6 December 2018
EMA/CVMP/IWP/235788/2018
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)' (EMA/CVMP/IWP/105506/2007-Rev.1)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope (AhE)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the changes made to the Guideline, as well as to the "responses to questions" document. Collectively, these documents provide the necessary clarity on the very useful (multi-strain) concept. Multiple companies have now successfully used the approach to register BTV and FMD vaccines. Influenza A virus causes avian influenza (AI) which is already included in the scope of this guideline. However, it also causes diseases of very similar nature in other species such as swine, equine and canine. Therefore, for these indications there is also a need for a similar type of approach (e.g. marketing authorizations including multiple vaccine strains that can be selected depending on the epidemiological situation and also a need for possible rapid and frequent changes in the vaccine strains). AnimalhealthEurope would appreciate the authorities considering the extension of the concept to influenza A viruses in general (avian, swine, equine and canine). AnimalhealthEurope understands that this may need the revision of legislation and would appreciate that this proposal is considered for the upcoming change of legislation (the comment has been shared during the review of the pharmaceutical legislation as well), knowing it impacts only the content of the annexes, which is not yet finalised. Next to influenza A viruses in general, it will be very valuable, if this concept of multi-strain dossiers could be extended to any other vaccine that protects against disease(s) caused by several	The current legislation (Dir. 2001/82/EC, Annex 1, Title IV) restricts the use of the multi-strain dossier approach to vaccines against BT, FMD and AI. If the revision of the legislation takes into account the comments of AhE, the CVMP/IWP will have the opportunity to propose a redrafting of the guideline.

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	serotypes/subtypes within a family of viruses (e.g. Infectious Bronchitis in chickens) or other microbial organisms (e.g. *Streptococcus suis*). That would allow the manufacturers to: • register multiple strains of pathogens of the same family and produced by a sufficiently similar process within the same (multi-strain) dossier and • adjust the vaccine strain composition within the dossier to specific epidemiological situations, not only over time, but also at the same time in different locations. In AnimalhealthEurope's opinion, this fits very well within the "Veterinary Vaccines availability initiative".	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Questions and answers document – Question 3.	1	Comments: The current document states: “Concerning different dose-volumes for the same target species, it is considered this could not be accommodated within the framework of one multi-strain dossier. Safety and efficacy could be demonstrated for monovalent products at different dose-volumes but the safety and efficacy for combination products at different dose-volumes is considered too complex to address within one dossier.” We agree with the above, but (provided the need is appropriately justified), we recommend that the document still allows the flexibility to have different dose-volumes for different strains within the same target species, but only for multi-strain dossiers covering monovalent vaccines. Including this possibility would still be beneficial for all parties, and is in AnimalhealthEurope’s opinion fully manageable (both for companies and the authorities), even within the currently revised multi-strain guideline. Proposed change: **3. Is it possible to have different dose-volumes for the same target species?** Concerning different dose-volumes for the same target species, it is considered this could not be accommodated within the framework of one multi-strain dossier**, with the exception of multi-strain dossiers covering only monovalent vaccines**. Safety and efficacy could be demonstrated for monovalent products at different dose-volumes but the safety and efficacy for combination products at different dose-volumes is considered too complex to address within one dossier. **Therefore, the possibility to register vaccines with**	Accepted.

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		different dose-volumes for the same target species is restricted to multi-strain dossiers covering monovalent vaccines only.	
Guideline document: lines 249, 251, 256, 259 and 260	1.	Comments: There is a need to review some of the numbering quoted in the guideline. Proposed change: (lines 249, 251,256, 259 and 260 on page 8 – should refer to "5.x" instead of "6.x").	Accepted.
Guideline document: lines 166-168	1.	Comments: The current document states: "A specific test for identification (e.g. monoclonal antibodies, sequencing) should be available for each antigen. The development of *in vitro* methods to quantify the antigens (e.g. ELISA, PCR) is recommended as it will normally facilitate the control of a vaccine containing different strains". "Monoclonal antibodies" and "sequencing", *per se,* are not a test. Moreover, identification can also be achieved using specific polyclonal antisera. Likewise, sequencing is not necessarily needed for the purpose (having a positive PCR result – on a sequence specific of the virus "type" - would typically be sufficient). To allow for all possible methods that can be used for identification AnimalhealthEurope proposes to state "e.g. using immunological methods, nucleic acid amplification techniques (NAT)". This covers both classical as well as novel methods. Also, other immuno-assays than just ELISA are available for antigen identification and quantification, e.g. the high-throughput AlphaLISA and comparable platforms. Finally, just PCR (id est, qualitative PCR) may not be the best example of a (unique) test for antigen quantification but quantitative NAT such as qPCR may be suitable.	Accepted.

