10 September 2015
EMA/CVMP/IWP/254498/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on the replacement of cell lines used for the production of immunological veterinary medicinal products' (EMA/CVMP/IWP/37620/2014)

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

Stakeholder no.	Name of organisation or individual
1	International Animal Health Organisation (IFAH)-Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes the opportunity to comment on this Reflection Paper. The paper provides useful guidance on the requirements for the replacement of cell lines used in the manufacturing process of IVMPs, but would benefit from harmonization of definitions and additional flexibility (see specific comments). Additionally there should also be harmonisation of the references to legislation (, *i.e*. refer to Dir 2009/9 or Dir 2001/82 as amended). The document could also benefit from reference to the already existing guideline on data requirements for the replacement of established master seeds (MS) already used in authorised immunological veterinary medicinal products (IVMPs) by new master seed of the same origin (EMEA/CVMP/IWP/105504/2007)	The harmonisation is done.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
37	1	This sentence is problematic as there could be situations where changes on the production process, while kept to the minimum possible, would still lead to the need for adjustments of the product specifications. Also, there could be situations where significant changes to the production process are required (in fact, a change from one defined cell line to another defined cell line is by itself a significant change), and adjustments of the product specifications are needed. As an example, an increased antigen content per dose may be needed as a result of a change of defined cell line. Insofar as additional quality, safety and efficacy data are generated to support the changes (as described in the current version of the draft reflection paper), this should be acceptable (and described in the paper). **Proposed change:** delete: "…without significant changes to the production process and maintaining finished product specifications". And address the changes in the relevant sections of the paper (as is already done, for example, on lines 112-117 and 143-146).	Not accepted. The proposed deletion of the sentence "…without significant changes to the production process and maintaining finished product specifications" states that a change of cell lines may lead to an increased content of antigen per dose. Such a consequence of change of a cell line will lead to a significant change of the final product specifications and requires a new license application as well as additional data on safety and efficacy. It is not the purpose of the reflection paper to bypass the criteria for new application being in line with current legislation.
43-44	1	**Comment:** Conditions for one or other option should be clarified (*e.g.* cells of same origin = variation, cells of different origin = line-extension).	Accepted.

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59-61	1	**Comment:** The scope should refer to the already existing guideline EMEA/CVMP/IWP/105504/2007 **Proposed change : This reflection paper contains complementary/additional information to the already existing guideline EMEA/CVMP/IWP/105504/2007, in the event it is not possible to replace the MCS by a pre-MCS or a post-MCS but needs to be replaced by a cell seed of the same defined cell line obtained from a different source or by a cell seed of a different defined cell line.**	Accepted.
60-61	1	**Comment:** Mixed definitions. **Proposed change:** This reflection paper applies to the replacement of a ~~defined~~ master cell seed (MCS) used to produce a vaccine by a MCS of the same **defined** cell line and to the replacement of a MCS by a MCS of **a** different **defined** cell line.	Accepted.
77-82	1	**Comment:** Mixed definitions. **Proposed change:** 5. Data requirements for the replacement of a MCS by a MCS of the same **defined** cell line. The replacement of a ~~defined~~ MCS by another MCS of the same **defined** cell line may have an impact on the finished product. A prerequisite for the acceptance for this change is therefore confirmation that the change of the **cell** seed does not change the finished product. The replacement of a MCS by another MCS of the	Accepted.

