EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 November 2014
EMA/CVMP/IWP/97961/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on data requirements for changes to the strain composition of authorised equine influenza vaccines in line with OIE recommendations

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
Agreed by Immunologicals Working Party	30 September 2014
Adoption by CVMP	6 November 2014
Date for coming into effect	7 May 2015

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

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Executive summary

This document provides guidance on the data requirements to support changes to the strain composition of authorised, equine influenza vaccines in line with recommendations from the Office International des Épizooties (OIE) Expert Surveillance Panel on Equine Influenza Vaccine Composition.

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 on Equine Influenza Vaccine Composition.

The guideline has to be read in conjunction with the Guideline 'General requirements for the production and control of immunological veterinary medicinal products'; the European Pharmacopoeia monographs 62 'Vaccines for veterinary use' and 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 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, which may compromise vaccine efficacy.

An Expert Surveillance Panel, including representatives from the World Health Organisation (WHO) and the World Organisation for Animal Health (OIE) reference laboratories, review annually the epidemiological and virological information on equine influenza. Based on this review, the OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition is 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 provide an optimal level of efficacy 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 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 on Equine Influenza Vaccine Composition.

The guideline is relevant to both authorised inactivated equine influenza vaccines containing antigens produced by 'conventional' methods (i.e. manufactured using a strain or strains of equine influenza virus grown in cell cultures or in embryonated hens eggs), and vaccines produced using recombinant technologies where the active substance is non-replicating in the target species. For recombinant vaccines, the requirements of Directive 2001/18/EC must also be met.

This guideline replaces the existing Note for Guidance on the 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 on Equine Influenza Vaccine Composition 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 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 however 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[1] or a relevant strain of the same lineage and clade (if appropriate) as the recommended strain, if justified (recommended-like strain). 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 (MSV) of the recommended-like strain is antigenically similar to the antigenically characterised recommended virus held at the OIE Reference Laboratory.
- 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 European Pharmacopoeia monographs 62 'Vaccines for veterinary use' and 249 'Equine influenza vaccine (inactivated)', should be provided.
- Details of the inactivation control test(s) for each new strain(s):
    - If the production process of the new strain(s) is based on that of the original strain(s) and one of the European Pharmacopoeia monograph 249 'Equine influenza vaccine (inactivated)' recommended methods for testing of residual live virus is used it should be demonstrated how the chosen test has been determined to be the most sensitive method for the new strain(s) as required by the European Pharmacopoeia monograph 249.
    - If an alternative method to those described in the European Pharmacopoeia monograph 249 is used, 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 the European Pharmacopoeia monograph 62 'Vaccines for veterinary use' should be given. In particular, the method used to generate the Master Seed of the replacement/additional strain(s) should be suitable to provide sufficient guarantee that the seed contains only the recommended strain or the recommended-like strain proposed for inclusion in the vaccine. A suitable method must have been applied to identify the new strain(s) in the master seed(s) and to distinguish it as far as possible from related ones.

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

- Details of the quality control tests proposed for release of the reformulated vaccine. 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.
- The batch potency test system should remain the same and the following points must be taken into account:
    - Where the specification is based on a comparison of test and reference vaccine batches, the reference vaccine should be a reformulated vaccine batch for which efficacy in horses has been demonstrated (refer to 3.2.3 below).
    - Where the specification is based on a comparison of test and reference antisera from an animal model (e.g. guinea-pigs), the reference antiserum should be generated using a batch of the reformulated vaccine which has been demonstrated to be efficacious in horses.
    - The minimum specification should be appropriately justified for the new strain(s) and rejustified based on data obtained from the reformulated vaccine for each of the remaining strains.
- Quality control release testing results for 1 x pilot scale size reformulated vaccine batch should be provided in the submission with a commitment to provide data from an additional two commercial batches post authorisation. These batches should be tested in accordance with the testing specified in the European Pharmacopoeia monographs 62 ‘Vaccines for veterinary use’ and 249 ‘Equine influenza vaccine (inactivated)’ unless other testing requirements are specified in the original marketing authorisation dossier.
- As the production process(es) of the new strain(s) is similar to that of the original strain(s), it is acceptable to apply the shelf life for the original vaccine to the reformulated vaccine, provided a commitment is made that a minimum of three of the reformulated batches are entered into the ongoing stability program and tested at regular intervals to confirm the shelf life of the reformulated vaccine.
- Where the vaccine contains antigens produced using recombinant technologies, updated details according to the requirements of Directive 2001/18/EC must also be provided.

3.2.2 Safety data

If there is no increase in the number of component strains, specific studies investigating the safety of the modified vaccine are not required. 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). 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 summary of product characteristics (SPC).

If the reformulation increases the number of strains in the vaccine, safety testing should be performed according to the vaccination schedule in a minimum of eight horses. If a third dose is intended to be administered for primary vaccination, it may be given two weeks after the second one to evaluate the safety of a repeat 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

The immunogenicity of the reformulated vaccine should be examined according to the immunogenicity testing requirements of the European Pharmacopoeia monograph 249 'Equine influenza vaccine (inactivated).

This requires that a challenge for at least one of the strains in the modified vaccine has been performed as described in section 2.3.2.1 of the European Pharmacopoeia monograph 249. 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 on Equine Influenza Vaccine Composition, 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 on Equine Influenza Vaccine Composition) 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 the European Pharmacopoeia monograph 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 SRH (single radial haemolysis) test or other suitable test methods. The test method used to determine the antibody response should be sufficiently validated.

In relation to acceptance criteria for post vaccination antibody titres, the European Pharmacopoeia monograph 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, it also states that 'the acceptance criteria depend on the strain'. Furthermore, the required titre may depend on the claim made for the vaccine as higher titres may be needed to confer protection from infection and shedding of virus than are needed to protect against clinical disease. Similarly, chapter 2.5.7 (Equine influenza) of the OIE 'Manual of diagnostic tests and vaccines for terrestrial animals' recommends a minimum SRH titre of 150mm^2 to confer protection. 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). The proposed acceptance criteria should therefore be justified in relation to the strain and the level of protection claimed.

The use of reference equine influenza antisera available from the EDQM is described in the European Pharmacopoeia monograph 249. 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 within an agreed timeframe, and (ii) to revise the SPC appropriately should this be required based on the DOI data for the reformulated vaccine.

3.2.4 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 6-monthly intervals for the first two years, annually for the next two years and thereafter at 3-yearly intervals, or immediately on request).

3.2.5 Removal of a strain(s)

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 on Equine Influenza Vaccine Composition.

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