28 January 2022
EMA/CVMP/IWP/532516/2021
Immunologicals Working Party (IWP)

Overview of comments received on 'Draft revised guideline on data requirements for multi-strain dossiers for inactivated veterinary vaccines' (EMA/CVMP/IWP/105506/2007 Rev. 2)

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

Stakeholder no.	Name of organisation or individual
1	European College of Poultry Veterinary Science (ECPVS)
2	AnimalhealthEurope

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	• ECPVS welcomes any initiatives that promote the availability of safe and efficacious veterinary medicinal products that contribute to the effective control of significant infectious diseases to safeguard poultry health and welfare, and public health. • Avian influenza vaccination is not currently widely used in Europe for AI control, with the agreed concept of early detection of infected flocks and their depletion with rapid return to country and region freedom to maintain animal health and allow free international trade in poultry and poultry products. • Strategic vaccination for avian influenza may need to be considered at a European and global level through OIE if current control measures do not give effective control if the epidemiological pressure of the infection changes. • In such a scenario in terms of poultry the proposed guidelines have the potential to impact in the development or availability of avian influenza vaccines if it is possible through surveillance to identify quickly subtypes that should be considered for targeted and appropriate emergency vaccines paralleling the process used in some countries for producing the annual human influenza vaccines. • There may also be opportunities for the same approach to be followed for other infectious diseases.	Noted

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	• If safe, effective and targeted vaccines can be developed and be made available in a timely manner in specific circumstances through the procedures outlined in the proposed guidelines then this approach would have the support of ECPVS	
2	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. A separate EMA guideline "recommendation on the submission of multi-strain dossier applications for vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD) [EMA/43283/2010]" exists. Within the scope of extending the multi-strain dossier approach to other viral and bacterial diseases, does the CVMP envisage to also update this guideline?	The need for an update of the existing procedural recommendation (EMA/43283/2010) in line with the changes in the regulatory framework for multi-strain dossier applications is acknowledged and will be considered by the Agency.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 85-86, 143-144	2	"Each multi-strain dossier is applicable **only to one** virus species, bacteria genus or **vector** for a given disease;.." **Comment:** The current guideline already describes the possibility to apply for a multi-strain dossier approach for vaccines produced by biotechnological processes such as vaccines obtained by purification or controlled expression of genes, virus-like particles, virus-empty capsid particles. The current guideline therefore allows to apply for a multi-strain dossier approach when using the same vector to express one protein from different strains of the same virus (*e.g.* BTV, one construct per serotype), if the manufacturing process is identical for each construct. However, in such situations, could it be envisaged that vaccine safety demonstrated with a "high amount of antigen content" for a vector expressing one protein could be used to demonstrate safety for the same vector/same max content but expressing two proteins from the same strain or from different strains of the same virus (assuming the total antigen content of any new combination would be lower than the amount of antigen shown to be safe)? In addition, could it be envisaged that safety data from a construct expressing a ruminant viral protein (*e.g.* BTV) could be used to demonstrate safety for a new vaccine using the same vector for expressing another ruminant virus, assuming both viruses are manufacturing according to the same production method? It may be worth to expand how to address such potential situation.	Not accepted. The vaccine safety demonstrated with a "high amount of antigen content" for a vector expressing one protein cannot be used to demonstrate safety for the same vector/same max content but expressing two proteins from the same strain or from different strains of the same virus as the method of preparation would not be the same for all vaccine strains. Therefore, the definition of a multi-strain dossier does not apply. The question related to the demonstration of safety (safety data from a construct expressing a ruminant viral protein could be used to demonstrate safety for a new vaccine using the same vector for expressing another ruminant virus) is out of scope of multi-strain dossier and should be addressed by the GL on platform technology.

