15 March 2010
EMA/81346/2010
Committee for medicinal products for veterinary use (CVMP)

Overview of comments received on 'Guideline on data requirements to support in-use stability claims for veterinary vaccines' (EMEA/CVMP/IWP/250147/2008-CONSULTATION)

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

Name of organisation or individual
IFAH-Europe

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) – **IWP Rapporteur's comments** *(To be completed by the Agency)*
	IFAH-Europe welcomes this summary and clarification of the general requirements for in-use stability data. We are pleased to see that the principle of a longer in-use shelf life for vaccines is now accepted when supported with data generated *"under defined conditions of use for the proposed in-use period".* Hopefully this means that the guideline is intended to provide opportunity to have approval of extended in-use shelf lives for vaccines, as EU regulators often have quoted the Ph Eur monograph 0062, section 2.3.5 which states *"….during use of a vaccine which is expected to be no longer than 10h after first broaching"* as being the justification for not awarding in-use shelf lives of more than 10 hours, even when supported by data. Although the guideline contains several useful specific examples as explanation, there is a risk that other examples would not fall within the scope of the guidance.	IWP accept that in-use shelf life can be longer than 10 hours provided data are available to support the proposed in-use shelf life.

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 – IWP Rapporteur's comments** *(To be completed by the Agency)*
Line 63-64		*"For multi-dose parenteral vaccines, it is generally accepted that a shelf-life of no longer than one working day (8-10 hours) should be proposed, and the claim must be supported by relevant in-use stability data."* This indication is in line with section 2.2.5 of Ph. Eur. monograph 0062 where it is stated: *"Antimicrobial preservatives are used to prevent spoilage or adverse effects caused by microbial contamination during use of a vaccine which is expected to be no longer than 10 h after first broaching"*. However, a longer shelf life should be acceptable if this is supported by adequate data and appropriate information on the SPC to ensure proper handling of a broached bottle over time. Non-conventional inactivated vaccines in multi-dose containers that have a 2 dose vaccination schedule and are known to be very stable would benefit from this approach: an in-use shelf covering the interval between the first broaching and the administration of the second dose would be justifiable if results of appropriate mimicking studies are satisfactory. Proposed change (if any): *For multi-dose parenteral vaccines, it is normally ~~generally~~ accepted that a shelf-life of no longer than one working day (8-10 hours) after first broaching is expected, but a longer shelf life may be acceptable if ~~should be proposed~~ ~~and~~ the claim ~~must be~~ is supported by relevant in-use stability data.*	Changes proposed by IFAH acceptable.

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 – IWP Rapporteur's comments *(To be completed by the Agency)*
Lines 84-89		*"In-use stability data from a larger combination vaccine may be used in support…"* *1.* According to Directive 2009/9/EC, information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient. In addition, the stability of lower combination may be based on stability data from larger combination. This approach should be reflected in the in use stability guideline as well. *2.* Given the nature of live vaccines presented in multi-dose containers (mostly freeze-dried), it is highly unlikely that in-use stability of any of the active components in a combination vaccine would be depending on the presence or absence of one or more of the other active components. If the composition of the excipients is identical then the stabiliser is the same for the different combinations anyway. For inactivated combination vaccines, potency testing is not indicated and other stability parameters can hardly be different between larger and smaller combination vaccines. Hence we think that in-use stability obtained for a larger combination vaccine can be used for a smaller combination vaccine right away. Proposed change (if any): *In-use stability data from a larger combination vaccine may be used in support of the in-use stability of a vaccine for which the composition is identical with the exception that there are fewer active ingredients. ~~This would be acceptable provided that there is no reason to suspect that the in-use stability~~*	1.Acceptable to include a reference to preservative efficacy data from similar immunological products as this is now included in the amended Annex 1. However, as the performance of the preservative may be effected by the composition of the vaccine formulation, the container etc, IFAH'S proposed statement has been expanded to take account of these considerations. 2. Changes proposed by IFAH acceptable.

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 – IWP Rapporteur's comments *(To be completed by the Agency)*
		~~*would be any different on the basis of different antigen combinations, e.g. if the stability of the finished product of the larger combination vaccine is demonstrated to be comparable to the smaller vaccine.*~~ *Information on the efficacy of preservatives in other similar immunological veterinary medicinal products from the same manufacturer may be sufficient*.	
Lines 98-107		*"For inactivated vaccines, if the proposed in-use shelf-life is within one working day (maximum 10 hours) it is acceptable to omit the potency testing from the in-use shelf-life stability study.* *In the case of vaccines for which a suitable in vitro method…"* 1. We welcome the sensible statement that potency testing is not required in support of a 10 hour in-use shelf life for inactivated vaccines. 2. It does not seem to make sense that if there is no suitable *in vitro* method available, data from one batch should be submitted and subsequently data from a second batch is also required. This would certainly not be in line with the 3Rs approach, as more experimental animals would have to be sacrificed. Proposed change (if any): *"In the case of vaccines with proposed shelf-life of more than 10 hours for which a suitable in vitro method is not available for the batch potency test, in-use stability data from one batch, rather than two, may be submitted.* ~~*with the initial application. This approach would be acceptable if the results from one batch are supportive of the proposed in-use shelf-life and a commitment should be made that at the next time*~~	IFAH'S proposal for potency data from only 1 batch not acceptable particularly as in-use shelf lives of >10 hours are now proposed to be accepted by the guideline. Guideline currently accepts data from 1 batch at submission with requirement to provide data from 2nd batch when the next batch potency test is being conducted. As in-vitro animal potency testing generally applies to inactivated vaccines and is only required when the in-use shelf life is > 10 hours, it is considered that the number of vaccines that this applies to will be limited and hence the animals used will be minimal.

