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Guideline on data requirements for multi-strain dossiers for inactivated veterinary vaccines

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This guideline replaces the 'Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)' (EMA/CVMP/IWP/105506/2007-Rev1).

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Executive summary

The main aim of the guideline is to address the use of a multi-strain dossier for inactivated vaccines against antigenically variable viruses or bacteria and to provide information on criteria for eligibility to use the multi-strain approach and on data to be included in a multi-strain dossier. Due to the extension of the multi-strain approach to viral diseases in addition to avian influenza (AI), bluetongue (BT) and foot-and-mouth disease (FMD) and to bacterial diseases requiring a need for rapid or frequent change in the strains included in the final product, a revision of the guideline on data requirements for multi-strain dossiers for inactivated vaccines against AI, BT and FMD was necessary.

1. Introduction

The concept of a multi-strain dossier was first included in the revised Technical Annex I to Directive 2001/82/EC, Directive 2009/9/EC and in the revised Variation Regulation (EC) 1234/2008 in order to provide regulatory incentives for marketing authorisation applications for inactivated vaccines against avian influenza, blue tongue and foot-and-mouth disease.

The Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council recommends that the multi-strain concept is introduced for inactivated vaccines against viral diseases, in addition to AI, BT and FMD, and also for bacterial diseases requiring a need for rapid or frequent change in the strains included in the final product.

The advantage to the applicant (and authorities) of a multi-strain dossier, as proposed, is the possibility to maintain only one dossier which can cover a wide range of vaccine strains. Although some specific information will be needed for each strain, other aspects can be dealt as "globally" where the same information is relevant for vaccines produced using any of the strains. This will avoid the need for a separate authorisation for each vaccine strain and also each possible combination of vaccine strains that might be envisaged. It can then be selected which strains are needed to deal with a particular disease situation in the field and companies are enabled to manufacture vaccines using the respective strains that are already authorised in the appropriate formulation.

The advantage for the user is the availability of vaccines that best suits the current epidemiological situation or OIE/EU/National requirements.

The development of appropriate and proportionate guidance for multi-strain dossiers is considered a key action towards the goal to address emerging health threats and promote the availability of veterinary vaccines (EMA Regulatory Science to 2025). It will allow authorisation of inactivated vaccines against antigenically variable viruses or bacteria for which rapid or frequent change in the composition of vaccine formulations is needed. This is important to ensure efficacy with regard to the epidemiological situation in the field, or to adapt the formulations to the variable distribution of strains of different viruses or bacteria between different geographical areas within the EU.

2. Scope

This guideline applies to new applications for authorisation of multi-strain dossiers for inactivated vaccines against antigenically variable viruses or bacteria:

- for which rapid or frequent change in the composition of vaccine formulations is needed, or

- to adapt the formulations to the variable distribution of strains of different viruses or bacteria between different geographical areas within the EU.

This guideline presents also the requirements for variations to multi-strain dossiers with regard to the addition or replacement of strains in these inactivated vaccines.

Each multi-strain dossier is applicable only to one virus species, one bacteria genus or one vector for a given disease. Mixtures of various viruses belonging to different families, genera, species or bacteria belonging to different families or genera cannot be approved in the context of a multi-strain dossier.

This guideline describes the requirements that should be presented in the quality, safety and efficacy parts of the multi-strain dossier.

It is envisaged that submission of a multi-strain dossier would not be appropriate in response to an emergency situation. The minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use are therefore not considered within the scope of this guideline.

This guideline does not apply to live vaccines.

3. Legal basis

The multi-strain dossier concept is included in the Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products, which provides the legal basis for the first marketing authorisation for a multi-strain dossier.

For the addition or replacement of a new serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine based on a multi-strain dossier, guidance on the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 is applicable.

The applicant can follow the vaccine antigen master file and/or the vaccine platform technology master file approaches in the context of a multi-strain dossier. In this case, the requirements of the guideline on vaccine antigen master files and the guideline on vaccine platform technology master files are also applicable.

4. Definitions

Strain

In order to ensure easier reading of this text, the term "strain" is used; this does not preclude the strains from belonging to different subtypes, serotypes, serovars and serogroups of the same virus species, bacteria genus, bacteria toxoids or vector.

Inactivated vaccine

In the context of the guideline, the term "inactivated vaccine" is used as opposed to the concept of live vaccine. This means that an inactivated vaccine contains an active substance that is not able to replicate. It covers conventional inactivated vaccines and vaccines produced by biotechnological processes such as vaccines obtained by controlled expression of genes, virus-like particles, virus-empty capsid particles, non-replicative vector (in the target species) or inactivated platform product.