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		same **defined** cell line requires sufficient proof of the equivalence between the two	
90	1	**Comment:** Is this similarity in these parameters necessary. The assessment of the impact on the final product is the key factor.	Partly accepted. The message that the MCSs need to comply with the current provisions on quality (e.g. freedom of extraneous agents) is covered.
92	1	**Comment:** There is no requirement to have GMP or GLP for seed establishment. What matters is the fully tested MCS not the site at which it was maintained prior to testing. Whilst it may increase possible confidence in quality it is not essential, this should be deleted to prevent the creation of additional requirements. **Proposed change:** the site(s) where each MCS was maintained / established. ~~Wherever possible, the sites should be of comparable quality, e.g. laboratories run under GMP/GLP conditions or equivalent~~	Partly accepted. The message that the MCSs need to comply with the current provisions on quality (e.g. freedom of extraneous agents) is covered. GLP/GMP may be a useful tool.
94-97	1	**Comment**: In many cases the number of passages a defined cell line has obtained, under which conditions and in which media before arrival in a laboratory is often not known or not known precisely. In order to avoid future misunderstandings or discussion on the interpretation clarification is necessary. **Proposed change:** - the number of passages performed **since the defined cell line was obtained** in the production of	Accepted.

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		each MCS should be as close as possible. - the equipment and conditions of propagation **of both MCSs** should be similar. Larger differences (e.g. monolayer versus suspension culture) require further justification. - the media/solutions used for propagation **of both MCSs** should be similar, concerning composition and purity **unless otherwise justified, since a change in media/solutions composition could sometimes be useful to clear extraneous agents, such as RD114. In this case, and depending on the changes, new relevant safety and efficacy trials to support the changes may be needed.**	
98	1	**Comment:** The MCS may not have undergone treatments. **Proposed Change:** the treatments that both MCSs **may** have undergone (e.g. cloning,) need to be described as precisely as possible and should not be too different	Accepted.
107-108	1	**Comment:** MCS from the same origin may still have extraneous agents such as RD114 present.	Not accepted. The purpose of the exchange of the MCS is to replace a contaminated MCS by a non-contaminated.
112	1	**Comment:** Differences in the performance of both MCS should be acceptable if this does not impact final antigen parameters.	Partly accepted. The original text includes already this approach. Some clarification is added.
113-114	1	**Comment:** Amend to improve clarity.	Accepted.

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		Proposed change: Changes in the manufacturing process **should be kept to the minimum and**, if any **change** is needed, **it** need**s** to be described and justified.	
115	1	**Comment:** The removal of controls could be justified (e.g. test for a contaminant that is removed by the MCS change). **Proposed change:** The in process controls should remain unchanged or additional controls may be added. **Removal of controls may be justified if the reason for control has been removed by the change in MCS.**	Accepted.
122-124	1	**Comment:** Why is this additional testing necessary if the new MCS has proved negative for the viral contamination which provoked the change. **Proposed Change:** delete the paragraph	Accepted.
125-126	1	**Comment:** Stability requirements greater than those for a new product, which is not justified. At a maximum, the requirements should be no higher than those for a new product. Extract of the GL EMA/CVMP/IWP/206555/2010, Section 4. Stability tests: "Stability testing shall be carried out as specified in the Directive 2001/82/EC and in the European Pharmacopoeia monograph 0062 Vaccines for Veterinary Use on not fewer than 3 representative consecutive batches. The three consecutive production runs may be carried out on a pilot scale, providing this	Accepted with slight modifications.

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		mimics the full-scale production described in the application. The sterility of the vaccine has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test for container/closure integrity). Where bulk material is to be stored before formulation and final manufacturing, stability data should be provided." **Proposed change:** If the equivalence between the two MCS is sufficiently demonstrated, the stability results of ~~two~~ **three** pilot batches ~~and one full scale batch~~ produced with the new MCS are sufficient to grant the same shelf life to the finished product.	
136-139	1	**Comment:** The current wording implies that, if the equivalence of the two MCS is not demonstrated, this requires automatically new safety AND efficacy tests. There could be situation where only safety OR efficacy tests would be justified, depending on the data (and changes needed). Additionally full testing may not be necessary; Onset of Immunity and Overdose/Repeated Dose should be sufficient in many cases. **Proposed change:** If the equivalence between the two MCS is not demonstrated, laboratory safety and**/or** efficacy tests as required in Dir. 2009/9/EU, annex 1, Title II ~~should be provided~~ **may be required**. **A selected set of well-designed safety and efficacy trials may be sufficient to confirm target animal safety and efficacy. An onset of immunity challenge study against the concerned antigen(s)**	Accepted.