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 – IWP Rapporteur's comments *(To be completed by the Agency)*
		~~*the batch potency test is conducted for routine release of the product, that the potency will also be tested at the end of the proposed in-use shelf life. The complete in-use stability study should be submitted when the remaining data from the second batch are available.*~~*"* Lines 67-68, should also be amended accordingly: *"In support of the proposed in-use shelf-life, data from two different batches of finished product should be provided, unless otherwise specified under section 4.3 Potency testing."*	
Lines 112-117		*"If an antimicrobial preservative is included in the vaccine, the efficacy of the antimicrobial preservative under in-use conditions should be demonstrated, this may include evaluation of the efficacy of the antimicrobial preservative at T0 and at T0+X hours. The efficacy of the antimicrobial preservative should be evaluated as per the European Pharmacopoeia monograph Vaccines for Veterinary Use (0062), which includes the requirement that samples are tested at suitable intervals over the proposed in use shelf-life."* 1. The first sentence of this paragraph may be read as indicating that separate preservative efficacy tests have to be started at begin (T_0) and at end of the in-use shelf life (T_0 + X). Assuming that it is actually intended that T_0 and T_0 + X are included as time points in the preservative efficacy test, we propose a text adaptation to solve this ambiguity. 2. In the second sentence, reference is made to Ph. Eur. 0062, where it is stated that *"Antimicrobial preservatives are used to prevent spoilage or adverse effects caused by microbial contamination during use of a vaccine which is*	IFAH's proposals are not acceptable based on the following: 1. Ph. Eur. 5.1.3 describes the test recommended to demonstrate the efficacy of an antimicrobial preservative (AMP). This is a 28 day test. 2. The Ph. Eur. 62 acceptance criteria for a successful test are not as strict as those specified in 5.1.3 however the Ph. Eur. 62 acceptance criteria are based on a 28 day test. 3. Ph. Eur.62 also requires efficacy testing of the AMP 'at suitable intervals over the proposed shelf life'. In effect once the efficacy of the APE is tested in the T0+Xhrs vaccine sample from the in-use stability study, this should be sufficient to support the efficacy of the AMP throughout the in-use shelf life. 4. As compliance with Ph. Eur.

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 – IWP Rapporteur's comments *(To be completed by the Agency)*
		expected to be no longer than 10 h after first broaching. [….] The efficacy of the antimicrobial preservative is evaluated as described in chapter 5.1.3 and in addition samples are tested at suitable intervals over the proposed in-use shelf life". The standard preservative efficacy test according to Ph. Eur. general chapter 5.1.3 lasts 28 days. This does not seem to be appropriate in the case that the period to be covered is not more than 10 hours. 3. Unfortunately no reference is made to III/3469/92 (Eudralex 7BIm14a) ("Inclusion of Antimicrobial Preservatives in Immunological Veterinary Medicinal Products"), although this long existing guideline is relevant here. 4. Presently 4 different sets of acceptance criteria exist for the preservative efficacy test: the A and B criteria of Ph. Eur. 5.1.3, the criteria included in Ph. Eur. monograph 0062 and the criteria included in III/3469/92. The three sets of acceptance criteria from the Ph. Eur. have no criterion for fungi within the first 24 hours of the test. It therefore does not seem to make sense to include fungi in the preservative efficacy test for IVMPs if the in-use shelf life claimed is no longer than 10 hours. 5. It seems appropriate that this new guideline will define the length of the preservative efficacy test for IVMPs and provides one final acceptance criterion for the test, if the in-use shelf life claimed is no longer than 10 hours. Proposed change (if any): *If an antimicrobial preservative is included in the vaccine, the efficacy of the antimicrobial preservative under in-use conditions should be demonstrated~~, this may include~~*	monographs is mandatory, the 28 test period specified in Ph. Eur. 5.1.3 is mandatory and therefore takes precedence over III/3469/92 (Eudralex 7BIm14a) which refers to reduced testing times for vaccines with shelf lives of less than one working day). III/3469/92 (Eudralex 7BIm14a) will need to be reviewed to determine if it is still necessary and if so, it will need to be amended to remove the reference to the reduced sampling times.

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 – IWP Rapporteur's comments *(To be completed by the Agency)*
		~~*evaluation of the efficacy of the antimicrobial preservative at T0 and at T0+X hours or later*~~*. The efficacy of the antimicrobial preservative should be evaluated as per the European Pharmacopoeia monograph Vaccines for Veterinary Use (0062),* ~~*which includes the requirement that samples are tested at suitable intervals over the proposed in-use shelf-life*~~*. If the shelf life claimed is no longer than 10 h after first broaching, testing can be restricted to the indicated bacteria and the sampling time points be restricted to t = 0 and at least the end of the in-use shelf life or later. The minimum acceptance criterion is: no significant increase over at least the in-use shelf life period. This criterion is in line with the criterion of Ph. Eur. monograph 0062 and is to replace the criteria published earlier in III/3469/92 (Eudralex 7BIm14a).*	