EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 April 2013
EMA/CVMP/IWP/97961/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the compliance of authorised equine influenza vaccines with OIE requirements

Draft

Draft agreed by Immunologicals Working Party	January 2013
Adopted by CVMP for release for consultation	11 April 2013
Start of public consultation	30 April 2013
End of consultation (deadline for comments)	31 October 2013

This guideline replaces the Note for Guidance: Harmonisation of requirements for equine influenza vaccines – Specific requirements for substitution or addition of a strain or strains (EMEA/CVMP/112/98-FINAL).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu.

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

Guideline on the compliance of authorised equine influenza vaccines with OIE requirements

Table of contents

Executive summary

This document provides guidance on the data requirements to support modifications to authorised, equine influenza vaccines based on recommendations from the OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition (OIE Expert Surveillance Panel).

These modifications include the removal, replacement or addition of viral strains used to produce the antigenic components of authorised equine influenza vaccines, in accordance with recommendations from the OIE Expert Surveillance Panel.

Advice is also given on ways to demonstrate that authorised equine influenza vaccines which are not modified in accordance with the OIE recommendations, will provide protection against current circulating equine influenza viral strains.

The guideline has to be read in conjunction with the CVMP guideline on General requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010); European Pharmacopoeia (Ph. Eur.) monograph 249 'Equine Influenza Vaccine (Inactivated)' and Directive 2010/63/EU on the protection of animals used for scientific purposes.

1. Introduction

Equine influenza is an acute contagious respiratory disease of horses worldwide caused by infection with equine influenza A virus. 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.

It is known that antigenic drift occurs in the gene coding for the haemagglutinin (HA) protein of equine influenza A viral strains. This drift eventually leads to the circulation of influenza viral strains in the equine population which are antigenically heterologous to those used to produce the antigenic fraction of authorised equine influenza vaccines, thus compromising vaccine efficacy.

The OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition, including representatives from the WHO and OIE reference laboratories, review annually the epidemiological and virological information on equine influenza. Based on this review, the Expert Surveillance Panel conclusions and recommendations are published on an annual basis outlining recommendations on suitable viral strains to use in the manufacture of the antigenic fraction of equine influenza vaccines in order that they are protective against circulating equine influenza virus strains.

On the basis of this annual review, it is expected that modifications, to the equine influenza viral strains used to manufacture the antigenic fraction of authorised vaccines will be necessary on a regular basis. This document outlines the types of modification which can be accepted in order to meet OIE recommendations and the data requirements to support applications for these modifications.

2. Scope

This document is applicable to existing, authorised equine influenza vaccines – specifically to modifications to the antigenic components of these vaccines in accordance with recommendations from the OIE Expert Surveillance Panel.

The guideline is relevant to both authorised equine influenza vaccines containing (a) antigens produced

by 'conventional' methods i.e. manufactured using a strain or strains of equine influenza virus grown in cell cultures or in embyronated hens eggs and (b) antigens produced using recombinant DNA technology due to expression in genetically modified organisms (GMO vaccines). In the case of GMO vaccines, the requirements of Directive 2001/18/EC must also be met.

Methods by which authorised equine influenza vaccines which are not modified in accordance with the OIE recommendations can be shown to protect against current circulating equine influenza viral strains are also discussed in this guideline.

This document is therefore intended to replace the existing guideline:

Note for Guidance: Harmonisation of requirements for equine influenza vaccines – Specific requirements for substitution or addition of a strain or strains (EMEA/CVMP/112/98-FINAL).

3. Modifications to authorised vaccines

3.1 Specific requirements:

It is expected that the modifications required to meet the recommendations from the OIE Expert Surveillance Panel will involve changes to the antigenic fraction of the vaccine due to the addition, replacement or removal of a strain or strains of equine influenza virus used in the manufacturing process.

In order that the data already assessed during authorisation of the existing vaccine formulation may be used as support for the modified formulation, the following requirements apply:

- The proposed additional or replacement strain(s) should be an OIE recommended strain(s) or recommended like strain(s) (refer to Section 3.2.1 below for more details).
- The production process of the new strain(s) should be based on the same principles as that of the original strain(s) e.g. manufacture in cell culture or embryonated hen eggs for conventional vaccines and using the same vector system for GMO vaccines.
- 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 and the method of production of these existing strain(s) (other than increasing the degree of concentration applied by the currently approved method) should remain unchanged.
- The adjuvant(s) and the concentration(s) of adjuvants(s) used in one dose of the vaccine should remain unchanged – it is recognised that a change in the ratio of antigen to adjuvant(s) may be necessary depending on the final number of strains used to manufacture the modified formulation.

