6 November 2014
EMA/CVMP/IWP/36240/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on the compliance of authorised equine influenza vaccines with OIE requirements' (EMA/CVMP/IWP/97961/2013)

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
2	World Organisation for Animal Health (OIE) Experts Surveillance Panel (ESP)
3	The British Equine Veterinary Association (BEVA)
4	Federation of Veterinarians of Europe (FEV)

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1. General comments

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes this update for the Note for Guidance EMEA/CVMP/112/98. This proposal rectifies two shortcomings of the old NfG: inclusion of the option to omit a strain and providing guidance in case a MAH wishes to show that his/her vaccine is still efficacious against infection/disease caused by recent field strains of equine influenza virus (EIV). However, there are some points on which we would like to comment. First of all we propose to correct the title of this guideline. The OIE Expert Surveillance Panel provides **recommendations**, not requirements for the strain composition of equine influenza vaccines. The distinction between 'recommendations' and 'requirements' is important for the perspective of this guideline. We therefore propose to change the title of this guideline accordingly. The development of new veterinary vaccines, including equine influenza vaccines, takes many years. Although antigenic drift of the HA protein is lower for equine than for human influenza viruses, it is almost inevitable that when a new equine vaccine obtains a marketing authorisation its strain composition is no longer completely compatible with the most recent recommendation of the OIE Expert Surveillance Panel (ESP). A strain update for an existing equine influenza vaccine (without DOI data) takes at least 2 years, often longer, and chances are high that the updated vaccine still does not contain the most recently recommended strain composition. Hence a way forward to show that such an updated vaccine is a good contribution to a better protection against field challenge, provided by this GL, is welcomed. However, the relevance of prompt implementation of changed OIE ESP	Accepted. Data supporting the claim that a similar level of

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	recommendations is to be questioned. The efficacy of equine influenza vaccines with a strain composition according to the 1995 OIE recommendations against viruses isolated more than a decade later has repeatedly been shown, both in publications and in-house by manufacturers. And although literature provides examples of apparent vaccine break-throughs, mainly in race horses, pharmacovigilance data give a different impression: in a 2 year period, 2011-2012, where 3 x 10^6 doses were sold of a Europe-wide (and further) licensed equine influenza vaccine with a strain composition conform the OIE ESP recommendation of 1995 and not containing any of the strains recommended since 2009, not a single case of suspected lack of expected efficacy (SLEE) has been reported. Recent experience showed that a vaccine with an EIV strain composition conform the 1995 recommendations induces the same high HI antibody levels and the same high level of protection against challenge with 2003 and 2007 EIV isolates in horses as an update of that vaccine with an EIV composition conform the 2008 recommendations. This may explain why sometimes the choice is made to keep the vaccine as it is but to show its continued efficacy against currently circulating EIV strains in a challenge study. The OIE ESP applies the same criteria for a strain update recommendation as those in use for the human vaccines against seasonal influenza: a greater than 8-fold difference in HI titre with post-infection ferret antisera. A basic difference between human and equine influenza vaccines is not taken into consideration here: seasonal human influenza vaccines are containing antigens only whereas equine influenza vaccines in addition contain an effective adjuvant. Due to this adjuvant, the protective antibody levels induced by equine influenza vaccines are much higher and hence serotypically broader than those induced by human influenza vaccines. Further, the difference in structure and scale between the animal and human vaccine	protection against 2003/2007 isolates was afforded by both a vaccine containing 1995 OIE recommended strains and a vaccine containing 2008 recommended strains is not provided.

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	industry and the difference in the commercial aspects (free market *versus* government-sponsored vaccination programmes) makes it practically and economically impossible to apply the same approach and establish the same infrastructure for updating equine influenza vaccines as has been established for the yearly update of human seasonal influenza vaccines. The European animal health industry (IFAH-Europe) expressed its concern on this matter to the OIE Expert Panel in December 2010. A meeting was organised which took place on December 9, 2011, at the OIE Headquarters in Paris (Summary report - Meeting with OIE Expert surveillance panel (ESP) on Equine Influenza). IFAH-Europe members highly appreciate the activities of the OIE ESP and its contributing laboratories and fully agree that the antigenic drift occurring in equine influenza virus forces a strain update of the vaccines from time to time. To determine the appropriate moment for a strain update is a complicated matter, since the lead time of minimally 2-3 years for such an update (including development and licensing) makes it necessary to initiate the work long enough before vaccine breaks may occur. Continuous field surveillance and comparative serological (HI and VN) studies using sera obtained from vaccinated horses are essential in this respect. IFAH-Europe hopes that dialogue and cooperation of the European animal health industry with the OIE Expert Surveillance Panel will lead to a more balanced estimation of the appropriate time points for strain updates. **Requirements for rapid implementation of compliance with the OIE recommendations** In our view, the presently proposed guideline is not a stimulus for companies to arrange regular strain updates following the OIE ESP recommendations. The amount		