Multi-strain dossier

A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of inactivated vaccines against antigenically variable viruses or bacteria for which rapid or frequent change in the composition of vaccine formulations is needed to ensure efficacy with regard to the epidemiological situation in the field. According to the epidemiological situation where the vaccine is

intended to be used, a number of strains could be selected from those included in the dossier to formulate a final product.

A multi-strain dossier covers a number of different strains of a single virus species, bacteria genus or vector produced according to the seed lot system. The formulation of the final product should be specified in the application in line with the recommendation of this guideline and should include a specification for the maximum antigen content per strain and the maximum number of strains in accordance with the safety data submitted with the application.

Marketing authorisation for a multi-strain dossier

The authorisation for a multi-strain dossier will specify the strains that may be included in the final product as well as the maximum amount and number of strains and the qualitative and quantitative description of the other components (adjuvants and excipients) present in the vaccine. The number and type of strains included in the final product should be adapted to the current epidemiological situation at the time of formulation of the final product and in accordance with the requirements of the competent authorities, where applicable.

5. Eligibility for the multi-strain approach

For new multi-strain dossier marketing authorisation applications, where no authorised multi-strain vaccine already exists for a particular virus/bacterium/disease, the applicant has to demonstrate that the vaccine fulfils certain criteria to be eligible for multi-strain approach:

- It contains only strains of one virus species, one bacteria genus or one vector for a given viral or bacterial disease,
- The relevance of the strains with regard to European current epidemiological situation and the epidemiological situation that might occur in the future shall be shown, and
- The need for a rapid or frequent change of strains or geographical variability adaptation of viral or bacterial strains due to the current or emerging epidemiological situation in the field shall be justified.

Before submission of the application, the European Medicines Agency (EMA) shall confirm the eligibility for the multi-strain dossier approach.

The multi-strain approach is still applicable to marketing authorisation applications for inactivated vaccines against avian influenza, blue tongue disease and foot-and-mouth disease and multi-strain dossiers for these diseases are exempt from the eligibility process.

6. General remarks

The requirements in Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products apply to applications for marketing authorisation for vaccines, which are submitted as multi-strain dossiers.

Different scenarios have to be taken into account depending on the way the applicant decides to develop the initial multi-strain dossier:

▪ New full marketing authorisation:

The multi-strain dossier consists of a new vaccine containing one or more strains never authorised before by the MAH (initial application of a multi-strain dossier).

or

▪ Combination of authorised vaccines:

The multi-strain dossier is obtained by the combination of authorised vaccines (vaccines authorised under exceptional circumstances are excluded) containing one or more strains (multi-strain dossier obtained by the combination of authorised vaccines).

or

▪ Variation of authorised vaccines:

The multi-strain dossier is obtained through a variation procedure in order to convert a dossier of an existing vaccine (containing one or more strains already authorised) to a multi-strain dossier.

Changes to existing multi-strain dossiers:

The multi-strain dossier is updated by the addition or replacement of a strain(s) to an authorised multi-strain dossier containing one or more strains (addition or replacement of strains to an authorised multi-strain dossier).

In the case of an increase in the maximum number of strains to be included in the final product, see section 11 below.

It should be emphasised that this guideline should be taken as a whole, once the development of a multi-strain dossier in compliance with this guideline is considered. Some parts and data normally required under Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products were indeed adapted in this guideline to the multi-strain concept, by reducing or reviewing the level of requirements; but this was conceivable and implemented only because some scientific compensations are provided elsewhere in the dossier (and taken into account in this guideline), restoring the balance of scientific knowledge and relevance, and ensuring the benefit-risk assessment to remain equivalent. Hence, it is important not to use only certain parts of this guideline for the development of a multi-strain dossier as the scientific balance between all parts of the dossier and the global level of scientific requirements might not be achieved anymore.

This guideline should be read in conjunction with the document "Questions and Answers on data requirements for multi-strain dossiers for inactivated vaccines (EMA/CVMP/IWP/466888/2017-Rev.1).

7. Initial application of a multi-strain dossier

7.1. Quality documentation (Section IIIb.2 Part 2)

For each antigen to be included in the multi-strain dossier, the applicant should provide the full set of requirements. The specific requirements of the quality part are summarised below:

IIIb.2.A1. Qualitative and quantitative composition

The applicant has to define the maximum number of antigens that can be included in the vaccine and specify the quantity for each antigen. If a fixed amount of antigen is not targeted during the formulation process, minimum and maximum quantities for each antigen should be specified. In all cases, the maximum antigen content (whatever the number of strains) that may be present in the vaccine has to be defined.

IIIb.2B. Description of the manufacturing method

The method of preparation should be the same for all vaccine strains. Deviations from this approach need to be explained and justified.

If applicable, the inactivation kinetics and tests for complete inactivation should be provided for all strains separately, unless justification is provided that the inactivation process and/or the tests for complete inactivation are valid for other strains.

