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

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*The current revision consists of administrative changes made in order to align the guideline to the new definitions and terminology provided by Article 4 of Regulation (EU) 2019/6. The references to the legislation applicable and other scientific guidelines have also been updated. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary.

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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 World Organisation for Animal Health (WOAH, formerly 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 WOAH Expert Surveillance Panel on Equine Influenza Vaccine Composition.

1. Introduction

Equine influenza (EI) is a highly contagious though rarely fatal respiratory disease of horses, donkeys, mules and other Equidae. Nowadays, outbreaks still have a severe impact on equine health. Historically, EI was caused by two subtypes of influenza A viruses: H7N7 and H3N8 (Eurasian and American lineage) of the family *Orthomyxoviridae*.

Current causative viral strains (since 2010) are H3N8 (American lineage, clades 1 and 2). 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 (WOAH) reference laboratories, annually reviews the epidemiological and virological information on equine influenza. Based on this review, the WOAH 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 to 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, may be required over the time. 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 changes in the antigenic components of these vaccines in accordance with recommendations from the WOAH 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 chicken eggs), and vaccines produced using recombinant technologies where the active substance is non-replicating in the target species.

3. Legal basis

This guideline should be read in conjunction with the introduction and general principles of Annex II to Regulation (EU) 2019/6 relevant to immunological veterinary medicinal products (IVMPs), and all other relevant EU and VICH guidelines as well as relevant European Pharmacopoeia (Ph. Eur.) texts and monographs applicable to IVMPs. These include but are not limited to the Guideline 'General requirements for the production and control of immunological veterinary medicinal products'; the Ph. Eur. general monograph 0062 'Vaccines for veterinary use' and the specific Ph. Eur. monograph 0249 'Equine Influenza Vaccine (Inactivated)'.

For vaccines containing genetically modified organisms, the requirements of Regulation (EU) 2019/6 must also be met.

Guidelines related to limited markets, vaccine antigen master file (VAMF), vaccine platform technology master file (vPTMF) and/or multi-strain dossier should be also taken into account, when applicable.

All animal experiments should be conducted taking into account section I.1.7 of Annex II of Regulation (EU) 2019/6 and the 3Rs principles (replacement, reduction and refinement). Alternatives to in vivo test methods should be employed whenever possible.

4. Changes in strain composition of authorised vaccines

4.1 Specific requirements

It is expected that the variations required to meet the recommendations from the WOAH 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 a WOAH 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 chicken eggs for conventional vaccines and using the same vector system for recombinant 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.

4.2 Data requirements

4.2.1 Quality data

An updated Part 2 (quality) dossier should be provided. This should include amended versions of the relevant chapters of Annex II, section IIIb of Regulation (EU) 2019/6 to take account of changes due to the addition, replacement or removal of an equine influenza viral strain(s) or antigen(s) 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 WOAH 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 WOAH 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 WOAH 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.
- In case of inactivated antigens, the inactivation kinetics and controls should follow recommendations in the general guideline on requirements for the production and control of immunological veterinary medicinal products and the Ph. Eur. general monograph 0062 'Vaccines for veterinary use'
- About the 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 Ph. Eur. monograph 0249 '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 Ph. Eur. monograph 0249.
    - Other available methods to those described in the Ph. Eur. monograph 0249 can be used, if it is demonstrated by validation that the alternative method is equivalent to the official method or more suitable.
- Details of the preparation and testing of the master and working seeds for the replacement/

[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 WOAH 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 WOAH 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.

additional strain(s) should follow the legislation and guidelines applicable, mainly taking into account extraneous agents' risk-assessment and should be given in accordance with the Ph. Eur. general monograph 0062 ' 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.

- 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 re-justified based on data obtained from the reformulated vaccine for each of the remaining strains.
- For batch-to-batch consistency, quality control release testing results for at least one pilot scale size reformulated vaccine batch should be provided in the submission, and the full protocol of the first two batches of the vaccine re-formulated containing the new strains should be submitted on completion. These batches should be tested in accordance with the testing specified in the Ph. Eur. general and specific monographs, unless other testing requirements are specified in the original marketing authorisation dossier.
- About the stability testing: As the production process(es) of the new strain(s) is similar to that of the original strain(s), it is acceptable to apply and accept the shelf life for the original vaccine to the reformulated vaccine, even with an ongoing stability study, but the marketing authorisation holder should provide stability results of one reformulated full-scale batch (for standard manufacturing methods) or two reformulated full-scale batches (for non-standard manufacturing methods) post authorisation to confirm the shelf life of the reformulated vaccine.

4.2.2 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 vaccines with a changed composition can be evaluated in the efficacy studies (for example by monitoring systemic and local reactions) described below (refer to 4.2.3). 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 product information.

If the reformulation increases the number of active substances (strains) in the vaccine, safety testing should be performed with the new product according to the vaccination schedule in a minimum of eight horses. 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 product information.

4.2.3 Efficacy data

In principle, the efficacy of the vaccine with the new composition shall be demonstrated by a challenge study in laboratory conditions and/or by an indicator of protection correlated with the efficacy in the target species. The onset of immunity of the reformulated vaccine then should be demonstrated according to the applicable legislation, guidelines and in line with the immunogenicity testing indicated in Ph. Eur. monograph 0249 '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 0249. 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 WOAH 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 WOAH 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 0249 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 Ph. Eur. monograph 0249 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 WOAH 'Manual of diagnostic tests and vaccines for terrestrial animals' recommends a minimum SRH titre of 150 mm^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 Ph. Eur. monograph 0249. 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 product information.

About duration of immunity, a specific justification and/or study is expected when a new antigen (strain) is included in the vaccine composition. The proposed duration of immunity should be reflected in the product information.

4.2.4 Field data

Clinical (field) studies are not required if the pre-clinical (laboratory) efficacy studies adequately establish and validate the efficacy and it is justified that they are representative of efficacy under field conditions.

If needed, the performance of the vaccine under field conditions can be further evaluated as part of the pharmacovigilance signal management which manufacturers are required to conduct and report regularly to the competent authorities in accordance with Articles 77(4) and 81 of Regulation (EU) 2019/6.

4.2.5 Removal of a strain(s)

For changes in composition 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 WOAH Expert Surveillance Panel on Equine Influenza Vaccine Composition.

References

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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.

WOAH Expert Surveillance Panel document(s) on Equine Influenza Vaccine Composition - latest version.