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	of data required seems too unnecessarily extensive. In our view, there is no need for new challenge and DOI data for a properly updated vaccine as ample knowledge and experience is available that serology is adequate for this purpose. Ph. Eur. monograph 0249 and all available literature, including articles from OIE ESP members, testifies that serology against the vaccine strains is predictive for protection against challenge, provided that the infecting virus is antigenically similar to the vaccine strain. Therefore, where the updated vaccine includes (a) strain(s) of the same antigenic sub-type as recommended by the OIE ESP, a vaccination/challenge and a DOI study should not be necessary if the seroresponse against the vaccine strain(s) induced by the updated vaccine (e.g. SRH antibodies) is not lower using appropriate statistical methods than the seroresponse against the vaccine strains induced by the vaccine (or earlier versions) with which efficacy against challenge has been shown earlier. Successive strain update processes may eventually lead to a vaccine for which challenge data against one of the current vaccine strains are no longer available, but if the strain update has followed the serology equivalence rule formulated above this should be acceptable as the Ph. Eur. policy allows validated alternatives for tests described in a monograph. **Requirements for demonstrating efficacy of a non-updated vaccine against an OIE ESP recommended strain** Where the vaccine strain(s) is/are not conform the OIE recommendation, an appropriate scientific justification is required to claim efficacy of the vaccine against the newly circulating strain(s). In this respect, it is the seroresponse against the newly circulating strain(s) that is relevant. If the antibody levels (e.g. virus neutralising (VN) or haemagglutination-inhibiting (HI)) induced by the vaccine against	Disagree. Ph. Eur. 249 requires justification for use of serology and states 'justification for protection against these strains (i.e. vaccine strains) may be based on published data on correlation of the antibody titre with protection against antigenically related strains'. Also IFAH/OIE meeting document suggests that cross-reaction does not always mean cross protection i.e. '2003 Newmarket outbreak showed that cross-reaction in HI, as seen between Florida Clade 2 viruses and sera raised against Kentucky lineage (American) strains, does not necessarily mean cross-protection'. Therefore data supporting correlation between serological response to vaccine strains and protection against circulating strains is necessary.

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	the currently circulating strain(s) is not lower using appropriate statistical methods than those against the vaccine strain(s), a non-updated vaccine is acceptable and a vaccination/challenge and a DOI study should not be necessary if those levels have been shown protective against challenge and resulting in the claimed DOI earlier. On the contrary, if they are lower than those against the vaccine strain a vaccination/challenge and a DOI study will be necessary to claim efficacy against currently circulating strains.	
2	The OIE Expert Surveillance Panel for Equine Influenza (ESP) supports the revision of the guidelines for equine influenza vaccines, such that vaccine manufacturers wishing to update their strains can do so quickly as is the routine practice for human influenza vaccines. At the moment, the process takes too long and is overly expensive. We welcome the ability to change, remove or add strains as this adds much-needed flexibility. However, the ESP objects to the inclusion of section 4 ("No modification to existing vaccine") as this facilitates the circumvention of the OIE recommendations and the retention of suboptimal vaccines.	Section 4 has been removed from guideline. IWP consider that the scope of the guideline should not include requirements for studies where changes per OIE recommendations are not made.
3	Vaccine efficacy plays an essential role in the prevention of disease outbreaks due to Equine Influenza virus. BEVA believe that the proposals to enable a more rapid change in viral strain are a vital part of maintaining the vaccine efficacy for this disease. We welcome the proposal that the annual review by OIE Expert Surveillance Panel on Equine Influenza will form the basis on which viral strains are used to guide manufacturers for the production of vaccines. However we would like to highlight that vaccine efficacy is not only a function of viral strains, and other factors, including vaccine potency and the varied host immune response, are important in the protection provided to an individual. Therefore, although we would hope that these changes would bring about a further reduction in disease occurrence in vaccinated	

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	animals, it may still occur. BEVA welcomes the proposal set out in section 3, to facilitate rapid strain addition or replacement based upon the recommendations of the OIE. The proposed changes to the regulatory framework should ensure that these enable timely and cost-effective release of strain updates. While we acknowledge that these changes will affect production costs by vaccine manufacturers, these costs must be minimised to prevent vaccines becoming unaffordable by the majority of horse owners. Although high-value animals would continue to receive vaccination even at a significantly increased cost, the failure to vaccinate lower valued animals due to these costs could impact negatively on the occurrence of this disease in all populations.	
4	FVE welcomes this consultation on Guidelines for the compliance of authorised equine influenza vaccines with OIE requirements. For veterinarians it is very important that the vaccines they use are effective. While it is recognised that vaccine effectiveness depends on many factors such as the host's immune system and the infection itself, for the horse owners it is difficult to grasp that vaccines do not always guarantee complete protection from a disease. FVE welcomes the annual review of the OIE expert Surveillance Panel on Equine Influenza Vaccine Composition. However, due to the present regulatory framework it is recognised that a strain update for an existing equine influenza vaccine takes at least 2 years or longer. This is much longer than it takes to update human influenza vaccines. While recognising that antigenic drift for equine is less than for human influenza, FVE believes that the regulatory framework should facilitate a rapid update of vaccine strains when such recommendations are made. We are very pleased that the CVMP is reviewing the regulatory framework at the moment and the message we	

