaccines (where relevant or unless otherwise justified). This sentence was therefore included in this guidance in order to clarify that despite this new Ph. Eur. text (and in accordance with the general chapters of the Ph. Eur.) the benefit-risk balance of a vector vaccine may still be positive even if the monograph requirements are not met. The sentence was updated in order to further clarify this point. The proposal to insert the term 'protective' is not accepted, since the exception for a non-protective component (vector backbone) is explained in the text of the section already.

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		*Live IBD vaccine individual EP Monograph: "Avian infectious bursal disease vaccine (live) [Gumboro disease vaccine (live)] is a preparation of a suitable strain of infectious bursal disease virus type 1. This monograph applies to vaccines intended for administration to chickens for active immunisation; it applies to vaccines containing strains of low virulence but not to those containing strains of higher virulence that may be needed for disease control in certain epidemiological situations." *Live Marek vaccine individual EP Monograph: "Marek's disease vaccine (live) is a preparation of a suitable strain or strains of Marek's disease virus (gallid herpesvirus 2 or 3) and/or turkey herpesvirus (meleagrid herpesvirus 1). This monograph applies to vaccines intended for administration to chickens and/or chicken embryos for active immunisation." **Proposed change:** Please reword as follows: "The efficacy of each of the **protective** components of a vector vaccine shall be demonstrated. ~~Immunogenicity tests described in relevant Ph. Eur. monographs (i.e. for corresponding live vaccines) shall be performed and vector vaccines should comply with the requirements. If monograph requirements for immunogenicity cannot be met, the benefit-risk evaluation may still be positive if the safety of the vector vaccine is superior to that of the live vaccine and depending on the level of protection shown."~~	
213-215	2	Comment: We would welcome clarification if this refers to booster vaccination with vector vaccine, not with conventional vaccine with the same antigen. If this could be clearly stated that would be appreciated.	Not accepted. The term 'booster vaccinations' is intended to be general and could indicate any type of booster vaccine/vaccination schedule that is used in order to achieve particular claims.