10 September 2015
EMA/CVMP/IWP/254504/2015
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Reflection paper on the use of heat treatment to inactivate retrovirus RD114 in live immunological veterinary medicinal products' (EMA/CVMP/IWP/37924/2014)

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. A note should be made on the restricted use of heat treatment as a means to inactivate RD114 or other extraneous retroviruses in vaccines. In the case of RD114, it is canine parvovirus (if produced on feline cells), feline panleukopenia virus and feline calicivirus that could benefit from such heat treatment. The other canine and feline vaccine viruses, such as feline herpesvirus, canine adenovirus = canine hepatitis virus, canine parainfluenza virus and canine distemper virus are more or less equally sensitive to heat treatment as retroviruses. Hence heat treatment of preparations of these viruses or heat treatment at the finished product level of combined vaccines containing one or more of these components is not an option. However, we do feel that this text is relevant to other retroviruses, not just RD114, and its scope should be expanded accordingly.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
5	1	**Comment:** In line with our general comments we would suggest amending the title to broaden the scope to all retroviruses. **Proposed change:** Reflection paper on the use of heat treatment to inactivate retrovirus**es** ~~RD114~~ in live immunological veterinary medicinal products (IVMPs)	Accepted.
25-28	1	**Comment:** The executive summary seems to cover a broader topic than only RD114 ("heat treatment to inactivate retroviruses"). Although it is understood that the Reflection paper deals with RD114, it could be beneficial to extend the considerations more broadly, to retroviruses in general. **Proposed change:** Consider extension to retroviruses in general	Accepted.
60-61	1	**Proposed change:** Therefore this document considers the possible use of heat treatment for the inactivation of replicative **retroviruses** ~~RD114~~ applied to active substances of currently authorised vaccines in order to inactivate th~~is~~**ese** extraneous agent**s** in live vaccines.	Accepted.
61-62	1	**Comment:** Amendment for clarity **Proposed Change:** RD114 applied **during production of or at the** ~~to~~ active substance~~s~~ **level** of currently authorised vaccines in order to inactivate this extraneous agent in live vaccines.	Accepted.

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65-67	1	**Proposed change:** Before process changes such as heat treatment to remove/inactivate **a retrovirus**, can be accepted, a standardised, validated retroviral ~~RD114~~ detection test still needs to be developed and the acceptable limit for retroviral ~~RD114~~ content has to be established (the term 'limit' takes into account the detection limit of the test as well as the retroviral ~~RD114~~ levels in current vaccines which to date are not considered to be associated with a significant risk).	Accepted.
80-81	1	**Proposed change:** Define the parameters of the treatment and provide evidence that this treatment will effectively inactivate the replicative retrovirus ~~RD114~~.	Accepted.
83	1	**Comment :** The studies could be conducted using model relevant viruses spiked in the active substance, and not necessarily wild type RD114 due to the difficulty to have a reference of calibrated live RD114 with a defined titre. **Proposed change:** A spiking with amount of live retrovirus **(*i.e.*** RD114**), or relevant virus,** of the active substance….	Accepted. The wording is slightly amended.
89	1	**Comment :** The use of a detection test for the validation of the treatment could be allowed. **Proposed change :** A validated quantitative infectivity assay should be performed to titrate the retrovirus before and after the treatment. **When the retrovirus is identified, its absence after the treatment can**	Not accepted. The quantification of the retrovirus is essential to validate the heat treatment. Furthermore, it allows also the detection of the virus.

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		be demonstrated by using a detection method.	
92	1	**Proposed change:** The method of quantification **or detection** of the ~~RD114~~ retrovirus should have adequate sensitivity and reproductibility and should be performed with sufficient repetitions to ensure statistical accuracy of the results.	Not accepted. See above.
107-108	1	**Comment:** In our view the risk depicted in these lines is very unrealistic. Unless literature evidence is provided that a single heat treatment without further selection procedures can lead to the selection of live temperature-resistant virus mutants, we propose that these lines are deleted. **Proposal:** Please delete lines 107-108	Not accepted. See the publication: Selection of Thermostable Newcastle Disease Virus Progeny from Reference and Vaccine Strains D. J. King. AVIAN DISEASES 45:512-516, 2001
111-112	1	**Proposed change :** If the treatment is introduced in the production process, the marketing authorisation holder has to demonstrate that this treatment has no negative impact on the quality, the safety and the efficacy of the finished product. **If no impact of the treatment (as described in paragraph 5) is demonstrated on the finished product, it is not necessary to conduct new efficacy and safety studies**	Not accepted. See above.
118	1	**Comment:** This may be an opportunity to also introduce an improvement into the manufacturing process. **Proposed Change:** unchanged, the manufacturing process of the vaccine should not be modified **unless justified by corresponding data**. The results	Accepted.

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		obtained	
121-125	1	**Comment:** the current wording implies that where a live vaccine virus is part of a combined vaccine, it would be required to test the safety of the combined vaccine, using the newly produced - heat treated – live vaccine virus under test. It is not considered appropriate or useful to demonstrate again the safety of the combined vaccine especially if no antigen content increase is required as a result of the treatment, but instead, focus should be on the heat treated live vaccine virus. A safety test of a 10-times overdose of that live virus would appear sufficient (and probably more sensitive) to detect any major issue linked to the potential selection of live virus mutants. **Proposed change:** with regard to the safety of the vaccine, the safety of an overdose administration **of the heat-treated live active substance** has to be demonstrated in laboratory in compliance with the requirements of Directive 2001/82/EC as amended. **Where the concerned active substance is part of combined vaccine(s), and the heat treatment does not require an increase of its antigen content, it is sufficient to demonstrate the safety of a monovalent vaccine containing the heat-treated live active substance under assessment.** ~~and with the Ph. Eur. General monograph "*Vaccines for veterinary use*" referring to~~	Accepted.

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		~~the 123 Ph. Eur chapter 5.2.6 "*Evaluation of safety of veterinary vaccines and immunosera*".~~ The results obtained should **confirm that the heat treated live active substance is safe for use.** ~~be similar to those obtained with the original vaccine.~~	
126-129	1	**Comment:** The current wording implies that, in any case a live active substance is heat-treated to inactivate RD114, there will be a need to confirm efficacy in the target species. There should be room for flexibility, especially if the in vitro and manufacturing data generated to support heat inactivation of RD114 do indicate that the heat treatment does not affect the viability of the live organism, and there is no need to adjust the manufacturing specifications. In those cases, it should not be required to confirm efficacy in the target species. It should be sufficient to continue to rely on reaching the minimum live titre (previously approved) to consider the vaccine as efficacious. **Proposed change:** **In case the in vitro and manufacturing data generated to support the heat inactivation of the retrovirus indicate that the heat treatment does not affect the viability of the live vaccine organism, and there is no need to adjust the manufacturing specifications, there is no need to confirm efficacy of the heat treated substance in the target species. Whenever there is an indication that the efficacy of the concerned**	Accepted.

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		active substance may be impacted by the heat treatment, the efficacy of the vaccine containing the heat treated active substance has to be tested in laboratory conditions according to the requirements of the immunogenicity test described in the Ph. Eur. monograph corresponding to the active substance. The results should be in compliance with the threshold defined in this Ph. Eur. monograph.	