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	want to convey very clearly is that the system needs to be as fast, easy and cheap as possible in order for vaccine manufacturers to make the strain updates recommended by OIE. Vaccine breakdown can be due to several causes namely inadequate vaccine potency, an inappropriate vaccination Schedules or the use of outdated vaccine viruses. All these causes we should try to prevent. Promoting horse owners to vaccinate regularly there horses is in this of extreme importance.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Title and footer	1	**Comment:** Please see general comments. **Proposed change:** *Guideline on the compliance of authorised equine influenza vaccines with OIE r~~equirements~~* ***recommendations***	Accepted
44-46	1	*Current epidemiological surveillance suggests that equine influenza A viral strains of the H3N8 subtype (i.e. influenza A /equine 2 virus) are the major causative viral strains.* **Comment:** For many years H3N8 strains have been the only EIV strains circulating. **Proposed change:** *Current epidemiological surveillance suggests that equine influenza A viral strains of the H3N8 subtype (i.e. influenza A /equine 2 virus) are the ~~major~~ causative viral strains.*	Accepted
50	1	*….. thus compromising vaccine efficacy.* **Comment:** Please see the general comment above. **Proposed change:** *….. thus* ***possibly*** *compromising vaccine efficacy* ***eventually****.*	Accepted. Text re-worded as 'which may compromise vaccine efficacy'.
53-54	1	**Comment:** Based on our knowledge, the update of strains is not needed as	No change required. Text refers to 'annual OIE publication' and not to

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		frequently as annually. **Proposed change:** *This point should be checked.*	requirement to update strains annually.
55-57	1	**Comment:** "... that they are protective ..." tends to indicate that non-updated vaccines are not protective what is not necessarily true (otherwise such vaccine should be removed from the market). **Proposed change:** *Should be replaced by "... **that they provide optimal protection against circulating** ..."*	Accepted.
78-98	1	*3.1 Specific requirements:* **Comment:** No requirements (*e.g.* with regard to the OIE ESP recommendations) are set for the omission of a strain. **Proposed change:** Please include (a) requirement(s) for the omission of a strain, if necessary.	Comment not understood. Requirements are given for removal of existing vaccine strains.
90-92	1	*If strain(s) present in the existing vaccine formulation are retained for the manufacture of the reformulated vaccine, there should be no change to the antigen content of the strain(s) per vaccine dose…* **Comment:** It is possible that after the introduction of antigen(s) of (a) new strain(s) the antigen dose of the remaining antigen(s) must be adapted to maintain the same potency and immunogenicity of the vaccine for that antigen**.** Then the change in antigen dose of the retained antigen is justified and should be allowed.	Not accepted. A change in content/dose will require either new safety or efficacy data.

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		Proposed change: ~~*If strain(s) present in the existing vaccine formulation are retained for the manufacture of the reformulated vaccine, there should be no change to the antigen content of the strain(s) per vaccine dose…*~~	
107-110	1	*Where possible, the replacement / additional strain(s) should be one of the recently recommended OIE strains, however manufacturers may use a locally selected strain(s) if justified.* **Comment:** OIE ESP members have recommended manufacturers to use the most recent isolate of the current EIV lineage (which may be newer than the recommended strain) or a strain of the same lineage as the recommended strain but with better growth properties. **Proposed change:** *Where possible, the replacement / additional strain(s) should be one of the recently recommended OIE strains* ***or a newer or better growing strain of the same lineage as the recommended strain if provided by the OIE ESP****; however manufacturers may use a locally selected strain(s) if justified.*	Accepted – text re-worded as ' .. or a relevant strain of the same lineage as the recommended strain..' Reference to use of local strains was deleted as it is no longer applicable.
119	1	**Proposed change:** *… the replacement / additional strain(s) in the reformulated vaccine may differ* ~~*to*~~ ***from*** *the more recently recommended strains …*	Accepted.
134-135	1	*Details of the inactivation control test(s) and validation of the method(s) for each new strain(s) should be given.* **Comment:** If the production method of the new and remaining strains is the same and unchanged and if the test for residual virus as described in sections	Accepted. Text amended to state that validation only required if test other than that recommended in Ph. Eur. 249 is used.

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		2.4.1.1 or 2.4.1.2 of Ph. Eur. monograph 0249 is applied, validation for each new strain(s) is not necessary. **Proposed change:** ***If the production method for the new strain(s) is not the same as the one for the remaining strain(s) or if the test applied does not conform to the test(s) described in Ph. Eur. monograph 0249,*** ~~*D*~~***d****etails of the inactivation control test(s) and validation of the method(s) for each new strain(s) should be given.*	
136-138	1	*Details of the preparation … should be detailed.* **Proposed change:** *Details of the preparation … should be* ~~*detailed*~~ ***given****.*	Accepted.
138-140	1	*In particular, the master seed of the replacement / additional strain(s) shall be shown to contain only the recommended strain or the recommended-like strain proposed for inclusion in the vaccine.* **Comment:** As it is expressed now, this requirement seems difficult if not impossible to meet. Given the close relationship between different EIV strains it is not possible to unequivocally establish that only one strain is present in a seed. The way the seed is derived from the starting material (virus cloning or recombinant technology) should be sufficient to guarantee that the seed contains only the intended strain. **Proposed change:** ~~*In particular,*~~ ***The method used to generate*** *the master seed of the replacement / additional strain(s) shall* ~~*be shown*~~ ***provide sufficient***	Accepted.