The blending of the final product should be established and described for the maximum number of strains to be incorporated in the final product.

The blending should be standardised. The quantity of the ingredients, other than the antigens, and the volume of one dose of vaccine should be the same whatever the number and quantity of antigens that are included in the vaccine. However, the volume of the antigen phase may be adjusted with a suitable solution if necessary.

As the concerned vaccines are inactivated, the applicant is strongly encouraged to target a fixed amount for each antigen (which can be different between antigens) at the formulation step. This will allow the use of standard batches in safety and efficacy studies.

The final product can contain up to a maximum number of strains and a maximum antigen content that have to be defined by the applicant.

IIIb.2C. Production and control of starting materials

The production of each antigen is based on a seed lot system, whenever possible. The results of the tests of all starting materials shall comply with the requirements of Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products and of the European Pharmacopoeia (Ph. Eur.).

IIIb.2D. Control tests during the manufacturing process

The tests should preferably be the same for all strains. Any deviations in these tests need to be explained and justified. For critical tests (e.g. inactivation tests and antigen quantification tests), specific validation will normally be required for each strain.

IIIb.2E. Control tests on the finished product

The full range of tests, as required by the legal provisions in place, should be provided.

A specific test for identification, e.g. using immunological methods or nucleic acid amplification techniques (NAT) should be available for each antigen. The development of in vitro methods to quantify the antigens (e.g. ELISA, PCR) is recommended as it will normally facilitate the control of a vaccine containing different strains.

The potency test of a multi-strain vaccine cannot be elaborated in the way normally required for conventional dossiers of vaccines because of all the possible combinations of antigens. Therefore, mono-strain vaccines should be manufactured (in compliance with section 7.1 - 2.A to 2.D - of this guideline) for each of the available master seed, and a validated potency test should be elaborated for each of these mono-strain vaccines.

The validations and specifications established through the potency testing of each mono-strain vaccine can then be extrapolated to any multi-strain vaccine containing a combination of these antigens (within the maximum number of antigens previously established). The potency test for each mono-strain vaccine should be conceived in such a way that cross-reaction between strains will be limited as much as possible when the potency tests are applied to multi-strain vaccines containing these strains. If cross-reaction cannot be avoided in an in vivo potency test, additional in vitro tests (e.g. serotype- or strain-specific antigen ELISAs on finished product of the complete antigen bulk) may be introduced. Deviations from this principle need justification.

IIIb.2F. Batch-to-batch consistency

Batch-to-batch consistency data according to Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products should be provided.

A full protocol of three consecutive batches representative of routine production giving the results for all tests performed during production and on the finished product should be provided.

The batch to batch consistency may be demonstrated by using approaches that are considered equivalent:

- the demonstration of consistency of each strain formulated as a vaccine containing only this strain by providing a full protocol of three batches of vaccine for each strain.
- the demonstration of consistency of a multi-strain vaccine. In this case, the study shall be carried out using three batches manufactured with the maximum number of strains proposed within the multi-strain dossier application. The three batches provided must contain the same strains.

In the case of marketed finished products which contain strains not previously approved in the EU, the full protocol of the first three batches of a multi-strain vaccine containing the new strains should be submitted on completion.

IIIb.2G. Stability tests

Stability data according to Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products should be provided.

For the finished product, the tests shall be real-time studies carried out on three batches. The stability of a multi-strain vaccine may be demonstrated by using two approaches that are considered equivalent:

- If the demonstration of the stability of each strain formulated as a vaccine containing only this strain is available, the shelf life of the multi-strain vaccine containing different strains corresponds to the shelf life of the formulated strain which has the shortest stability.
- The stability data of a multi-strain vaccine may also be used to define the shelf life. In this case, the study shall be carried out using three batches manufactured with the maximum number of strains proposed within the multi-strain dossier application. The three batches tested must contain the same strains.

In the case of marketed finished products which contain strains not previously tested in stability studies, additional real-time studies on three batches of a vaccine containing only this new strain or a multi-strain vaccine containing the new strains should be performed and submitted on completion; any out of specification results during the stability evaluation should be reported immediately. The shortest shelf life for the currently authorised strains is applied in the meantime.

7.2. Safety documentation (Section IIIb.3 Part 3)

The complete range of safety tests mentioned in the Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products should be provided unless justified.

The tests should be carried out using a batch manufactured with the maximum antigen content to be included in any vaccine combination (whatever the number of strains), unless there is a fixed target antigen amount at the formulation step.

A standardised final product with respect to the composition of excipients and adjuvants (including the antigen phase/adjuvant phase ratio) should be used (key composition).

Safety should be demonstrated for the most sensitive category of each species and for each recommended route of administration. Extrapolation from one category or even species to another or one route of administration to another would be possible based on scientific justification for all safety studies including those for reproductive performance.

Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials. If clinical trials in third countries are available, they should be provided to support data from pre-clinical studies.

7.3. Efficacy documentation (Section IIIb.4 Part 4)

The efficacy tests mentioned in Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products should be provided unless justified.

Efficacy of a multi-strain vaccine cannot be demonstrated in the way normally required for conventional vaccines because of all the possible combinations of antigens. Therefore, mono-strain vaccines should be manufactured (in compliance with section 7.1 – 2.A to 2.D - of this guideline) for each of the available master seeds, and efficacy should be shown for each of these mono-strain vaccines. It will be accepted that efficacy of any multi-strain vaccine containing a combination of these antigens (within the maximum number of antigens previously established) will be at least as efficacious as shown for each of the mono-strain vaccines. The efficacy claim of the multi-strain vaccine corresponds to the sum of the claims of each antigen included in the vaccine.

Differences in the level of efficacy between strains or target species are acceptable, if adequately justified. In such cases, the product information must reflect these differences.

Possible known negative impact induced by certain strains should be taken into account. This evaluation could be based on published scientific data relating to the strain under evaluation.

The tests should be carried out using a batch containing the minimum amount of antigen to be included in any vaccine combination, unless there is a fixed target antigen amount at the formulation step.

The efficacy of each vaccine strain shall be demonstrated for each category of target animal species, by each recommended route of administration and using the proposed schedule of administration, unless scientific data can be provided demonstrating that extrapolation from one species to another species or from one category of a species to another category of the same species is possible.

The requirement for establishing onset of immunity, duration of immunity and the interference of maternally derived antibodies would depend on the claims and indications and anticipated conditions of use (e.g. for FMDV vaccines it may not be necessary to establish a duration of immunity).

In principle, the efficacy of the vaccine shall be demonstrated by a challenge study in laboratory conditions for each strain.

If an indicator of protection is used, the challenge may be omitted. For an indicator to be acceptable as a correlate of vaccine efficacy, it shall be demonstrated that a sufficient correlation exists between the indicator measured and the claimed protection in the target species. An indicator for protection should be shown to play a substantial role in the immune response, relevant for protection of the target species against the disease concerned. Reference to literature may be used to support the role of the indicator in the protection but it may not be sufficient to define the level necessary to guarantee efficacy of vaccination. It must be demonstrated that the level of response obtained for the indicator in clinical trials is equal to the one observed in vaccinated animals at the time of challenge in pre-clinical trials and for which protection was demonstrated.

Unless otherwise justified, results from pre-clinical studies shall be supplemented with data from clinical trials. When pre-clinical studies fully support the claims made in the summary of product characteristics, trials carried out in field conditions are not required. If clinical trials in third countries are available, they should be provided to support data from pre-clinical studies.

8. Addition or replacement of strains to the multi-strain dossier

Based on the condition that the key composition of the final product is not changed by the addition or replacement of a strain(s) of the multi-strain dossier (e.g. maximum number of antigens, same maximum antigen content, as described in section 7.1, and same composition of adjuvants and excipients), additional quality and efficacy data for the added or replaced strain(s) have to be provided according to the provisions in sections 7.1 and 7.3.

9. Multi-strain dossier obtained by the combination of authorised vaccines

The multi-strain dossier is obtained by the combination of authorised vaccines through a variation procedure.

Based on the condition that the key composition of the final product is not changed by the combination of authorised vaccines in a multi-strain dossier (e.g. maximum number of antigens, same maximum antigen content, as described in section 7.1, and same composition of adjuvants and excipients), no additional data have to be provided if it can be shown that the minimum requirements laid down in this guideline are already met. Should these minimum requirements not be met, additional data have to be provided according to the provisions in section 7 to update the multi-strain dossier.

The stability is based on the shortest shelf life presented for the combination, in compliance with section 7.1 Stability tests of this guideline.

10. Multi-strain dossier obtained by variation of authorised vaccines

The multi-strain dossier is obtained through a variation procedure in order to convert a dossier of an existing vaccine (containing one or more strains already authorised) to a multi-strain dossier and therefore no additional data have to be provided.

11. Variation to increase the maximum number of strains in a multi-strain dossier

Based on the condition that the key composition of the final product (except the number of strains) is not changed by the addition of a strain to the multi-strain dossier (same maximum antigen content, as described in section 7.1, and same composition of adjuvants and excipients), additional quality and efficacy data for the added strain have to be provided according to the provisions in sections 7.1 and 7.3.

If the addition of a new strain increases the maximum antigen content defined in the multi-strain dossier, additional quality, safety and efficacy data for the added strain have to be provided according to the provisions in sections 7.1, 7.2 and 7.3.