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		We suggest clarifying the wording as follows: Proposed change: "A specific test for identification (using e.g. ~~monoclonal antibodies, sequencing~~immunological methods or nucleic acid amplification techniques [NAT]) should be available for each antigen. The development of *in vitro* methods to quantify the antigens (e.g. ~~ELISA~~ quantitative immuno-assay~~, PCR,~~ quantitative NAT) is recommended as it will normally facilitate the control of a vaccine containing different strains".	
Guideline document: line 98	1.	Comments: To allow for future innovative vaccines produced by biotechnology processes the following change of the text is proposed: Proposed change: It covers conventional inactivated vaccines and vaccines produced by biotechnology process **~~including~~such as ~~subunit~~** vaccines obtained by purification or controlled expression of genes, virus like particles, virus empty capsid particles. NB: in case this proposal is accepted the following change of the title of this GL should be considered: **Guideline on data requirements for multi-strain dossiers for inactivated vaccines and vaccines produced by biotechnology process against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)**	Accepted. Not necessary: The definition of" inactivated vaccine" in section 3 covers this aspect.
Guideline document: lines 39 and 69 Guideline document:	1.	Comments: "Vaccines against AI, BT and FMD diseases represent a special case in terms of the need for rapid and frequent change in the strains included". This statement is true and was indeed experienced by manufacturers and authorities. Currently this guideline does not address properly the addition of new emerging strains reducing	Not accepted. The sentence "It is envisaged that submission of a multi-strain dossier would not be appropriate in response to an emergency situation" means that if an outbreak appears with a new (emergent) strain not already included in a multi-strain dossier, the

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line 119		greatly the value of such registration frame (Currently, there is a need to have separate authorisation(s) for (a) new strain(s) under emergency situation. As seen in the past, as some combination are needed by the field and as some exemption for studies are allowed in this guideline, the specific situation of the n10th strain added to the MS should be including here (indeed once quality/efficacy features are developed for more than 2 or 3 strains, the lack of scientific knowledge for a new strain is probably not as impacting as feared). This is already implied within Q/A No.5. Proposed change: Page 3 L69: **Except in very specific cases (addition of a new strain to the authorised list of minimum 2-3 strains)** it is envisaged that submission of a multi-strain dossier would not be appropriate in response to an emergency situation. The minimum… Page 5 L 119: * **Except in very specific cases (addition of a new strain to the authorised list of minimum 2-3 strains)** vaccines authorised under exceptional circumstances are excluded	submission of a variation to introduce this strain in the MS dossier (according to section 6 of this GL) might be more complex and longer than defining the minimum data requirements for an authorisation under exceptional circumstances. Nevertheless if, within a reasonable timeframe, the applicant wishes to introduce a new strain necessary to fight an emergency in a MS dossier and is able to demonstrate that the requirements of section 6 of the GL are fulfilled, the submission of a variation of the MS dossier is acceptable. Q/A 5 deals only with the absence of efficacy data for one or more target species when a new strain is added. This is possible as long as the indications for use are limited and the product information clearly reflects the situation.
Guideline document:lines 113 and 250	1.	Comments: Of note, replacement of a strain should not be so frequent nor encouraged. Those diseases are quite variable and an old strain may fit immunologically with the new epidemic situation. The strain portfolio would keep growing but its regulatory maintenance should not be a burden (any request for update should be proportionate and work on few strains as an example). This will be very welcome when dealing with efficacy. Proposed change:	The GL does not encourage the replacement of a strain. It gives only the possibility to industry to update the vaccine when necessary and for once provides the flexibility that is usually requested by the applicants.
Guideline document: lines 209	1.	Comments: Some extrapolations are listed as possible “based on scientific justification”. IWP/CVMP should take benefit of the Q/A document to	The IWP can agree with the comment and would like to ask AhE to propose clear examples to be added in the Q/A document.

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and 233		give some examples of what seems acceptable based on their experience (such information can easily be anonymised and would be very useful to better understand what the very broad –so difficult to predict- acceptability is). Such an exercise has been done for example by the EU commission in guidance for the Nagoya protocol and was found impactful and useful. Proposed change: add clear example in the Q/A.	
Guideline document: line233	1.	Comments: Extrapolation from one strain to another should also be considered. After developing some strains for the same disease, the pattern may appear quite similar. Asking all data for all features may just divert resources from work on possible threatening strains. Proposed change: Include extrapolation among strains in the GL and give some more exemplified situations in the Q/A document.	The IWP can agree with the comment and would like to ask AhE to propose clear examples to be added in the Q/A document.
Questions and answers document – Question 7 Guideline document:233	1.	Comments: The recognition of extrapolation to other species/categories is welcome. Being a Q&A document, giving more flexibility in wording and content, examples based on already known vaccines from several manufacturers (AI or BTV) are needed otherwise we do not know what may be specifically accepted for extrapolation (e.g. from cattle to buffalo)? If the formulation is already known and used in buffalo and a BTV vaccine is registered for cattle, buffalo should be accepted as a species for safety aspects. For efficacy a serology pattern may be enough if the SPC appropriately state the limited data considered. We would welcome such an example that allows not only to state extrapolation is possible but also explains how this could be done.	The IWP can agree with the comment and would like to ask AhE to propose clear examples to be added in the Q/A document.

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		Proposed change: Include extrapolation among strains in the GL and give some more examples in the Q/A document.	