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		guarantee that the seed ~~*to*~~ *contain**s*** *only the recommended strain or the recommended-like strain proposed for inclusion in the vaccine.*	
140-141	1	*A suitable method shall be provided to identify the new strain(s) and to distinguish it from related ones.* **Comment:** Depending on how closely related the strains are it may not be possible to meet this requirement with classical methods. In current practice, sequencing of the gene for the HA protein is the method applied to identify the master seed virus. However, this method cannot be applied for routine strain identification. **Proposed change:** *A suitable method* ~~*shall be provided*~~ ***must have been applied*** *to identify the new strain(s)* ***in the master seed(s)*** *and to distinguish it from related ones.*	Accepted.
146-147	1	*Quality control release testing results for 3 pilot scale size reformulated vaccine batches should be provided …* **Comment:** Since the manufacturing process must remain unchanged, 3 pilot batches are not necessary. **Proposed change:** *Quality control release testing results for* ~~*3*~~ ***at least one*** *pilot scale size reformulated vaccine batches should be provided …*	Partly accepted – text revised to state that data from 1 x pilot batch to be submitted with application and data from additional 2 x commercial batches to be submitted post authorisation.
146-148	1	**Proposed change:** Please add: ***…, unless specified otherwise in the original marketing authorisation dossier.***	Accepted.

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149-153	1	**Comment:** As before, if the whole manufacturing process & controls are kept identical, the stability should remain unchanged. **Proposed change:** lines 149 to 153 to be replaced by: *"As the shelf-life should remain unchanged, stability data on the reformulated vaccine can be provided as post approval commitment."*	Accepted- text revised to state that 3 x reformulated batches should be entered into stability program to confirm the shelf life.
153-155	1	**Comment:** For greater clarity we would suggest amending this sentence as follows: **Proposed Change:** A commitment should also be given to report immediately to the competent authorities any **confirmed** out of specification results.	Text deleted as it is GMP requirement to report OOS result from on-going studies hence it is not necessary to specify this in the guideline.
159-172	1	*Specific studies investigating the safety of the modified vaccine are not required if there is no increase in the number of component strains. The safety of the modified vaccine can be evaluated by monitoring systemic and local reactions in the efficacy studies described below (refer to 3.2.3 (a)).* *If the reformulation increases the number of strains in the vaccine, safety testing according to the safety testing requirements specified in Section 2-3-1 of Ph. Eur. 249 should be performed which specifies the administration of 2 single vaccine doses with a minimum of a 14 day interval between doses. Additionally a third single dose should be given two weeks after the second dose to evaluate the safety of a repeat dose. Monitoring should be performed according to Section 2-3-1 of Ph. Eur. 249 i.e. daily for up to 14 days after the final (third) dose. The results should be compared to historical safety data for the existing formulation. Any change in the safety profile of the modified vaccine compared to the authorised formulation should be taken into account by*	Not accepted. Where the reformulation does not involve a change to number of component strains, a specific safety test is not considered necessary. In situations where the number of strains increases, IWP consider that safety study according to vaccination schedule is justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		an appropriate revision of the SPC. **Comment:** It is not only the number of strains included in the vaccine, but also differences in the exact status of the antigens included (*e.g.* different concentration factors) that may influence the product's safety. However, if the essential nature of the antigens included in the vaccine must remain the same, a 'repeated administration of one dose' safety study is not necessary. In the past (NfG EMEA/CVMP/112/98), the batch safety test was used to provide additional assurance that the change in strain composition does not influence the product's safety profile. The batch safety test no longer existing anymore, we propose to subject the pilot scale size reformulated vaccine batches referred to in lines 146-148 to safety testing. **Proposed change:** *Specific studies investigating the safety of the modified vaccine are not required ~~if there is no increase in the number of component strains~~. The safety of the modified vaccine can be evaluated by monitoring systemic and local reactions in the efficacy studies described below (refer to 3.2.3 (a)).* ***In addition, the pilot scale size reformulated vaccine batches indicated in section 3.2.1 of this guideline ~~is~~ subjected to a safety test as described in section 2.3.1 of Ph. Eur. monograph 0249 in at least 4 (instead of 8) horses.*** *~~If the reformulation increases the number of strains in the vaccine, safety testing according to the safety testing requirements specified in Section 2.3.1 of Ph. Eur. 249 should be performed which specifies the administration of 2 single vaccine doses with a minimum of a 14 day interval between doses. Additionally a third single dose should be given two weeks after the second dose~~*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~to evaluate the safety of a repeat dose. Monitoring should be performed according to Section 2-3-1 of Ph. Eur. 249 i.e. daily for up to 14 days after the final (third) dose.~~ The results should be compared to historical safety data for the existing formulation. Any change in the safety profile of the modified vaccine compared to the authorised formulation should be taken into account by an appropriate revision of the SPC.	
177-187	1	*This requires that a virulent challenge for at least one of the strains in the modified vaccine has been performed. The vaccine strain(s) for which challenge data are available and the challenge strain used should be appropriately justified and the relevance of the data to support the efficacy of the reformulated vaccine against the strains currently circulating in the field as documented by the OIE Expert Surveillance Panel should be demonstrated.* *For other strains present in the modified vaccine and not tested by challenge, if a correlation between antibody levels induced by the vaccine strains and protection against the most recent circulating strains (as documented by the OIE Expert Surveillance Panel) has been established / published or can be appropriately justified by the applicant, testing according to the immunogenicity requirements described in Section 2-3-2-2 of Ph. Eur. 249 is acceptable (i.e. based on serological response – a challenge is not required).* **Comment:** Here the Ph. Eur. is interpreted too strictly and unnecessary animal studies are requested. This is not aligned with current 3Rs thinking. Ph. Eur. 249 monograph requires in section 2-3-2 that "*A test with virulent challenge is carried out for at least one vaccine strain (see test under 2-3-2-1). For other strains in the vaccine, demonstration of immunogenicity may, where*	Not agreed. Reference to S+E studies being required only once in lifetime of product cannot be accepted as justification for challenge data not being available for at least one of the component strains of the reformulated vaccine. If this was the case, it is possible that eventually the only challenge data available for the vaccine is that for a strain(s) that was removed a number of years earlier or prior to a number of subsequent reformulations and is not antigenically relevant to current circulating strains.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		justified, be based on the serological response induced in horses by the vaccine (see test under 2-3-2-2); justification for protection against these strains may be based on published data on the correlation of the antibody titre with protection against antigenically related strains`. Section 2.3.2 is part of 2.3: 'Choice of vaccine composition'. The Ph. Eur.´Technical Guide for the Elaboration and Use of Monographs for IVMPs' states for this part: "*This sub-section refers to the safety and efficacy tests to be conducted during the development of a vaccine, as described in chapters 5.2.6. and 5.2.7. These tests are usually carried out once in the lifetime of the vaccine. Unless otherwise stated, test methods given for verification of these characteristics and acceptance limits where appropriate, are provided for information as examples of suitable methods and associated suitable limits. Nevertheless, the developmental tests have to be conducted in such a way that assurances are obtained that the product is of pharmacopeial quality*" Finally, in chapter 1.1. ('General Statements') the Ph. Eur. states: "*The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used".* Therefore, given the well-established correlation between antibody levels and protection against influenza and the recognition thereof as an acceptable alternative to challenge by Ph. Eur. monograph 0249, showing efficacy by serology is sufficient to comply with the Ph. Eur. in case of a strain update, even	