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		If assurance can be provided that the production and formulation of a multi-component product is performed with maximal standardisation (i.e. defined quantity of ingredients other than the antigens and the same volume of one dose whatever the number and quantity of antigens included in the vaccine), and if appropriate justification is provided, could the scope of the multi-strain dossier approach then be expanded to bi-/multi-valent products, especially if the additional antigens can be added to the formulation in a fixed composition (*e.g.* bivalent vaccines containing both equine influenza virus and tetanus toxoid)? This question also aligns to the reference in the concept paper to the AnimalhealthEurope request for the possibility to apply the multi-strain approach to multi-component dog and cat vaccines. It may be beneficial to address the latter in the Guideline.	The definition of a multi-strain dossier in the draft Annex to the Commission Delegated Regulation amending Annex II to Regulation (EU) 52 2019/6 on veterinary medicinal products is restricted to only one virus species, bacteria genus or vector for a given disease. The combination of a multi-strain vaccine with another antigen is still possible provided that the requirements for combined vaccines and associations of IVMPs (EMA/CVMP/IWP/594618/2010) are fulfilled. The association GL may be revised in the future if needed.
Lines 124-126, 128-131, 133-135	2	"According to the epidemiological situation where the vaccine is intended to be used, **a number of strains could be selected** from those included in the dossier to formulate a final product." **Comment:** For existing infectious diseases for which a lot of knowledge about circulating/variable distribution of strains of different viruses or bacteria in the field is available, it is considered appropriate/relevant to select a maximum number of strains in the dossier to formulate the final product. However, how will this work for new infectious diseases for which this knowledge is not available at the moment of vaccine development and authorisation? In such situations, could it be	Accepted. Section 11. Variation to increase the maximum number of strains is added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		envisaged to cover the vaccine safety with "high amount of antigen content" for the "first strain", with the idea to cover the addition of new strains (assuming the total antigen content of any new combination would be lower than the amount of antigen shown to be safe) without the need to generate additional safety data? It may be worth to expand how to address such potential situation.	
Lines 133-134	2	*The authorisation for a multi-strain dossier will specify the strains that may be included in the final product as well as the maximum amount and number of strains"* **Comment:** It is anticipated that a manufacturer may need to expand the maximum number of strains or antigen content of a previously authorized multistrain vaccine, *e.g.* whenever an emerging strain becomes epidemiologically relevant/threat and should be added to multistrain vaccine already containing the maximum strain number compared to the others and this would be more than the maximum antigen content. It is assumed that it would be feasible to change the antigen contents by means of a variation to the multistrain dossier (providing safety data). Similarly, flexibility is being requested in the situation where the applicant aims to increase the maximum number of strains to the multistrain dossier. As long as the maximum antigen content has not been exceeded by the addition of a new strain, it should be justified to not generate additional safety data (and only generate efficacy data). In the case of an increase in the maximum antigen content of the final product, additional safety data will need to be generated.	Accepted. Section 11. Variation to increase the maximum number of strains is added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: **"(…/…)** **It is possible to increase the maximum antigen quantity and number of strain authorised for a multi-strain vaccine by submission of a variation. The data to be provided is such that the requirements described in this document would be fulfilled for the updated larger antigen quantity (i.e. additional safety data) and / or strain number (i.e. efficacy and/or safety data)."**	
Lines 141-142	2	**Comment:** Clarifications were brought into the guideline to address the responsibility for defining the most appropriate combination of products with regard to epidemiological situation in the field (the responsibility lies with the applicant) and then confirmation of the eligibility by EMA. To address this point, it should be clarified on which grounds this work of demonstration of eligibility should be done (bibliographical data, worldwide reference organisations, recent data, the duration of validity of data submitted…)	Not accepted. Eligibility for the multi-strain dossier approach shall be confirmed by the Agency before submission of the application. The criteria have to be defined by the Agency.
Lines 145-148	2	*The relevance of the strains with regard to European current epidemiological situation shall be shown - The need for a rapid or frequent change of strains … due to the current epidemiological situation in the field shall be justified* **Comments:** considering	Partly accepted. "The relevance of the strains with regard to European current epidemiological situation and the epidemiological situation that might occur in the future shall be shown"

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		• the overall process duration (time to fulfil the GDL requirement and registration process from eligibility to licence) . • The intend of the GDL (concept paper 140-142 "*to contribute to increase veterinary vaccine availability by authorising vaccine strains that might be envisaged or needed to deal with a particular disease situation in the field, and thereby benefit public and animal health*") • The European Commission intent for better preparedness and response to emerging disease The relevance of the strains should not consider the current epidemiological situation at time of eligibility process but envisaged the epidemiological situation that might occur at time of approval and the following years of vaccine use. **Proposed Change:** *The relevance of the strains with regard to European ~~current epidemiological situation~~ **dynamic epidemiology** shall be shown -* *The need for a rapid or frequent change of strains … due to the ~~current epidemiological~~ **dynamic epidemiology** situation in the field shall be justified*	
Lines 145-149	2	**Comment:** To facilitate the eligibility process, a non-exhaustive list of products eligible to multi-strain approach may be proposed and managed as an annex to this guideline (as already done for other topics such as extraneous agents).	Not accepted. In the future, a list of active substances declared eligible by the Agency may be published on EMA website.

