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Recommendation on the submission of multi-strain dossier applications for vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Introduction (background)

Commission Directive 2009/9/EC amending Directive 2001/82 EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use introduced the concept of 'multi-strain' dossiers for vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-mouth disease (FMD). The requirements for maintenance of such dossiers have also been included in the revised Variation Regulation (EC) 1234/2008.

Vaccines against these diseases represent a special case in terms of the need for rapid and frequent change in the strains included and therefore they do not fit well within the general regulatory model for vaccines.

The advantage to the applicant (and authorities) of the multi-strain dossier approach is the requirement 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. In order to safeguard appropriate identification of the final product, the regulatory approach to multistrain dossiers identifies each strain, or combination of strains, that will be placed on the market as a separate presentation within a single global authorisation with its unique number (EU number for centrally authorised products = CAPs). This avoids the need for a separate authorisation for each vaccine strain and also each possible combination of vaccine strains that might be envisaged. Marketing Authorisation Holders (MAH) can then select which strains are appropriate to deal with a particular disease situation in the field and manufacture vaccines using the respective, authorised strains in the already approved formulation. These measures aim to encourage the authorisation of vaccines against these three antigenically variable viruses in a way that ensures that the most effective measures can be taken swiftly by the Community against incursion or spread of epizootic diseases while granting marketing authorisations for products on the basis of objective criteria of quality, safety and efficacy.

2. Scope

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

The guideline on data requirements for multi-strain dossiers for inactivated vaccines against AI, BT and FMD describes the technical requirements [EMA/43283/2010] that should be met in terms of the analytical, safety and efficacy parts of the multi-strain dossier.

This recommendation addresses the procedural issues specific to applications for multi-strain dossiers through the centralised procedure.

It is envisaged that submission of a multi-strain dossier would not be appropriate in response to an emergency situation. This recommendation does not apply to live vaccines.

In order to ensure easier reading of this text, the term "strain" relates to a particular master seed virus (MSV) and therefore covers strains, subtypes and serotypes.

3. Legal basis

Commission Directive 2009/9/EC amending Directive 2001/82 EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use introduces under Title IV B the concept of multi-strain veterinary immunological products for vaccines against AI, BT and FMD. It is therefore possible to apply for Marketing Authorisations for a multi-strain

dossier through the centralised procedure, the decentralised procedure, the national procedure and the mutual recognition procedure. This concept has also been included in Variation Regulation (EC) 1234/2008 where additions of strains to multistrain dossiers have been specifically excluded from extensions and are listed under Type II variations requiring a 90 day timetable

4. 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 guideline on data requirements for multi-strain dossiers for inactivated vaccines against AI, BT and FMD [EMA/43283/2010] 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 (multi-strain product)

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.

5. Multi-strain dossier procedural issues

Initial MS dossier application

The advantage to the applicant (and authorities) of a multi-strain dossier as proposed is 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.

In order to safeguard appropriate identification of the final product the regulatory approach for multistrain dossiers identifies each strain, or combination of strains, that will be placed on the market as a separate presentation within a single global authorisation with its unique Marketing Authorisation number. For example an avian influenza multi-strain dossier could contain 5 different AI strains out of which a maximum of 2 AI strains will be included in any one final product. The Applicant will have to identify all potential combinations of strains they wish to place on the market as a final product and these will then be assigned separate presentation numbers. A fictitious example of the possible list of presentations for such an AI multi-strain dossier is included in Table 1 at the end of this document in the form of the Annex A that would be appended to an authorisation for a centrally authorised product under Regulation (EC) 726/2004. Please note that in this case there are also two different bottle sizes which are also separately identified thereby doubling the number of possible presentations to 30.

In the case of a FMD vaccine with 15 possible strains out of which a maximum of 5 can be included in the final product the maximum number of possible combinations would rise to 4943 highlighting the importance of defining likely choices early and limiting the number of possible combinations as well as the maximum number of strains allowed in the final product.

The intention therefore is not that the Applicant should seek to authorise every possible combination of strains that would be possible as this could run to several hundred. Rather, the Applicant should consider which presentations they wish to place on the market and include each of these within the authorisation. Each presentation must be supported by data and an appropriate SPC and labelling as specified below.

Maintenance of a MS dossier

If the Marketing Authorisation Holder wishes to add or replace a strain to an existing multi-strain authorisation this can be done via a Type II variation procedure running to a 90 day timetable.

