EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2024
EMA/CVMP/IWP/390313/2023
Committee for Veterinary Medicinal Products (CVMP)

Guideline on live recombinant vector vaccines for veterinary use

Draft

Draft agreed by Immunologicals Working Party (IWP)	15 November 2023
Adopted by CVMP for release for consultation	17 January 2024
Start of public consultation	26 January 2024
End of consultation (deadline for comments)	31 May 2024

This guideline replaces the 'Guideline on live recombinant vector vaccines for veterinary use' (EMEA/CVMP/004/04-FINAL)

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

Keywords	***Vector vaccines, veterinary, quality, safety, efficacy***

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Guideline on live recombinant vector vaccines for veterinary use

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Executive summary

The main aim of the guideline is to advise on the data to be presented in applications for a marketing authorisation of live recombinant vector vaccines, taking into account their particular properties.

This guideline replaces the Guideline on live recombinant vector vaccines for veterinary use (EMEA/CVMP/004/04-FINAL).

1. Introduction (background)

The Guideline on live recombinant vector vaccines for veterinary use (EMEA/CVMP/004/04-FINAL) was adopted in December 2004 and came into effect on 8 June 2005. The guideline was developed at a time when only a few vector vaccines were available. Considering the scientific and regulatory developments since then and experiences gained, the CVMP/IWP considered that this guideline should be updated in order to reflect current knowledge and ensure continued relevance for development of commercial vaccines.

The requirements for the production and control of immunological veterinary medicinal products (IVMPs) laid down in Regulation (EU) 2019/6 as amended fully apply to live recombinant vector vaccines.

The objective of this guideline is to define what should be presented in the quality, safety and efficacy part of the application taking into account the particular properties of live recombinant vector vaccines in the target and non-target species, including the natural host of the parental organism (where relevant).

This guideline does not repeat the requirements for environmental risk assessment, already developed in the Note for Guidance on environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95).

In addition, as per the requirements of Regulation (EU) 2019/6 as amended, the applicant has to provide the information relating to the genetically modified organisms (GMOs) as requested in Annex IIIA of Directive 2001/18/EC. As not all the points included in this Annex IIIA will apply to live recombinant vector vaccines, it is not expected that the applicant will address all the points of this Annex.

As the headings or titles and the definitions of starting materials differ slightly between Directive 2001/18/EC and Regulation (EU) 2019/6, the required data on starting materials, construction of the recombinant organisms and the recombinant vaccines are regarded as part of the history of the master seed as defined in Regulation (EU) 2019/6, Annex II, Section IIIb, Part 2.C.2.1.

2. Scope

Guidance is provided on the data that are expected on quality, safety and efficacy in support of an application for a marketing authorisation for veterinary live recombinant vaccines.

Vaccines containing live replication competent or replication-defective micro-organisms (bacteria, viruses, fungi or parasite species) that have been modified to express foreign proteins and/or to include foreign DNA or RNA sequences with the aim to induce an immune response and where the vector acts as a carrier and may itself act as a protective immunogen fall within the scope of this guideline.

The current revision concerns in particular an update to align with the new legislation.

Deviations from this guideline may be acceptable provided they are scientifically justified.

3. Legal basis

The legal basis for the authorisation of a veterinary medicinal product is laid down in Regulation (EU) 2019/6. The present document should be read in particular in conjunction with the introduction and general principles and Section IIIb (requirements for immunological veterinary medicinal products) of Annex II to Regulation (EU) 2019/6, as amended.

In addition, Ph. Eur. chapters 5.2.6 and 5.2.7, monograph 0062 and relevant individual monographs should be taken into account, as well as all other relevant EU and VICH guidelines.

In addition, for vaccines within the scope of this guideline containing GMOs, the legal requirements as outlined in Article 8.5 of Regulation (EU) 2019/6 will apply.

If the vector is to be used as a platform for multiple vaccines, the use of a vaccine platform technology master file (vPTMF) may be applicable. Specific guidance on data requirements for a vPTMF is provided in the respective guideline (EMA/CVMP/IWP/286631/2021).