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Line 149	2	**Comment:** Could it please be confirmed that an eligibility request shall always need to be submitted to CVMP?	An eligibility request shall always need to be submitted to the Agency. The COMMISSION DELEGATED REGULATION (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council states that for new applications to multi-strain dossier marketing authorisations where no authorised multi-strain vaccine already exists for a particular virus/bacterium/disease, eligibility for the multi-strain dossier approach shall be confirmed by the Agency before submission of the application
Line 152	2	The multi-strain approach is still applicable to marketing authorisation applications for inactivated vaccines against avian influenza, blue tongue disease and foot-and-mouth disease. **Comments**: please specify that these applications are exempted from the eligibility process (previous section) **Proposed Change:** The multi-strain approach is still applicable to marketing authorisation applications for inactivated vaccines against avian influenza, blue tongue disease and foot-and-mouth disease and exempted from eligibility process.	Accepted.
Lines 169-171, 342-344	2	"The multi-strain dossier is obtained through a variation procedure in order to convert a dossier of an existing vaccine (containing **one** or more strains already authorised) to a multi-strain dossier and therefore no additional data have to be provided." **Comment:** It should be clarified how a multi-strain dossier for a vaccine containing only one strain may be created.	Not accepted. An applicant can apply for a multi-strain dossier even if he has only sufficient data for one strain. When data for other strains are available, he can add these strains to the multi-strain dossiers taking into account the requirements of section 8. Addition or replacement of strains to the multi-

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			strain dossier. In this case, the vaccine will contain only one strain to be selected among the strains of the portfolio.
Line 207-210	2	"The blending should be standardised. The quantity of the ingredients, other than the antigens, and the volume of one dose of vaccine should be the same whatever the number and quantity of antigens that are included in the vaccine. However, the volume of the antigen phase may be adjusted with **water or saline** solution if necessary." **Comment:** Adjustment of the volume should be done with a solution that best suits. A neutral term instead of water or saline would be preferred. In addition, there might be the situation where the volume of one dose is different, if the same product is intended to be used in different target species. As long as all other criteria are met, this should be considered acceptable and fitting the scope of the guideline. A rewording is therefore proposed. **Proposed change:** The blending should be standardised. The quantity of the ingredients, other than the antigens, and the volume of one dose of vaccine should be the same whatever the number and quantity of antigens that are included in the vaccine. However, the volume of the antigen phase may be adjusted with ~~water or saline~~ **a suitable** solution if necessary. In addition, in specific situations (e.g. vaccine intended to be used in different target species) and if justified, it might be appropriate to have different dose volumes per target species.	Partly accepted. A reference to the Questions and Answers document is included in the document to deal with specific situations (e.g. vaccine intended to be used in different target species).
Lines 244-247	2	**Comment:** "*Batch-to-batch consistency data should be provided according to Commission Delegated Regulation (EU) 2021/805 amending Annex II to*	Accepted. See below

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		Regulation (EU) 2019/6 on veterinary medicinal products." It should be clarified whether batches to demonstrate consistency may consist of any combination of strains possible within the concept of the respective multi-strain dossier.	
244-247	2	**Comment**: There are no further details regarding the batches to be included in the batch to batch consistency. **Proposed change:** "**For finished product batch to batch consistency, a similar approach as for stability is proposed which are considered equivalent:** **Or, the demonstration of consistency of each strain formulated as a vaccine containing only this strain is available** **Or, the demonstration of consistency of a multi-strain vaccine. In this case, the study shall be carried out using three batches manufactured preferably with the maximum number of strains proposed within the multi-strain dossier application. The three batches tested must contain the same strains.** **Or In the case of marketed finished products which contain strains not previously approved in Europe , the BRPs of the first three batches of a multi-strain vaccine containing the new strains should be submitted on completion** Can the intention of CVMP be confirmed in this regard and be added into the guideline wording please?	Accepted. Proposal slightly amended.
Lines 261-263	2	**Comment:** Depending on the product (galenic form, conditions of storage, formulations, nature of active substance…) the stability can be ensured whatever the strain used. Indeed, existing supportive stability	Not accepted. Stability test for the finished product is a requirement of Annex II section IIIb.2.G. Furthermore, a new strain can be introduced very quickly without providing