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		(i.e. the antigen impacted by the change of defined cell line) and a GLP overdose safety study in the most sensitive subcategory of animal species may be sufficient to address the safety and efficacy in the target species. Field trials should be performed in exceptional cases only, when the laboratory tests cannot confirm the safety and**/or** efficacy of the vaccine produced on the MCS of same **defined** cell line.	
147	1	**Comment:** All of the data may not be required as it is unaffected by the change. **Proposed Change:** All of the Part 2 data **affected by the change** required in Directive 2001/82/EC, annex	Accepted.
156-158	1	**Comment:** Stability requirements greater than those for a new product, which is not justified. At a maximum, the requirements should be no higher than those for a new product. Extract of the GL EMA/CVMP/IWP/206555/2010, Section 4. Stability tests: "Stability testing shall be carried out as specified in the Directive 2001/82/EC and in the European Pharmacopoeia monograph 0062 Vaccines for Veterinary Use on not fewer than 3 representative consecutive batches. The three consecutive production runs may be carried out on a pilot scale, providing this mimics the full-scale production described in the application. The sterility of the vaccine has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test	Accepted.

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		for container/closure integrity). Where bulk material is to be stored before formulation and final manufacturing, stability data should be provided." There should be also additional room for specifications changes, if need be. In that case, increased requirements in terms of quality, safety and efficacy may be appropriate. **Proposed change:** If specifications of the finished product are the same for the products obtained from both MCSs, the stability results of ~~two~~ **three** pilot batches ~~and one full scale batch~~ produced with the new MCS are sufficient to grant the same shelf life to the finished product. Testing results at release and after three months storage including potency test results should be sufficient for the immediate acceptance of the application. The necessary additional real time data on three batches confirming the full shelf life of the vaccine are requested as a commitment. **If the specifications of the finished product are different, additional real-time stability data may be needed at submission of the application.**	
163-170	1	**Comment:** The current wording implies that all safety and efficacy trials (at least laboratory trials) required for a new MA would need to be repeated with the new formulation. This is almost certainly not needed, especially if the product specifications do not change,	Accepted.

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		and (apart from special requirements for live vaccines), a selected set of well-designed safety and efficacy trials should be sufficient to confirm target animal safety and efficacy “equivalence”. For example, an onset of immunity challenge study against the concerned antigen(s) (ie, the antigen impacted by the change of cell line) and a GLP safety study in the most sensitive subcategory of animal species should be sufficient to address the safety and efficacy in the target species (if they confirm similar safety and efficacy versus the “old formulation”). Finally, there should be room for risk/benefit assessment, especially in case of a reduced efficacy, or a different, but still satisfactory safety profile(s). **Proposed change:** The use of a different cell line for vaccine production requires detailed confirmation that the finished product remains unchanged with respect to safety and efficacy, **or remains of an acceptable safety and efficacy, supported by an updated benefit/risk evaluation**. Laboratory safety and efficacy tests as required in Directive 2001/82/EC, annex 1, Title II should be ~~provided~~ **considered. A selected set of well-designed safety and efficacy trials may be sufficient to confirm target animal safety and efficacy. An onset of immunity study against the concerned antigen(s) (ie, the antigen impacted by the change of defined cell line) and a GLP safety study in the most sensitive subcategory of animal species may be sufficient to address the safety and efficacy in the target species.** To	

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		reduce animal trials and for animal welfare reasons, challenge trials can be replaced by valid alternative methods, whenever possible, by comparing results obtained with finished product batches derived from the original and the new MCS. Field trials should be performed in exceptional cases only, when the laboratory tests cannot confirm the safety and efficacy of the vaccine produced on the MCS of different cell line.	