3.2 Data requirements:

3.2.1 Quality data

An updated Part 2 (quality) dossier should be provided. This should include amended versions of the relevant sections of Title II of Annex I to Directive 2009/9/EC updated to take account of changes due to the addition, replacement or removal of an equine influenza viral strain or strains used to manufacture the antigenic fraction of the vaccine.

The following aspects are of particular importance:

- The rationale for addition, replacement or removal of the strain(s) should be described. 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. Under these circumstances, the following requirements apply:
    - The relationship between the OIE recommended strain and the proposed recommended-like strain should be documented.
    - It should be demonstrated that the Master Seed Virus of the recommended-like strain is antigenically similar to the antigenically characterised recommended virus held at the OIE Reference Laboratory.

  *Due to the time involved in generating data to support the use of replacement / additional strain(s) (e.g. testing of the MSV, etc.), it is possible that by the time an application is submitted for the reformulated vaccine, the replacement / additional strain(s) in the reformulated vaccine may differ to the more recently recommended strains in the latest annual OIE publication.

  Under these circumstances, the relationship between the replacement / additional strain(s) in the reformulated vaccine and the more recently recommended strains in the latest OIE publication should be documented and the relevance of the replacement / additional strain(s) to provide protection against current circulating equine influenza viral strains should be discussed.

- The method of manufacture of the replacement and / or additional strain(s) including in process controls, shall be described.
- A clear description of any consequential changes to the preparation of the existing bulk antigens (e.g. concentration steps) should be detailed along with the updated details of the blending process, including in process controls, for the modified vaccine formulation.
- Inactivation kinetics data for the replacement and / or additional strain(s) determined in accordance with the principles laid down in the Ph. Eur. monographs 62: 'Vaccines for veterinary use' and 249: 'Equine influenza vaccine (inactivated)' should be described.
- Details of the inactivation control test(s) and validation of the method(s) for each new strain(s) should be given
- Details of the preparation and testing of the master and working seeds for the replacement / additional strain(s) in accordance with Ph. Eur. monograph 62: 'Vaccines for veterinary use' should be detailed. 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. A suitable method shall be provided to identify the new strain(s) and to distinguish it from related ones.
- Details of the quality control tests proposed for release of the reformulated vaccine should be provided. In particular, the methods used to determine the antigen content of each influenza component in the reformulated vaccine and the potency of the reformulated vaccine along with details of the validation of these test methods should be submitted.
- Quality control release testing results for 3 pilot scale size reformulated vaccine batches should be provided in accordance with the testing specified in the Ph. Eur. monographs 62: 'Vaccines for veterinary use' and 249: 'Equine influenza vaccine (inactivated)'.

- At a minimum, 6 months stability data for 3 pilot scale size reformulated vaccine batches are required. If these data do not suggest a decline in potency over the evaluation period, it may be possible to apply the shelf life for the original vaccine to the reformulated vaccine provided a commitment is made to test the stability batches at 12 and 18 months and to continue the stability evaluation to 3 months beyond the required shelf-life for the 3 batches. A commitment should also be given to report immediately to the competent authorities any out of specification results.
- Where the vaccine contains antigens produced using recombinant DNA technology, updated details according to the requirements of Directive 2001/18/EC must also be provided.

3.2.2 Safety data:

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)). Based on the results of this monitoring, 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.

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 an appropriate revision of the SPC.

3.2.3 Efficacy data:

(a) Immunogenicity of the modified vaccine in horses:

The immunogenicity of the reformulated vaccine should be examined according to the immunogenicity testing requirements of Ph. Eur. monograph 249.

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).

Where serology is used as a measure of immunogenicity, the post vaccination antibody titres should be determined using a suitable immunochemical method such as haemagglutination-inhibition (HI) testing or the single radial haemolysis (SRH) test or other validated test described.

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).

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.

In relation to acceptance criteria for post vaccination antibody titres, Ph. Eur. 249 states for equine influenza A virus strains of the H3N8 subtype, 'vaccines have usually been found satisfactory if the antibody titre of each serum is not less than 85mm^2 (SRH) or not less than 1:64 (HI)'. 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.

The authorised indication for the vaccine must also be taken into account when establishing this correlation as published data suggest that while SRH levels of ≥85mm^2 are likely to protect against clinical disease signs, levels of ≥150mm^2 may be necessary to provide protection against infection and virus shedding (Mumford 2001, Newton et al., 2000).

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.

Based on the results of the efficacy tests above, any changes to the indications for the vaccine should be reflected in an appropriate revision of the SPC.

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.

It is important that the modification of the vaccine strain(s) is done in a timely manner. However, as many authorised equine influenza vaccines have a minimum duration of immunity (DOI) of 1 year, it is recognised that data supporting the DOI of the reformulated vaccine may not be available at the time of application.