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		if no strain remains in the vaccine against which a challenge was performed. **Proposed change:** Replace lines 175 to 181 by: *If the current or an earlier version of the vaccine was tested at least once in accordance with Ph. Eur requirements (including challenge), the immunogenicity of the reformulated vaccine can be examined according to the immunogenicity testing requirements of section 2-3-2-2 of Ph. Eur. monograph 249. The antibody levels stimulated by the reformulated vaccine shall be not less using appropriate statistical methods than those achieved with the vaccine in the current license application.*	
190	1	**Proposed change:** … or other validated test ~~described~~ **methods.**	Accepted.
191-193	1	*The level of strain specific antibodies to each vaccine strain should be investigated by testing sera in the HI or SRH test or another suitable validated test after absorbing out specific and cross-reacting antibodies induced by the other component strain(s).* **Comment:** This test requires large efforts, especially for the HI test but in general for all tests, needing solid phase adsorbents for this purpose. The test may be of academic interest, but is of no practical relevance. Whether an infecting EIV is neutralised by cross-reacting or specific antibodies does not matter. By their specific nature, the HI and the VN assay are particularly appropriate for measuring relevant antibodies induced by vaccines containing more than one EIV strain.	Accepted. Advice obtained by IWP indicates that considering level of cross-reactivity between antibodies to HAs of H3N8 strains this testing is no longer scientifically justified. This was more relevant when both H7N7 and H3N8 strains were used as there is little cross-reactivity between antibodies to HAs of H7N7 and H3N8 strains.

