EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for medicinal products for veterinary use (CVMP)

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

Background

The aim of this question and answer document is to provide clarification on the CVMP 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), based on the experience gained since it came into effect in 2010.

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

1. Is it possible to have variable antigen contents for the same vaccine strain for one target species within one multi-strain dossier?

The possibility of variable antigen contents for a specific strain for one target species within one multi-strain dossier is considered acceptable providing the safety and efficacy was satisfactorily addressed respectively for the maximum and minimum levels of antigen formulated in a batch of final product. Efficacy should be demonstrated at minimum antigen content for potency and safety established at maximum content with the highest combination of representative strains.

2. Is it possible to have different dose-volumes for different target species?

The possibility of different dose-volumes for different target species is acceptable. The guideline states that blending should be standardised and 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, this does not exclude different dose-volumes for each target species and had been accepted for marketing authorisation applications for Immunologicals Veterinary Medicinal Products.

It is considered preferable that the dose-volume for each species, although they can be different, should be simple fixed-multiples to ensure user compliance and avoid vaccine wastage.

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3. Is it possible to have different dose-volumes for the same target species?

Concerning different dose-volumes for the same target species, it is considered this could not be accommodated within the framework of one multi-strain dossier. Safety and efficacy could be demonstrated for monovalent products at different dose-volumes but the safety and efficacy for combination products at different dose-volumes is considered too complex to address within one dossier.

4. Is it possible to have variable adjuvant content for a fixed dose-volume depending on strain and species?

Concerning variable adjuvant levels, it is considered this could not be accommodated within the framework of one multi-strain dossier. Safety and efficacy could be demonstrated for each monovalent product at different adjuvant concentrations but the safety and efficacy for combination products at different adjuvant concentrations is considered too complex to address within one dossier. The management of such a complex dossier would present regulatory and manufacturing challenges to ensure only the approved combinations were formulated within one multi-strain dossier. The existing guideline requires the quantity of ingredients, other than the antigens, and dose-volume to be the same to ensure a consistent product can be manufactured.

5. Is it possible to submit a dossier with efficacy data absent for one or more target species for a new strain?

The guideline states 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.

However, limiting the efficacy data for a particular strain to a restricted number of species for a product supported by one multi-strain dossier is considered possible within the framework of the current guideline. Limited efficacy data may be appropriate where a strain's pathogenicity follows an atypical pattern and causes disease only in one particular species. The product information should, however, reflect such limited efficacy data and the possible final product combinations should ensure the strain is not included in products intended for species for which efficacy had not been demonstrated.

To add a new strain it is considered acceptable to provide limited efficacy data for one or a limited number of species included in a multi-strain dossier. Even for strains relevant to all species included in the dossier a variation with supporting efficacy data for one or a limited number of species is considered acceptable.

6. Should there be a restriction in number of fixed combination products for a multi-strain dossier as a result of cross-reactivity in the final product potency test?

In a multi-strain dossier, vaccines should be able to contain any combination of the maximum number of strains proposed for the final product so that the final vaccine formulation, with regard to the type of strains, can be quickly adapted to match the strains circulating in the field at the time of formulation.

The possibility of restricted flexibility may be considered where only a limited number of combinations were possible as a result of cross-reactivity in the final product potency test. The potential for cross-

reactivity is addressed in the guideline and it is considered that the issue could be addressed by the development of additional *in vitro* test.

It is considered that all combinations, as permitted by the number of strains and maximum combination approved within the multi-strain dossier should be possible and not restricted by quality issues identified during development.

7. Is it possible to extrapolate existing safety / efficacy data to minor or "exotic" target species (goats, buffalos, etc.), especially for well-known formulations?

The guideline states that 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.

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 guideline gives therefore the possibility to extrapolate safety and efficacy data to minor or exotic target species.