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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper on the need of revision of the Note for Guidance: Harmonisation of requirements for equine influenza vaccines – Specific requirements for substitution or addition of a strain or strains

Draft

Agreed by Immunological Working Party	February 2012
Adoption by CVMP for release for consultation	March 2012
Start of public consultation	16 March 2012
End of consultation (deadline for comments)	31 May 2012

The proposed guideline will replace the Note for Guidance: Harmonisation or 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 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Concept paper on the need of revision of the Note for Guidance: Harmonisation of requirements for equine influenza vaccines – Specific requirements for substitution or addition of a strain or strains.

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1. Introduction

The current Note for Guidance (NfG): 'Harmonisation of requirements for equine influenza vaccines – specific requirements for substitution or addition of a strain or strains' was adopted by the CVMP in November 1998.

The purpose of the NfG is to outline situations and requirements where substitution or addition of one or more strains of the influenza A/equine 1 virus (H7N7) and/or influenza A/equine 2 virus (H3N8) subtypes of an equine influenza vaccine is necessary due to antigenic drift associated with the gene coding for the haemagglutinin (HA) (i.e. the major surface protein of influenza A strains).

However, the most recent recommendations from the OIE do not support the inclusion of H7N7 subtype in equine influenza vaccines.

2. Problem statement

The existing NfG outlines that antigenic drift which is known to occur in the gene coding for the haemagglutinin (HA) (i.e. the major surface protein of influenza A strains) will eventually lead to the vaccine virus strains becoming obsolete and thus compromising vaccine efficacy. Based on the rate of antigenic drift observed in equine influenza strains, the NfG considers that a regular update of the strains may be necessary every 3 to 5 years.

The NfG states that as equine influenza vaccines are well known and considering the availability of reliable in-vitro tests such as Single Radial Diffusion (SRD): measures HA content of vaccine bulk antigen) and Single Radial Haemolysis (SRH) measures antibody response to HA), it is unlikely that the replacement of one strain by another would lead to such substantial changes so as to justify a new full set of safety and efficacy tests to be carried out. Reduced safety and efficacy data requirements are therefore outlined in the NfG for applications for substitution or addition of a strain or strains compared to the data requirements for a new vaccine application.

The NfG lists a number of criteria that must be met in order that reduced data requirements apply i.e.:

A) It is not expected that manufacturers will modify their vaccine to exclude A/equine 1 (i.e. H7N7) virus strains as there is insufficient evidence to justify such a change.

B) In the case of adding strains it is not expected that there will be

1) A decrease in the antigen content of the original strains

2) Any change to the method of production of the original strains (other than increasing the degree of concentration applied by the currently approved method), or

3) A change in the quantity of adjuvants or ratio of the volume of antigen to adjuvants.

C) It is not expected that manufacturers will add two new strains of the same subtype to their vaccines at the same time.

The existing NfG states that if conditions (B) and (C) do not apply to the changes being made to the equine influenza vaccine, then additional data to that described in the NfG will be required.

The latest guidance from OIE does not support the inclusion of a viral strain of the H7N7 subtype in equine influenza vaccines– this contradicts criterion (A) currently referred to in the NfG. The existing NfG does not give any guidance on requirements in the event that option (A) is not met.

In relation to the H3N8 subtype, the latest recommendation from OIE does not support the inclusion of H3N8 virus of the Eurasian lineage (e.g. A/equine/Newmarket/2/93) which is included in many equine influenza vaccines currently authorised.

The OIE recommendation is for manufacturers to update their vaccines to include representative strains of the Florida sublineage of H3N8. As two clades of the Florida sublineage of H3N8 are known, if manufacturers are to reformulate to include a representative of each clade, criterion (C) of the existing NfG will also be contradicted.

The reduced data requirements listed in the NfG are no longer applicable as criteria (A) and (C) on which they are based cannot be met if manufacturers are to amend their vaccines in accordance with the latest OIE recommendations. An update of the NfG is therefore considered necessary to give guidance on the type of data required to support the removal / substitution / addition of vaccine viral strains to meet the current (and possible future) recommendations from OIE.

3. Discussion (on the problem statement)

Most of the currently authorised equine influenza vaccines contain a strain of the H7N7 subtype and one or more representative Eurasian and / or American lineage strains of the H3N8 subtype.

Characterisation of the HA sequences of influenza virus strains isolated from different countries worldwide over the last 5 years indicates that the majority were of the American lineage (Florida sublineage) of the H3N8 subtype which comprises 2 clades i.e. Clades 1 and 2.

In 2010, the majority of the isolated and characterised viruses were from the clade 2 lineage (e.g. A/equine/Richmond/1/07) with only one investigated outbreak being associated with a clade 1 virus (e.g. A/equine/South Africa/03). There was evidence of a lack of vaccine efficacy against clade 2 viruses i.e. vaccines containing earlier versions of the American lineage (such as A/equine/Newmarket/1/93) do not provide adequate protection against these viruses.

There was only a very low and sporadic isolation of Eurasian lineage viral strains over the last 5 years with none isolated in 2010.

On this basis, the most recent recommendation from OIE is that it is not necessary to include a H7N7 subtype or a H3N8 virus strain of the Eurasian lineage (e.g. A/equine/Newmarket/2/93) in equine influenza vaccines.

The OIE recommends that equine influenza vaccines for the international market should contain both clade 1 and clade 2 viruses of the Florida sub lineage – Clade 1 being represented by A/equine/South Africa/03-like or Ohio/03-like viruses and Clade 2 being represented by A/equine/Richmond/1/07-like viruses.

The existing NfG lists reduced requirements for safety and efficacy testing for applications for equine influenza vaccines involving substitution or addition of one or two vaccine strains. However these reduced requirements are based on the assumption that a H7N7 vaccine strain will continue to be a constituent of the vaccine and 2 strains of the same subtype will not be added to the vaccine at the same time. These conditions can no longer be met by vaccine manufacturers when changing vaccine strains to satisfy current OIE recommendations, therefore the reduced data requirements listed in the existing NfG are no longer applicable.

An update of the existing NfG is therefore considered necessary to provide guidance to manufacturers on the data requirements associated with updating the equine influenza strains in their vaccines to meet OIE recommendations for equine influenza vaccines.

4. Recommendation

To encourage vaccine manufacturers to update the equine influenza strains in their vaccines so that horses are adequately protected against circulating strains, a revision of the NfG is required to provide guidance on the data requirements necessary to support the deletion/substitution/addition of viral strains to meet OIE recommendations for equine influenza vaccines.

5. Proposed timetable

Discussion of first draft of the guideline at October 2012 IWP meeting. Finalisation of the guideline for release for consultation in Q3/4 2013.

6. Resource requirements for preparation

Appointment of a Rapporteur

Adequate time for discussion at IWP

EMA secretariat to manage the development of the document and consultation process

Discussions at CVMP

7. Impact assessment (anticipated)

The revised document is expected to assist manufacturers in designing the safety and efficacy studies and determine the type of data required for applications to support the change of strains in equine influenza vaccines in accordance with OIE recommendations. The revised document will also provide guidance for assessors on the data which needs to be assessed to support an application to change the strains of an equine influenza vaccine.

8. Interested parties

The revised guideline will have an impact for industry as it will outline the data requirements, including safety and efficacy data requirements to support the change in viral strains for equine influenza vaccines.

9. References to literature, guidelines etc.

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