15 March 2010
EMA/33491/2010
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), blue tongue (BT) and foot and mouth disease (FMD)' (EMEA/CVMP/IWP/105506/2007-CONSULTATION)

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

Name of organisation or individual
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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	IFAH-Europe welcomes the publication of the draft Guideline on the multi-strain dossier following revision of Annex 1 to Directive 2001/82/EC as amended by Directive 2009/9/EC to include the possibility of this kind of authorisation. The initiative will certainly advance the submission of applications for the listed diseases if the final Guideline takes account of the comments below.	
	Additional products, such as equine/swine influenza, infectious bronchitis, and multi-component dog and cat vaccines are scientifically justified and relevant for the multi-strain approach. Therefore, we would encourage the CVMP to consider vaccines for other relevant diseases to be covered by this proposal. The statement of the directive on multi-strain dossiers[1] does not appear to exclude the possibility to apply this approach for other veterinary medicinal products.	The current legislation (Dir. 2004/28/EC, Annex 1, Title IV) restricts the use of the multi-strain dossier approach to vaccines against BT, FMD and AI
	IFAH-Europe would also suggest broadening the scope of this GL, currently restricted to inactivated vaccines, to include single cycle, live deletion mutant, subunit and similar vaccines. As stated in the introductory section, a multi-strain dossier is appropriate *where the same information is relevant for vaccines produced using any of the strains*. We see no distinction for other relevant vaccines. If the initiative is to reduce the administrative burden, we would recommend the IWP/CVMP to consider	As there is currently no experience with multi-strain dossiers, the scope of the GL is restricted to the vaccines which are the most likely to become subject of a multi-strain dossier

[1] *"B. MULTI-STRAIN DOSSIER*
For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Sections B ***and C*** *on active substances the concept of the use of a multi-strain dossier is introduced."*

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	extending the scope of the GL.	
	Regarding administrative issues, it should be noted that although the GL does not address any of these, references to similar (but different) products under the same MA may affect trade name, its relation to the composition, labelling and even batch control. These remarks are important regulatory aspects to be considered. Ideally, an Annex to the GL addressing particular aspects of each virus included in the GL would provide better guidance to both regulators and industry. IFAH-Europe suggests therefore the establishment of a joint regulatory and industry working group to address these issues and work towards improvement of the current draft GL.	The CVMP/IWP issues Guidance on scientific aspects only. The administrative aspects are covered by Commission, EMEA and national authorities.
	Finally, some parts of the GL appear too general and re-stating general regulatory approaches for all vaccines, whereas it does not address the specific challenges faced by industry on regulatory aspects such as validation of the potency requirements for FMD vaccines. Many of the issues addressed in the CVMP Position Paper on requirements for Vaccines against Foot-and-Mouth Disease (EMEA/CVMP/775/02) should be integrated in the Multi-strain GL or at least cross-referred to relevant sections on Quality, Safety and Efficacy. Given the logistical difficulties for performing challenges with FMD vaccines, we would also propose the establishment of a specific joint working group to address the potency/efficacy requirements of the GL.	The problem is well known, but could not be solved on the level of this GL at this stage. Additional scientific documents from EMEA and Ph.Eur. should be considered as well.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	**Stakeholder number** *(To be completed by the Agency)*	**Comment and rationale; proposed changes** *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	**Outcome** *(To be completed by the Agency)*
Line 44		*"Following experience with the authorisation of avian influenza…"* Comment: The concept of a multi-strain dossier arose before the experience with avian influenza vaccines and came about following the approach of the UK and subsequently German Authorities with FMD vaccines in 2000 and 2003 respectively. Proposed change (if any): *"Following recent experiences with authorisations such as FMD vaccines in the UK and Germany and avian influenza vaccines at the EMEA level, the concept of…"*	accepted
Lines 69-70		*"It describes the requirements that should be presented in the analytical, safety and efficacy of the dossier."* Comment: IFAH-Europe considers that administrative issues like labelling and batch control are important regulatory aspects to be considered. Proposed change (if any): We would suggest the establishment of a joint regulatory and industry working group to address these and other issues.	accepted