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		Proposed change: ~~*The level of strain specific antibodies to each vaccine strain should be investigated by testing sera in the HI or SRH test or another suitable validated test after absorbing out specific and cross-reacting antibodies induced by the other component strain(s).*~~	
194-196	1	*The test method used to determine the antibody response should be validated according to the requirements of CVMP/VICH/591/98-FINAL 'Guideline on validation of analytical procedures: Methodology'. Details of the method validation should be provided.* **Comment:** If antibody responses are determined by a method used earlier, validation data are already available and validation does not have to be repeated. **Proposed change:** ***If different from the method(s) used earlier,*** ~~*T*~~***t****he test method used to determine the antibody response should be validated according to the requirements of CVMP/VICH/591/98-FINAL 'Guideline on validation of analytical procedures: Methodology'. Details of the method validation should be provided.*	Partly accepted – text revised to state that the test should be sufficiently validated.
200-205	1	*However, Ph. Eur. 249 also states 'the acceptance criteria depend on the strain' and published data suggest that higher antibody levels are required to induce protection against circulating viral strains which are heterologous to the vaccine strains (Newton et al., 1999; Daly et al., 2004). It is important therefore that the correlation between the antibody titres induced by each vaccine strain and protection against the most recent circulating equine influenza viral strains can be supported.*	Not accepted. OIE manual recommends SRH levels >150mm^2. Correlation between antibody response and protective levels is important.

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		Comment: Accumulated evidence shows that the acceptance criteria for the serological immunogenicity test (85 mm^2 for SRH level and 2^6 for HI titre) are widely valid for H3N8 EIV strains. The reference made to literature suggesting that "*higher antibody levels are required to induce protection against circulating viral strains which are heterologous to the vaccine strains*" is possibly based on a misunderstanding: whereas Ph. Eur. monograph 0249 refers to SRH or HI antibody levels against the strain to protect against, the articles referred to deal with HI and SRH antibody levels against the vaccine strains (or to the vaccine strains if vaccine and challenge strain are antigenically closely related) . Additionally due to the high level of antigenic relatedness in some cases it may not be possible to distinguish between the antibodies attributed to each strain. **Proposed change:** ~~*However, Ph. Eur. 249 also states 'the acceptance criteria depend on the strain' and published data suggest that higher antibody levels are required to induce protection against circulating viral strains which are heterologous to the vaccine strains (Newton et al., 1999; Daly et al., 2004). It is important therefore that the correlation between the antibody titres induced by each vaccine strain and protection against the most recent circulating equine influenza viral strains can be supported.*~~	
210-211	1	*Where relevant, the use of reference equine influenza antisera available from the EDQM in these serological investigations is recommended. The choice of reference antisera should be justified.* **Comment:** In the past these sera became available many years too late. This is unfortunate but probably inevitable.	Partly accepted. Text revised to indicate that the choice of reference sera should be justified.