4. Points to be addressed for a live recombinant vector vaccine

4.1. QUALITY

The vector, bacteria as producer of shuttle plasmids, any genetic material used in the construction, the inserted gene(s) and the final construct should be described in detail. In this context, the final construct is regarded as master seed. Bibliographical references for the source materials could be acceptable, provided they cover the material(s) used for the production of the final construct.

The identity and direct relation of the material described in the scientific publication with the master seed(s) of the vaccine should be justified.

The description of the starting materials shall include:

4.1.1. Substrates for production/parental organisms

A full description of the starting organisms and plasmids should be provided.

The description should cover the material to produce the master seed.

4.1.2. Genetic material used in the construction of the vector

For the plasmids used to construct the live recombinant vector vaccine, all the data available about the construction, the structure, the sequence and the properties should be provided.

The recombinant donor plasmid and the bacteria used to produce the plasmid should be described in detail and the information presented should indicate their characteristics and their detailed origin. All the elements in the plasmid should be described, including promoters, enhancers and the selected foreign coding sequences. Information on the analysis conducted to confirm the structure of the donor plasmid should be submitted.

As some plasmids are suspected to be insufficiently stable, plasmid instability must be excluded if it may have an impact on the final vector vaccine.

The use of antibiotic markers encoding resistance to antibiotics used for therapy should be avoided wherever possible. Transfer of the encoding resistance to the final vector vaccine is unacceptable.

4.1.3 Vectors

The strategy of the construction of the recombinant vector vaccine should be presented as described in Directive 2001/18/EC, Annex IIIA: Part II.C. Characteristics of the modified organism. 1. Information relating to the genetic modification.

The method used for construction of the vector vaccine should be described in detail (e.g. homologous recombination, gene knock-in using homology directed repair (HDR) or non-homologous end- joining mediated by Crispr Cas9 or TALENs). Whenever possible, the virulence genes of the vector should be characterised. If applicable, knowledge about the function of deleted and added genes and proteins expressed in the vector has to be provided; a detailed description of markers which are present should be provided.

Details of the integration of plasmid DNA into the vector should be presented and should address the impact of the gene insert on the expression of the neighbour genes in the vector, whenever possible. The effect of gene deletion on the biological properties of the live vector should be investigated.

The genetic characterisation of the vector should be presented. This should include at least the sequencing of the regions flanking the insertion sites and the sites themselves.

4.1.4 Sequences to be inserted

Characterisation of the inserted sequence with appropriate methods should be performed.

The sequences to be transferred to the vector should be clearly defined and sequenced as far as it appears to be necessary to evaluate quality, safety and efficacy of the product.

4.1.5 Characteristics of the final vector vaccine

Information should be presented on the genotype and phenotype of the live recombinant vector and on the methods used for its screening and identification. Data on its genotypic and phenotypic stability, virulence, tissue and host tropism should be submitted as part of the safety package. If the strain is deemed to be replication abortive in the target species, the applicant may confirm this *in vitro* using an appropriate range of cell types from the target species.

It should be demonstrated as part of validation of the production process that the recombinant vector vaccine is stable throughout the manufacturing process to the finished product and that the integrated sequences have not undergone any rearrangements or mutations.

The antigen(s) expressed by the recombinant vector vaccine should be characterised by biochemical, molecular and/or immunological methods, to demonstrate the quality of the final product.

The applicant should provide techniques that allow differentiation between the parent strains of the vector and the vector vaccine.

4.2. SAFETY

4.2.1. Target species

The safety of the live recombinant vector vaccine should be investigated in the target species for the vaccine according to the requirements of Regulation (EC) 2019/6, Annex II, Section IIIb, Part 3.

The following points in particular deserve attention:

4.2.1.1 Spread of the recombinant vector vaccine

If the live recombinant vector vaccine has been shown capable of spreading to target and non-target species, adequate evaluation should be performed. For this purpose, safety studies should be conducted for relevant species sharing the same ecosystem as vaccinated animals and focussing on species known to be susceptible to the vector, in particular the natural host species of the parental vector. The range of species to be addressed should be justified.