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Lines 72-73 and 84-86		*"…submission of a multi-strain dossier would not be appropriate in response to an emergency situation."* Comment: Given that the GL does not address the emergency situation, we would request further discussion on the mechanism for fast-tracking a new MSV into an existing MA. Commission Regulation 1234/2008 foresees a line extension procedure for the addition of new master seeds to a multi-strain dossier, but such procedure would certainly be too lengthy for emergency situations or where annual strain updates are necessary (as for FMD vaccine). A guideline for an accelerated regulatory procedure for the addition/substitution of a strain already exists for equine influenza vaccines (EMEA/CVMP/112/98) and similar work is undergoing for swine influenza. These documents could be used as a starting point for the development of guidelines for products authorised under a multi-strain dossier.	Concerning the exchange of MSV, scientific guidance was already issued by CVMP/IWP. Again, accelerated procedures are administrative issues and are not subject of an scientific GL.
Line 77		*"This guideline does not apply to live vaccines"* Comment: It is not clear if this statement means that the GL is limited to conventional inactivated vaccines or it also covers virus-like particle and other recombinant vaccines (although live they do not contain any live BTV virus). We would recommend consideration of these types of products, as there is no apparent reason for exclusion of live FMD vaccines, for instance.	As there is currently no experience with multi-strain dossiers, the scope of the GL is restricted to the vaccines which are the most likely to become subject of a multi-strain dossier

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		Furthermore, as the revised Annex I does not state that the multi-strain dossiers should be restricted to inactivated vaccines, we would propose extending the scope of the GL to "live vaccines where appropriate". In any case the use of recombinant vector vaccines should not be excluded, considering that in such cases each of the viral strains must satisfy the requirements of Directive 2001/18/EC. Proposed change (if any): *"This guideline does not apply to live classical vaccines, but recombinant/vectored vaccines may be admitted if in accordance to EMEA/CVMP advice."*	
Lines 87-101		*4.Definitions* Comment: The distinction between multi-strain dossier and MA for a multi-strain dossier is not clear. The definition of the "dossier" should be amended to consider that the dossier consists of quality, safety and efficacy data and that may be from one or more strains never authorised before, from an existing multi-strain MA with new data regarding the addition or replacement of a strain, or from existing authorised vaccines containing one or more serotypes or strains of the same virus. For clarity, we would suggest the amendment below. Proposed change (if any): *"A multi-strain dossier covers a number of different strains of the same virus produced according to the seed lot system. According to the current disease situation a number of antigens could be selected from those included in the dossier ~~and covered by the associated authorisation up to a specified~~*	accepted

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		~~and maximal limit,~~ to formulate a final product. The formulation of the final product should be specified in the dossier and should include the maximum antigen content per strain and the maximum number of antigens in accordance to the safety data submitted with the application."	
Lines 130-131		*"In the case of an increase in the maximum number of strains to be included in the final product a new multi-strain dossier needs to be submitted."* Comment: The requirement to submit a new multi-strain dossier in case of an increase in the maximum number of strains of the final product is too strict. The composition of the multi-strain vaccine is determined by the batch potency test data of the single vaccines and the safety of the product with more strains can easily be confirmed by testing. A new MA application would increase the administrative burden without any clear justification. IFAH-Europe considers more appropriate to handle the increase in number of strains through a Type II variation. Proposed change (if any): *"In the case of an increase in the maximum number of strains to be included in the final product a ~~new multi-strain dossier~~ Type II variation needs to be submitted with all appropriate supportive data and updates required in the dossier."*	Not accepted. The proposal does not comply with the current EU-legislation
Line 142		*"…specify the quantity for each antigen."* Comment: Please see proposal for amendment below and clarify if this quantity should be provided in volume or in biological activity.	

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		Proposed change (if any): *"…specify the minimum and maximum quantity for each antigen."*	accepted
Lines 148-150		*"The inactivation kinetics and tests for complete inactivation should be provided for all strains/subtypes separately, unless justification is provided that the inactivation process and/or the tests for complete inactivation are valid for other strains or legal provisions require regular validation for each batch (e.g. Ph.Eur. monograph on FMD)."* Comment: We propose to omit the reference to the exceptional Ph. Eur. monograph for FMD vaccines, since the requirement included herein to validate appropriate inactivation control test sensitivity for each batch produced, implies that inactivation control test validation data should be included in the dossier for all strains/subtypes separately anyway (through manufacturer's batch protocol information). However, in order to avoid uncertainties in the future, we would appreciate, however, that some guidance is provided on what type of data/justification would be sufficient to demonstrate that tests and kinetics can be extrapolated from one strain to another. Proposed change (if any): *"The inactivation kinetics and tests for complete inactivation should be provided for all strains/subtypes separately, unless justification is provided that the inactivation process and/or the tests for complete inactivation are valid for other strains*	accepted

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		~~*or legal provisions require regular validation for each batch (e.g. Ph.Eur. monograph on FMD)*~~. *Such justification may take the form of*… [to be indicated]… ".	
Lines 156-158		*"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."* Comment: Please note that to adjust for the standard volume, the volume of diluents will be variable. Proposed change (if any): *"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. The quantity of excipients (other than adjuvants) may vary to adjust for the variable antigen input."*	Not accepted. This proposal does not imply a production and formulation with maximal stanardisation.
Lines 159-161		*"As the concerned vaccines are inactivated, the applicant is strongly encouraged to target a fixed amount for each antigen at the formulation step."* Comment: Companies are aware that targeting *a fixed amount of antigen* is desirable, since this approach is not specific to multi-strain dossiers. However, this approach is not feasible for some multi-strain vaccines. For FMD vaccines for instance, antigen	