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		Proposed change: Consider omitting this sentence.	
214-216	1	*Where serology rather than challenge infection has been used to investigate the immunogenicity of additional or replacement strains, the SPC should indicate that the efficacy of these strains is based on antibody production.* **Comment:** Based on the conditions formulated in lines 177-187 (see comments above), the use of serology to proof immunogenicity is either acceptable or not. If acceptable, there should be no requirement to "devalue" this evidence in the SPC. **Proposed change:** ~~*Where serology rather than challenge infection has been used to investigate the immunogenicity of additional or replacement strains, the SPC should indicate that the efficacy of these strains is based on antibody production.*~~	Not accepted. IWP consider that claims should reflect way in which efficacy was demonstrated as required by Ph. Eur. 249.
217-228	1	Requirement for full DOI data. **Comment:** In our view, provision of full DOI data should not be required under all circumstances. If level and kinetics of the antibody response after the first two vaccinations, i.e. the vaccinations where the immunogenicity of the vaccine is tested most sharply, are not different from the level and kinetics obtained with the original vaccine, further DOI data are not necessary. **Proposed change:** Please add after line 220: ***It is not always necessary to submit full DOI data for the modified***	Not accepted. Important to reconfirm DOI but can be done as post authorisation commitment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		vaccine. If the level and kinetics of the antibody response after the first two vaccinations are not different from the level and kinetics obtained with the original vaccine, the DOI of the original vaccine may be retained in the SPC for the reformulated vaccine.	
229-246	1	*Interactions of the new / replacement strain(s) with each other and with the retained, existing strain(s) and/or other antigens (e.g. tetanus) of the vaccine to be tested in guinea pigs.* **Comment:** Please see also the comment to lines 191-193 above. In our view, the tests proposed here may be of academic interest, but are of no practical relevance. What is essential is that the modified vaccine induces the same antibody and protection levels against the vaccine viruses and against the viruses of the relevant OIE ESP recommendation as found for the original vaccine in the past. In our experience, this is obtained if the modified vaccine produces the same potency test values against the vaccine strains as the original vaccine. However, this cannot and should not be an absolute requirement: the Ph. Eur. requires that the potency test applied "*must provide assurance that the batch would comply with the Potency* [= Immunogenicity] *test. …[….]… The acceptance criteria must be established from correlation with the results obtained for a batch shown satisfactory in the Potency* [= Immunogenicity] *test* ('Technical Guide for the Elaboration and Use of Monographs for IVMPs'). It is sufficient when the potency test fulfils these requirements and the modified vaccine containing tetanus or another non-EIV component shows the same potency for this component as the original vaccine. For this, knowledge of the level of interactions between the various vaccine components is completely redundant.	Acceptable. Advice obtained by IWP indicates that studies in guinea pig model are not scientifically relevant for reasons outlined in lines 191-193. Taking 3Rs into account, requirement for guinea pig testing removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Omit the text of lines 232-243 and to retain the text of lines 244-246.	
258-265	1	*Note: For modifications involving only ….* **Comment:** This note does not solely belong to section 3.2.3.b, but belongs to the whole section 3.2. **Proposed change:** Give this note a separate section number (3.2.4) to improve clarity.	Accepted.
267-269	1	*Where there is no change to the equine influenza viral strains in an authorised vaccine and the manufacturer wishes to demonstrate that the vaccine provides protection against currently circulating strains as documented by the OIE Expert Surveillance Panel,* *the following approaches are recommended:* **Proposed change:** *….. as documented by the OIE Expert Surveillance Panel, an appropriate scientific justification is required. ŧThe following approaches are recommended:*	Section removed from guideline. IWP consider that scope of the guideline should not include requirements for studies where changes per OIE recommendations are not made.
271-297	1	**Comment:** Please see the general comment and the comments to lines 214-216 and 217-228 above. **Proposed change:** *(a) ~~Where a correlation between antibody titre and protection has been established / published:~~ If the difference between the post vaccination antibody levels determined using virus neutralising (VN),*	N/A – see comment above re lines 267-269.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		haemagglutination inhibiting (HI) or any other appropriate method and induced by the vaccine against the currently circulating strain(s) and those against the vaccine strain(s)are not lower using appropriate statistical methods: *~~As outlined under 3.2.3 (a) of this guideline, if a correlation between antibody levels induced by the vaccine strains and protection against the current circulating strains as documented by the OIE Expert Surveillance Panel has been established / published or can be appropriately justified by the applicant, t~~ Testing according to the immunogenicity requirements described in Section 2-3-2-2 of Ph. Eur. 249 is acceptable (i.e. serological data acceptable - challenge is not required).* *~~All of the requirements listed under 3.2.3 (a) of this guideline (in relation to the use of serology as a measure of immunogenicity) must be taken into account, in particular the fact that antibody levels higher than the Ph. Eur. 249 specified levels of 85mm^{2} (SRH) and 1:64 (HI) may be required to induce protection against circulating viral strains which are heterologous to the vaccine strains.~~* *(b) ~~Where a correlation between antibody titre and protection has not been established /published.~~* *If thedifference between the post vaccination antibody levels determined using virus neutralising (VN), haemagglutination inhibiting (HI) or any other appropriate method andnduced by the vaccine against the currently circulating strains and those against the vaccine strain(s) are lower using*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		appropriate statistical methods: *~~If an acceptance criterion or correlation between antibody titre induced by the vaccine strains and protection against the most recent circulating strains as documented by the OIE Expert Surveillance Panel has not been / cannot be established, t~~ Testing in accordance with the immunogenicity testing requirements specified in Section 2-3-2-1 of Ph. Eur. 249 (i.e. challenge using the current circulating strain or strains as documented by OIE or recommended like strains) should be conducted.* *The above tests should also include an evaluation of the DOI of the vaccine in the target species to protect against the current circulating field strains as outlined in 3.2.3 (a).* ***It is not always necessary to submit full DOI data. If the level and kinetics of the antibody response against the OIE recommended strain(s) after the first two vaccinations are not different from the level and kinetics obtained against the vaccine strains, the DOI of the vaccine may be retained.*** *If protection against current circulating strains can be supported based on data from (a) or (b) above, the indications in the SPC may be revised to reflect this. ~~In the case of serological studies performed as described in (a) above, the SPC should reflect the fact that efficacy of the vaccine is based on antibody production.~~*	
266-297	2	As it stands, section 4 offers a simple method for vaccine manufacturers to circumvent the requirement to update their vaccine strains. Section 4 also allows products, containing strains that are no longer likely to offer optimum protection, to be marketed in such a way as to potentially cause confusion to veterinary practitioners. Testing products against 'circulating strains' at the	Section 4 removed from guideline. IWP consider that the scope of the guideline should not include requirements for studies where changes per OIE recommendations are not made.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		peak of immunity is not the same as updating the vaccine strains. Each year laboratories from all over the world submit surveillance data to the ESP. Data relating to influenza outbreaks, vaccination breakdown and virus characterisation are carefully analysed by the OIE and WHO experts. Recommendations are made to update vaccine strains only when there is sufficient evidence that OIE-recommended strains are no longer believed to offer optimal protection. We therefore do not support the “no modification” option in principle. Proposed change (if any): This section should be removed from the guidelines.	
Lines 266-297	3	BEVA believe that section 4 is unnecessary and counterproductive. The OIE Expert Surveillance panel will consider the suitability of existing strains, before recommending additions, removal or replacement of viral strains in current vaccines. Therefore, we believe that this section undermines the scientific rigour that would be applied by the OIE. We would not support the ability for manufacturers to be able to make claims for vaccine strains that are considered obsolete by this panel, irrespective of any additional testing. Proposed change: We propose removal of this section. Any vaccine manufacturers who do not modify strains in accordance with OIE recommendations should not be permitted to make any marketing claims regarding efficacy.	Section 4 is removed from the guideline. IWP consider that the scope of the guideline should not include requirements for studies where changes per OIE recommendations are not made.
Section (b), from	4	Comment: if serological cross-protection has not been established in the target species, it is suggested to do a challenge according to section 2.3.2.1 Eur Ph	Section 4 is removed from the guideline as IWP consider that the scope of the