Three steps should be undertaken:

- Transmission from vaccinated target animals to non-vaccinated target animals.

- Transmission from vaccinated target animals to non-target animals.

This includes the most common domestic and, if relevant, wild species, which live in the same environment as the vaccinated target species or may have direct or close contact with them. A risk analysis concerning the extent of the exposure should be performed.

- Transmission from vaccinated target animals to humans.

If there is a reason to suppose the live recombinant vector vaccine is able to spread to humans, a risk analysis of the pathogenicity of the recombinant vector and of the parent strain in humans should be performed.

If transmission of the vector to animals or humans may occur, the conditions for use should be described in detail and suitable information provided in the SPC.

4.2.1.2 Dissemination in the vaccinated animals

The applicant should investigate possible changes of tissue tropism by comparing the behaviour of the vector and the recombinant vector vaccine.

If the recombinant vector is deemed to be replication abortive the applicant should demonstrate this in the target species. A sensitive, validated detection system for the recombinant vector vaccine should be available.

4.2.1.3 Increase in virulence

Vectors must be non-pathogenic or low pathogenic to a level that will ensure that the resulting recombinant vector vaccine is safe for the intended target species. It has to be demonstrated that the insertion of foreign gene(s) does not lead to an increase in virulence. When appropriate data on genetic and phenotypic stability is available, there is no need for reversion to virulence studies using subsequent passages of the vector vaccine.

4.2.2. Ecotoxicity

Ecotoxicity should fully rely on the requirements of Regulation (EU) 2019/6 (Annex II) and Directive 2001/18/EC (Annex II).

The possible ecotoxicological effects of the vector vaccine have to be assessed as follows:

- Study of virulence to target and non-target species at risk see also 4.2.1.1.

- Horizontal transmission and potential of recombination of the vector vaccine or part of it.

- Host-range specificity

- Potential for establishment in the environment (e.g. dissemination of baits in the environment, persistence of the product in the environment at various climate conditions).

- A validated method should be provided that is able to detect the vector vaccine in the field and to differentiate it from the wild-type microorganism/antigen and/or inserted sequences (see also Directive 2001/18/EC, Annex IIIA, Part V.A.1), especially if diseases caused by the wild strains are subject to eradication and control programs.

- Data from other assessments performed with the same vector but other inserted sequences could be used as well, as long as the new insert does not change the characteristics and specifications of the final construct.

4.3. EFFICACY

The requirements of Regulation (EU) 2019/6 Annex II, Section IIIb, Part 4 fully apply. The efficacy of each of the components of a vector vaccine shall be demonstrated. Immunogenicity tests described in relevant Ph. Eur. monographs (i.e. for corresponding live vaccines) shall be performed and vector vaccines should comply with the requirements. If monograph requirements for immunogenicity cannot be met, the benefit-risk evaluation may still be positive if the safety of the vector vaccine is superior to that of the live vaccine and depending on the level of protection shown.

In case of vectors for which no efficacy claim is made, the immune response against the vector after vaccination should be documented and the impact on current vaccination schedules must be considered. Appropriate information on the properties of the recombinant vector should be included in section 4 of the SPC (immunological information).

The effect of pre-existing immunity to the vector and/or the foreign antigen(s) expressed by the vector on the efficacy should be addressed.

The possibility to boost the induced immunity against the vector antigen and/or the foreign antigen(s) within a claimed/intended vaccination schedule should be investigated if booster vaccinations are deemed necessary.

Definitions

Vector vaccine: vaccines containing live replication competent or replication-defective micro-organisms (bacteria, viruses, fungi or parasite species) that have been modified to express foreign proteins and/or to include foreign DNA or RNA sequences with the aim to induce an immune response and where the vector acts as a carrier and may itself act as a protective immunogen.

Organism: any biological entity capable of replication or of transferring genetic material.

Genetically modified organism (GMO): an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

References

Guideline on data requirements for vaccine platform technology master files (vPTMF) (EMA/CVMP/IWP/286631/2021)

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 and repealing Council Directive 90/220/EEC

Regulation (EU) 2019/6 of the European parliament and of the council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Note for Guidance: Environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95)