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		input will depend on the serotype, strain and targeted potency. Safety studies will be performed at the maximum possible antigen input that may be required to achieve a stated potency. For potency, batches will be formulated to achieve the expected level of potency based on experience and will be significantly lower than the one used for safety studies. Although not properly addressed in this draft GL, the fact that FMD vaccines may be manufactured to different target potencies is an important issue to be considered. Please see also comments to lines 270-272 and 279-287. Proposed change (if any): *"~~As the concerned vaccines are inactivated, the applicant is strongly encouraged to target a fixed amount for each antigen at the formulation step.~~"*	Further discussion at workshop with IFAH on 18 February 2010 and after first experience with the use of the GL is proposed.
Lines 172, 176, 194		Comment: These sections should be in line with the new Annex I of the EU Directive. Proposed change (if any): Line 172: *II. ~~E~~ D*; Line 176: *II.~~F~~ E* ; Line 194: *II. ~~G~~ F*	accepted
Lines 173-174		*"Some tests (e.g. inactivation tests and antigen quantification tests) may need to be validated individually for each strain."* Comment: We are of the opinion that small variations in the IPC test should be allowed. Furthermore, as stated on lines 148-150, kinetics should be required for each strain included in the	

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		dossier, unless justified. Proposed change (if any): *II.E D. Control tests during production* *The tests should preferably be the same for all strains. Any deviations in these tests need to be explained and justified. For critical tests ~~Some tests~~ (e.g. inactivation tests and antigen quantification tests), specific validation will normally be required ~~may need to be validated individually~~ for each strain.*	accepted
Lines 179-181		*"A specific test for identification should be available…"* Comment: This paragraph needs further clarification. It is not clear how the development of *in vitro* tests will facilitate the control of vaccine containing different strains and how antigen quantification would be performed in this test. Is a serological assay (as suggested by PhEur monograph for FMD) an *in vitro* test? Is the IWP/CVMP proposing to quantify the antigen (such as ELISA test) in the final product or perform potency tests or both? A section with statements on test to establish the identity of strains included in the vaccine and another section for the potency test of each strain would facilitate interpretation. Proposed change (if any): Please clarify.	Clarification added to the text

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Lines 184 and 239		Comment: The text should be aligned with the revised Annex I. Proposed change (if any): *"…manufactured (in compliance with section II.A to II.~~E~~ D of this guideline)…"*	accepted
Lines 187-193		*"The validations and specifications established through the potency testing of each monovalent vaccine can then be extrapolated to any multi-strain vaccine …"* Comment: This is a little confusing – it is understood that, because testing all possible combinations would be lengthy and expensive, the potency test should be done for each strain on a monovalent vaccine to simplify the process. However, to address the issue of potential cross-reaction there is also need to do validation on combinations. Hence, potency test on the final combined vaccine (whatever that combo may be) would still be necessary, in order to ensure there is no cross-reactivity or a level of cross-reactivity with whatever test system was used even using serotype defining antigens such as VP2 in BTV. It is difficult to be clear how this guidance helps as although initial development should be done on monovalent, the potency test validation for each would still need to include testing on combinations. Developing the validation of a potency test for a new strain in a multi-strain dossier will provide more confidence of absence of interference than carrying the work with monovalent vaccines. Furthermore, we have the impression that much of the guidance draws upon the recent experience of BTV vaccines	

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		without taking account of wider issues related to the other viruses. The guidance has not considered the specific difficulties of performing this validation for FMD vaccines according to Ph. Eur. Proposed change (if any): *"~~The validations and specifications established through the potency testing of each monovalent vaccine can then be extrapolated to any multi-strain vaccine containing a combination of these antigens (within the maximum number of antigens previously established).~~ The potency test for each monovalent vaccine should ~~however~~ be conceived in such a way that ~~any~~ cross-reaction between strains will be ~~avoided~~ limited as much as possible when the potency tests is applied to multi-strain vaccines containing these strains ~~(e.g. choice of VP2 specific of each BTV serotype, rather than of VP7 common to all BTV serotypes)~~. If cross-reaction cannot be avoided in an in vivo potency test, additional in vitro tests (e.g. serotype- or strain-specific antigen-ELISAs on finished product of the complete antigen bulk) may be introduced. Deviations from this principle need justification."*	accepted