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line 284		249. Section 2.3.2.1 states "At least 2 weeks after the last vaccination, challenge each horse by aerosol with a quantity of equine influenza virus sufficient to produce characteristic signs of disease such as fever, nasal discharge and coughing in susceptible horse". I would advocate to change this section (b) requirement, and ask for a protection study, not an onset of Immunity (OOI, 2-3 weeks post V2, too short) but a challenge mid-way between the V2-V3 interval (i.e. around 3 months, for a normal interval of 4-6 months for most EI vaccines). Based on kinetics studies (papers from Gildea et al, 2011, Paillot et al 2013 and other references), levels measured around mid-way V2-V3 interval (i.e. 3 months) are usually close to antibody levels measured near V3+6months/1 year. Challenge at V2+3months should provide a reasonable idea of actual cross-protection, outside the peak of immunity (positive bias of protection) or Immunity Gap (close to V3, negative bias of protection, usually resolved after V3). This would provide a more representative picture of actual protection than current OOI as described in Eu. Ph. 249 (i.e. at least 2 weeks post last vaccination). Proposed change (if any): I would suggest the following for section (b), lines 289-291: ... immunogenicity testing requirements specified in Section 2.3.2.1 of Ph. Eur 249 (i.e challenge using the current circulating strain or strains as documented by OIE or recommended like strains) should be conducted, no sooner than 3 months after last vaccination.	guideline should not include requirements for studies where changes per OIE recommendations are not made.
Section b Line 292	4	Comment: The statement "The above tests should also include an evaluation of the DOI of the vaccine in the target species to protection against the current circulating field strains as outline in 3.2.3." should be more explicit and leave no ambiguity that the DOI needs to be conducted with a challenge using a recent circulating strain, especially in the context of section (b). Both short-term	N/A – refer to comment above for line 284

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		challenge and DOI would need to be conducted/provided to substantiate the protection claim of unmodified vaccine. Proposed change (if any):	
Section b line 287	4	Comment: The statement "… testing in accordance with the Immunogenicity testing requirements specified in Section 2.3.2.1 of PH. Eur. 249 (i.e. challenge using the current circulating strain or strains as documented by OIE or recommended like strains) should be conducted." would need to be more accurate as too open to interpretation at the moment (i.e. leave the possibility to test against an OIE recommended strain that could be quite old, such A/eq/South Africa/4/03). Proposed change (if any): I would suggest to modify the statement "… protection against the most recent circulating strains as documented by the OIE Expert Surveillance Panel…" with "…testing in accordance with the Immunogenicity testing requirements specified in Section 2.3.2.1 of PH. Eur. 249 (i.e. challenge using a recent circulating strain as documented by OIE or recommended like strains but no older than 2 years at the time of the study) should be conducted.". This time requirement takes into account the time necessary for the strain to be fully documented, characterised and evaluated in pilot studies. This is also taking into account the preparation phase of any study but allows the conduction of an efficacy study against a strain still recent.	N/A – refer to comment above for lines 284
Sections 3.2.3 & 4	4	Comment: For the measure of efficacy, I believe that virus shedding measurement should now include the qRT-PCR, alongside the egg titration. The titration in embryonated eggs is still the only method to measure live infectious virus in nasal secretion but is not considered to be the most sensitive method.	Not accepted. Section 3.2.3 outlines the efficacy data requirements for a strain change i.e.

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		In this context, I would suggest virus shedding to be also tested by qRT-PCR, which is now widely accepted and will provide an important complement in evaluating EIV shedding and therefore protection induced by vaccination. The use of a unique method, with limited sensitivity, does not favour an optimal evaluation of virus shedding and therefore vaccine efficacy. The current PH. Eur. 249 section 2.3.2.1. is not detailed enough concerning this point, as follows: "The average number of days on which virus is excreted, and the respective virus titres are significantly lower in vaccinated horses than in control horses". The detection methods to be used should be mentioned in the new Guidelines, both in section 3.2.3 "Efficacy data" and section 4. "No modification to existing vaccine". Proposed change (if any): I would suggest to add the following sentence between lines 181 and 182. "Vaccine efficacy would be demonstrated if signs of disease and reduction of virus excretion, measured with at least 2 different methods, are significantly lower in vaccinated horses than in control horses".	challenge or serological data in accordance with Ph. Eur. 249. For challenge studies Ph. Eur. 249 requires a significant reduction in viral shedding for vaccinates vs controls but does not define a specific test method for viral shedding. Therefore assessors can evaluate the suitability of the applicant's chosen test method(s) for viral shedding on a case by case basis. Taking this into account, it is not considered appropriate to include in this guideline, a requirement to use 2 test methods (as suggested) or to refer to a specific test method such as PCR to investigate viral shedding. Section 4 has been removed from the guideline so this comment is not relevant for Section 4.