Due to the structure of a multistrain dossier and the consequent amount of data necessary to add a strain to the number of maximum strains allowed in the final product such a variation is most likely to lead to an increase of the strains from which the final product can be formulated. This means in the above AI example that a 6th strain could be added but the final product would still contain only 2 strains. However, it is possible to apply for a Type II variation to replace or add a strain which also increases the number of maximum strains allowed in the final product. This means in the above example that a 6th strain could be added and the final product can contain 3 strains.

SPC, labelling and package leaflet

The amount of presentations possible as well as the desire to maintain the ability of manufacturers to respond to the urgent need of governments for a certain strain combination necessitates that the SPC, labelling and package leaflet requirements be streamlined for multi-strain dossier applications. It should be noted that the three diseases affected by these applications are under Community control and vaccination will only be performed in the context of a Community approved vaccination programme, thereby giving the necessary amount of assurance and control over the distribution and usage of vaccines originating from multi-strain dossiers. This guidance should be read in conjunction with the following additional guidance documents: Guideline on Summary of Product Characteristics - immunologicals, published by the European Commission; QRD Product Information Template with explanatory notes; Convention to be followed for QRD Templates.

SPC: For a multi-strain application the applicants can include all possible strains under section 2 of the SPC. The wording of the indications and warnings under section 4 should be able to cover all strains/ strain combinations. Should it be absolutely necessary to include a special indication or warning for a particular strain combination this should be clearly identified in the SPC. It should be clearly stated in the SPC that the exact strain/ strain combination can be identified on the label (see sentence below).

Labelling: For a multi-strain application the applicants can include all possible strains under section 2 of the labelling. It is imperative that the final label on the container containing the product will only include the strain or strain combination included in the container.

Package leaflet: For a multi-strain application the applicants can include all possible strains under section 3 of the package leaflet. The wording of the indications and warnings should be able to cover all strain combinations. Should it be absolutely necessary to include a special indication or warning for a particular strain combination this should be clearly identified in the package leaflet. It should be clearly stated in the package leaflet that the exact strain/ strain combination can be identified on the label. The following sentence should be used:

"The number and type of strains included in the final product will be adapted to the current epidemiological situation at the time of formulation of the final product and will be shown on the label."

Mock-ups and specimens

For centrally authorised products mock-ups and specimens should generally be provided in line with the revised checking process of mock-ups and specimens of outer/immediate labelling and package leaflets in the centralised procedure for veterinary medicinal products (EMEA/14522/2007). Nevertheless, it is understood that in the case of these three epizootic diseases there is a necessity to provide the final product to the appropriate market without any undue delay. Consequently the provision of mock-ups to the Agency should be done as soon as possible but should not delay the placing of the product on the market.

Data protection

It is important to note that there is an impact on the data protection of a multi-strain product as all presentations are considered part of the same global marketing authorisation. Consequently the data protection for all possible presentations starts counting on the day of the marketing authorisation of the multi–strain product.

Table 1: Example of the presentations of a multi-strain AI vaccine with *five* different AI strains included out of which a maximum number of *two* can be included in the final product. Please note that this vaccine also comes in two different bottle sizes.

EU Number	Invented Name	Strains	Strength	Pharmaceutical Form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/11/123/01	AI vaccine	H5N2	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/02	AI vaccine	H5N2	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/03	AI vaccine	H5N3	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/04	AI vaccine	H5N3	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/05	AI vaccine	H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/06	AI vaccine	H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/07	AI vaccine	H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/08	AI vaccine	H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/09	AI vaccine	H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/10	AI vaccine	H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/11	AI vaccine	H5N2 and H5N3	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/12	AI vaccine	H5N2 and H5N3	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/13	AI vaccine	H5N2 and H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/14	AI vaccine	H5N2 and H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/15	AI vaccine	H5N2 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/16	AI vaccine	H5N2 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/17	AI vaccine	H5N2 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/18	AI vaccine	H5N2 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/19	AI vaccine	H5N3 and H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days

EU Number	Invented Name	Strains	Strength	Pharmaceutical Form	Target species	Route of administration	Packaging	Content	Package size	Withdrawal period
EU/2/11/123/20	AI vaccine	H5N3 and H5N6	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/21	AI vaccine	H5N3 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/22	AI vaccine	H5N3 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/23	AI vaccine	H5N3 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/24	AI vaccine	H5N3 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/25	AI vaccine	H5N6 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/26	AI vaccine	H5N6 and H7N1	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/27	AI vaccine	H5N6 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/28	AI vaccine	H5N6 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days
EU/2/11/123/29	AI vaccine	H7N1 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	300ml	1 bottle	Zero days
EU/2/11/123/30	AI vaccine	H7N1 and H7N7	HI titre ≥ 6.5 log	Emulsion for injection	Chickens	Intramuscular	PET bottles	600ml	1 bottle	Zero days