The application may be submitted pending the DOI data – if the data are available by the end of the procedure, the DOI which can be supported for the reformulated vaccine should be specified in the SPC agreed at the end of the application procedure.

If DOI data are still pending by the end of the application procedure and if the onset of immunity (OOI) of the original and reformulated vaccines are comparable (based on serological or challenge data), the DOI for the original vaccine may be retained in the SPC for the reformulated vaccine provided a commitment is given to (i) submit the DOI data once it becomes available and (ii) to revise the SPC appropriately should this be required based on the DOI data for the reformulated vaccine.

(b) 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:

Tests in guinea pigs:

To provide information on the interactions of the new strain(s) with each other and with existing, retained strain(s) and/or other antigens (e.g. tetanus), HI testing or the SRH test or other suitable

validated tests shall be carried out on the one hand with sera of guinea pigs immunised with the reformulated vaccine and on the other with each single influenza strain.

The antibody response in guinea pigs immunised with the reformulated vaccine should be shown to contain strain specific antibodies stimulated by the new strain(s) as well as strain specific antibodies stimulated by the retained, existing strain(s). This should be demonstrated 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).

Any differences in the strain specific antibody responses of guinea-pigs administered the reformulated vaccine compared to the response obtained when each influenza strain is given alone and the impact of any interactions between the strains should be discussed and evaluated.

The antibody response in guinea pigs immunised with the new formulation should also be compared to that obtained for the original vaccine formulation. The impact of any differences in the antibody responses should be discussed and evaluated.

The test method used to determine the antibody titres 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.

(c) Field data:

The performance of the vaccine under field conditions can be evaluated as part of the routine pharmacovigilance monitoring which manufacturers are required to conduct and report regularly to the competent authorities. Where the vaccine has been modified based on the use of a new or replacement strain, the schedule for pharmacovigilance monitoring will revert to that for a newly authorised product in accordance with Article 75 (5) of Directive 2001/82/EC, as amended i.e. PSURs must be submitted at six-monthly intervals for the first two years, annually for the next two years and thereafter at 3-yearly intervals, or immediately on request.

Note: For modifications involving only the removal of one or more strains from the authorised vaccine, no safety or efficacy data are required provided that (i) there are no other differences to the formulation (e.g. no differences in composition of excipients and/or adjuvants per dose) (ii) an evaluation is made of the absence of any impact of the removal of the strain or strains on the induction of protection in the target species and (iii) for at least one of the retained strains, challenge data are available involving a relevant strain which is supportive of the efficacy of the reformulated vaccine against the currently circulating field strains as documented by the OIE Expert Surveillance Panel.

4. No modification to existing vaccine

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:

*(a) Where a correlation between antibody titre and protection **has been** established / published:*

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, 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 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, 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).

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.

References

Daly, J. M., Yates, P. J., Newton, J. R., Park, A., Henley, W., Wood, J. L., Davis - Poynter, N. and Mumford, J. A. (2004): Evidence supporting the inclusion of strains from each of the two co-circulating lineages of H3N8 equine influenza virus in vaccines, Vaccine, 22 (29-30), 4101-9.

European Directorate for the Quality of Medicines and Healthcare: European Pharmacopoiea monograph 249 Equine Influenza Vaccine (Inactivated).

European Directorate for the Quality of Medicines and Healthcare: European Pharmacopoiea monograph 62 'Vaccines for veterinary use.

European Medicines Agency (2010). CVMP guideline on General requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010).

European Medicines Agency (1998). VICH Topic GL2 guideline on validation of analytical procedures: Methodology (CVMP/VICH/591/98-FINAL).

European Parliament and Council (2001). Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms.

European Parliament and Council (2009). Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use as amended by Commission directive 2009/9/EC.

European Parliament and Council (2010). Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes.

Mumford, J. A. (2010): Biology, epidemiology and Vaccinology of equine influenza, Proceedings of the International Symposuim, Budapest, 10-11 December 2001, 7-12.

Newton, J. R., Verheyen, K., Wood, J. L., Yates, P. J. and Mumford, J. A. (1999): Equine influenza in the United Kingdom in 1998, Vet Rec, 145(16), 449-52.

Newton, J. R., Townsend, H. G., Wood, J. L., Sinclair, R., Hannant, D. and Mumford, J. A. (2000): Immunity to equine influenza: relationship of vaccine-induced antibody in young Thoroughbred racehorses to protection against field infection with influenza A/equine-2 viruses (H3N8), Equine Vet J, 32(1), 65-74.

OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition document(s) on documentations and on recommendation on Equine Influenza latest version