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Lines 194-201		*II.G. Stability tests* Comment: It is understood that real-time stability studies are needed for all strains but this can either be as a monovalent product or as part of a combination. If so, it should be clearer that this is the case for the initial dossier, as one could register 5 strains with a maximum of 3 per vaccine and could interpret this as doing 3 batches of 3 strains but not covering all possible strains. Also it is not clear if the 3 batches would need to be the same strain combination or would it be possible to have 3 different strain combinations when registering more than 3 strains. Proposed change (if any): Please clarify.	Clarification inserted
Lines 195-196		*"If possible, the stability of each strain formulated as a monovalent vaccine shall be demonstrated."* Comment: The guideline should state clearly which approach is favoured. The wording *"if possible"* suggests that stability studies should be performed with monovalent products. However, the usual regulatory approach would be to use the largest combination of antigens. Further clarity on the preferred approach should	

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		be provided. Proposed change (if any): *"… corresponds to the shelf-life of the ~~antigen~~ formulated strain which has the shortest stability."*	accepted
Line 197		*"… corresponds to the shelf-life of the antigen which has the shortest stability."* Comment: The wording *"shelf-life of the antigen"* may cause confusion with antigen stability during storage prior to formulation. Proposed change (if any): *"… corresponds to the shelf-life of the ~~antigen~~ formulated strain which has the shortest stability."*	accepted

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Lines 208-209		*"The Applicant should provide justification of the in-process storage time of live and inactivated bulks and its influence on the stability of the final product."* Comment: There is no reason to mention these requirements in the multi-strain guideline as these are standard requirements also applicable to normal dossiers. Proposed change (if any): ~~*The Applicant should provide justification of the in-process storage time of live and inactivated bulks and its influence on the stability of the final product.*~~	accepted
Lines 237-244		*"… efficacy should be shown for each of these monovalent vaccines."* Comment: This approach is very welcome. Please consider addition of the following alternative. Proposed change (if any): *"… efficacy should be shown for each of these monovalent vaccines. Alternatively, the multi-strain vaccine containing all wished strains could be tested for efficacy."*	Not accepted. The cumulative positive effect of strains/subtypes in a multivalent vaccine may induce higher efficacy than as a monovalent vaccine.
Line 246		*"Possible known negative impact induced by certain strains*	

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		should be taken into account." Comment: Would it be sufficient to do this as a paper exercise or would clinical studies/lab animal model studies be required? If scientific paper exercise is not accepted, it would undermine the approach based on testing monovalent vaccines only. Proposed change (if any): Please clarify.	Clarification inserted in the text.
Lines 251-252		*"The efficacy of each vaccine strain shall be demonstrated for each category of target animal species, by each recommended route of administration…"* Comment: This is the standard wording of Directive 2001/82/EC and does not take into account the specific issues for some multi-strain vaccines. For FMD vaccines it states that we should establish efficacy for *each* category of *each* target species by *each* recommended route. This requirement is too strict and goes beyond the Ph.Eur monograph for FMD which requires only a cattle challenge for ruminants. Again it seems that there is no consideration on difficulties faced by manufacturers of FMD vaccines. The above requirement would demand efficacy studies in all species (i.e. pigs, cattle, goats, and sheep) in each category (i.e. pregnant, young, males). Routinely either 3PD50 or 6PD50 vaccines are manufactured, but FMD vaccines may be formulated to variable potencies depending on the demands of the	The reference of Ph.Eur. monograph on FMD is not relevant, as the monograph is intended to verify the quality of each batch, and hence not covering all aspects of the efficacy part of a MA dossier.

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		customer. Would these require separate MAs? Furthermore, how the use of different adjuvant systems within the same authorisation would be handled? Please consider our General comments regarding the establishment of a working group to address some of these issues.	
Lines 270-272 279-281		Comment: Please note that the antigen content in a multi-strain vaccine will not be the same for all strains included. The amount of antigen needed is determined in the efficacy tests done with monovalent vaccines. Due to interactions between different antigens in a multi-strain vaccine, the antigen content of an individual strain in the multi-strain vaccine may differ from the antigen content of the monovalent vaccine of that strain. The amount of an individual antigen needed in the multi-strain vaccine is that amount that produces the same potency test result as the monovalent vaccine of that strain with which efficacy has been shown. Hence the condition laid down in lines 270-272 and 279-281 is not correct. Proposed change (if any): *"Based on the condition that the key composition of the final product is not changed by the addition or replacement of a strain/subtype of the multi-strain dossier (e.g. maximum number of antigens~~, same antigen content~~ and same*	Not accepted. The whole multi strain approach relies on the fixed antigen content.

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		composition of adjuvants and excipients)…"	
Lines 272-274		Comment: Appropriate accelerated procedures for the addition or substitution of a strain(s) in a multi-strain dossier in case of emergency or in case of an annual update of vaccine strains (e.g. for FMD) are necessary. Please also refer to our comment regarding lines 72-73 and 84-86 above.	Again, accelerated procedures are administrative issues and are not subject of an scientific GL.