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		data on finished products formulated with strains already authorised could be used to justify not to perform new stability studies on a strain close to the ones for which stability data are available. This could allow to be reactive and rapidly introduce a relevant strain (considering the duration of real-time stability studies and the availability of safety and efficacy data). Extrapolation of data or reduced set of data could therefore be considered/possible based on scientific justifications. **Proposed change:** *In the case of marketed finished products which contain strains not previously tested in stability studies, additional real-time studies on three batches of a vaccine containing only this new strain or a multi-strain vaccine containing the new strains should be performed and submitted on completion* ***unless justified.***	the corresponding stability study as the shortest shelf-life for the currently authorised strains is applied in the meantime.
Line 270	2	*7.2. Safety documentation (Section IIIb.3 Part 3)* *The tests should be carried out using a batch manufactured with the* ***maximum amount of antigen to be included in any vaccine combination****, unless there is a fixed target antigen amount at the formulation step.* **Comment:** As previously commented (lines 124-126, 128-131, 133-135), could it be envisaged to cover the vaccine safety with "high amount of antigen content" whatever the number of strains, with the idea to cover the addition of new strains (assuming the total antigen content of any new combination would be lower than the amount of antigen shown to be safe). For this purpose, it is suggested to use the same wording as in line 197. **Proposed change:** The tests should be carried out using a batch manufactured with the maximum ~~amount of antigen~~ **antigen content** to be included in	Accepted.

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		any vaccine combination **(whatever the number of strains)**	
Lines 280-281, 321-322	2	**Comment:** To avoid misunderstanding, could it please be confirmed that the GCP requirement for safety studies conducted in 3rd countries are being lifted in this regard?	Not accepted. Out of scope of the guideline
Lines 311-318	2	**Comment:** If an indicator of protection is used, the correlation between indicator and protection must be demonstrated in pre-clinical trials. If this information is already available in literature, animal trials should be avoided for animal welfare reasons. **Proposed change:** If an indicator of protection is used, the challenge may be omitted. For an indicator to be acceptable as a correlate of vaccine efficacy, it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator for protection should be shown to play a substantial role in the immune response, relevant for protection of the target species against the disease concerned. It must be demonstrated that the level of response obtained for the indicator in clinical trials is equal to the one observed in vaccinated animals at the time of challenge in pre-clinical trials and for which protection was demonstrated. **If correlation between the indicator and the protection is already known from literature, the reference should be included in the dossier and the additional demonstration in animal trials is not necessary.**	Partly accepted. Text amended. The indicator of protection has to be defined by challenge in pre-clinical trials. The reference to literature is acceptable but not sufficient to show a correlation between the indicator and the protection because the protocol of the published studies will certainly be very different from those provided in the dossier: target species, serological or other tests used, protection observed (parameters followed, level of protection),…

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Lines 342-344	2	**Comment:** *"The multi-strain dossier is obtained through a variation procedure in order to convert a dossier of an existing vaccine (containing one or more strains already authorised) to a multi-strain dossier and therefore no additional data have to be provided."* Please clarify how a multi-strain dossier for a vaccine containing only one strain may be created. In addition, confirmation should be obtained on whether a variation procedure could also be applied to convert different existing vaccines into one MS dossier.	Point clarified. An applicant can apply for a multi-strain dossier even if he has only sufficient data for one strain. When data for other strains are available, he can add these strains to the multi-strain dossiers taking into account the requirements of section 8. Addition or replacement of strains to the multi-strain dossier. In this case, the vaccine will contain only one strain to be selected among the strains of the portfolio. The possibility to convert different existing vaccines into one MS dossier is mentioned in section 9. Multi-strain dossier obtained by the combination of authorised vaccines. It is clarified that a variation procedure is the suitable regulatory mechanism for combining existing MAs into a multi-strain dossier.