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Guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)

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Introduction

Vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth (FMD) diseases represent a special case in terms of the need for rapid and frequent change in the strains included and therefore do not fit well within the general regulatory model for vaccines.

Following experience with the authorisation of such FMD and AI vaccines by various decentralised and centralised authorisation procedures, the concept of a multi-strain dossier approach was included in the revised Annex I to Directive 2001/82/EC and in the revised Variation Regulation (EC) 1234/2008 in order to provide regulatory incentives for marketing authorisation applications for vaccines against Avian Influenza, Foot-and-mouth and Bluetongue diseases.

The advantages to the applicant (and authorities) of a multi-strain dossier as proposed are the need 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 with “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. Competent authorities can then select which strains are needed to deal with a particular disease situation in the field and enable the companies 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, which are produced and tested according to the actual scientific knowledge.

This guideline was first published in 2010 based on general scientific and regulatory principles in advance of much practical experience from assessing applications through European authorisation procedures. This revision was prepared following a review by CVMP of issues raised by stakeholders based on their experience of operating the guideline. Only minor changes were considered necessary to the guideline itself and an accompanying ‘Question and Answer’ document was produced to address the topics raised by stakeholders that are not specifically addressed within the revised guideline.

In order to ensure easier reading of this text, the term “strain” covers strains, subtypes and serotypes.

1. Scope

This guideline applies to new applications for authorisation of vaccines defined in multi-strain dossiers and variations to such dossiers concerning the addition or replacement of strains of inactivated vaccines intended for use against AI, BT and FMD diseases.

It describes the requirements that should be presented in the analytical, 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.

2. Legal basis

The multi-strain dossier concept is included in the revision of Annex I to Directive 2001/82/EC, which provides the legal basis for the first marketing authorisation for a multi-strain dossier.

In order to allow for addition or replacement of new strains, Commission Regulation (EC) 1234/2008 introduces specific provisions that would allow the addition or replacement of a new Master Seed Virus (MSV) of a new strain onto the authorisation of a multi-strain dossier via a Type II variation.

3. Definitions

Multi-strain dossier

A multi-strain dossier covers a number of different strains of the same virus produced according to the seed lot system. 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. 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 maximal 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 in accordance with the requirements of the competent authorities.

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 biotechnology process including subunit vaccines obtained by purification or controlled expression of genes, virus like particles, virus empty capsid particles.

4. General remarks

The requirements of Annex I of Directive 2001/82/EC fully apply to the vaccine which is submitted via a multi-strain dossier.

As it is expected that not all strains presented and described in the multi-strain dossier will be present in a final product used in the field, some remarks on the data required for a Marketing Authorisation are regarded necessary.

Different cases have to be taken into account depending on the way the applicant has decided to develop the multi strain dossier:

- the multi-strain dossier consists of a new vaccine containing one or more strains never authorised before (Initial application of a multi-strain dossier),

or

- the multi-strain dossier is obtained by the addition or replacement of a strain to an authorised multi-strain dossier containing one or more strains (addition or replacement of strains to an existing multi-strain dossier),

or

- the multi-strain dossier is obtained by the combination of authorised vaccines* containing one or more strains (multi-strain dossier obtained by the combination of authorised vaccines containing one or more strains).

*vaccines authorised under exceptional circumstances are excluded.

In the case of an increase in the maximum number of strains to be included in the final product the full data requirements of this guideline will apply.

It should be emphasized 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 Directive 2001/82/EC 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 (or any other dossier), as the scientific balance between all parts of the dossier and the global level of scientific requirements might not be achieved anymore.

5. Initial application of a multi-strain dossier

5.1. Quality

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:

II.A. Qualitative and quantitative particulars

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.

II.B. Method of preparation

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

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 water or saline 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 which has been defined by the Applicant.

II.C. Production and control of starting materials

The production of each antigen is based on a seed lot system. The results of the tests of all starting materials shall comply with the requirements of the Directive 2001/82/EC as amended and of the Ph. Eur.

II.D. Control tests during production

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.

II.E. Control tests on the finished product

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

A specific test for identification (e.g. monoclonal antibodies, sequencing) 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 normal vaccines because of all the possible combinations of antigens. Therefore, mono-strain vaccines should be manufactured (in compliance with section II.A to II.D of this guideline) for each of the available MSVs, 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 is 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.

II.F. Stability tests

These 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 final products marketed 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.

5.2. Safety

The complete range of safety tests mentioned in Annex I of Directive 2001/82/EC should be provided unless justified.

The tests should be carried out using a batch manufactured with the maximum number of strains proposed for the final product and containing the maximum amount of each antigen 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). It is not expected that inclusion of fewer than the maximum number of strains incorporated in the antigen phase will have a negative impact on the safety of the final formulation.

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 justified, results from laboratory studies should be supplemented with data from field trials. If field trials in third countries are available, they should be provided to support data from laboratory studies.

5.3. Efficacy

The efficacy tests mentioned in Annex I of Directive 2001/82/EC should be provided unless justified.

Efficacy of a multi-strain vaccine cannot be demonstrated in the way normally required for normal vaccines because of all the possible combinations of antigens. Therefore, mono-strain vaccines should be manufactured (in compliance with section II.A to II.D of this guideline) for each of the available master seed viruses, and efficacy should be shown for each of these mono-strain vaccines. It will be admitted 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 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 a correlation can be demonstrated between specific parameters and protection induced by vaccination a follow up of these protection related parameters might be considered sufficient to substantiate the efficacy claim.

Unless justified, results from laboratory studies should be supplemented with data from field trials. If field trials in third countries are available, they should be provided to support data from laboratory studies.

6. 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 of the multi-strain dossier (e.g. maximum number of antigens, same antigen content (as described in section 6.1) and same composition of adjuvants and excipients), additional quality and efficacy data for the added or replaced strain have to be provided according to the provision in sections 6.1 and 6.3.

7. Multi-strain dossier obtained by the combination of authorised vaccines containing one or more strains

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 antigen content (as described in section 6.1) 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 provision in section 6 to update the multi-strain dossier.

The stability is based on the shortest shelf life proved, in compliance with section 6.1 II.F of this guideline.