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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the revision of the guideline on data requirements for multi-strain dossiers for inactivated vaccines against Avian Influenza (AI), Blue Tongue (BT) and Foot and Mouth Disease (FMD)

Agreed by Immunologicals Working Party	17 December 2020
Adopted by CVMP for release for consultation	20 January 2021
Start of public consultation	29 January 2021
End of consultation (deadline for comments)	31 March 2021

The proposed guideline will replace '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 Rev. 1).

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

Keywords	Multi-strain, veterinary vaccines, avian influenza, blue tongue, foot and mouth disease, AI, BT, FMD

1. Introduction

The concept of a multi-strain dossier was first included in the revised Technical Annex I to Directive 2001/82/EC, Directive 9/2009/EC, and in Regulation (EC) 1234/2008 in order to provide regulatory incentives for marketing authorisation applications for inactivated vaccines against Avian Influenza (AI), Blue tongue (BT) and Foot-and-Mouth Disease (FMD).

The draft Annex to the Commission Delegated Regulation amending Annex II to Regulation (EC) 2019/6 (still to be published by the European Commission at the time of publication of this document) recommends that the multi-strain dossier concept is introduced for viral diseases, other than Avian Influenza, Bluetongue and Foot-and-Mouth Disease, and also for bacterial diseases requiring a need for rapid and frequent change in the strains included in the final product.

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It will allow authorisation of inactivated vaccines against antigenically variable viruses or bacteria for which rapid and frequent change in the composition of vaccine formulations is needed 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.

The multi-strain dossier concept is seen as an opportunity to address some of the priorities around veterinary vaccine availability and is a key deliverable as part of the Network action plan on availability of veterinary vaccines.

The Immunologicals Working Party has been tasked with the revision of the existing guideline on data requirements for multi-strain dossiers for inactivated vaccines to adapt the guideline to Regulation 2019/6.

2. Problem statement

Until now, application of the multi-strain dossier approach was limited to Avian Influenza (AI), Blue tongue (BT) and Foot-and-Mouth Disease (FMD) inactivated vaccines as provided for in Directive 2009/9/EC: *For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) and by derogation from the provisions of Title II, Part 2 Section C on active substances the concept of the use of a multi-strain dossier is introduced.*

The possibility to apply the multi-strain approach to other veterinary medicinal products such as equine/swine influenza, infectious bronchitis, and multi-component dog and cat vaccines was requested by AnimalhealthEurope (AhE) during the drafting of the multi-strain guideline.

Recently, AhE contacted the European Commission (EC) and EMA to propose the extension of the multi-strain dossier approach not only to other viral diseases but also to bacterial diseases. In addition, the EC consulted with member states about the possibility to open the multi-stain dossier concept to inactivated vaccines against bacteria/bacterial diseases and there was general support for the proposal.

The draft Annex to the Commission Delegated Regulation amending Annex II to Regulation (EU) 2019/6 on veterinary medicinal products defines a multi-strain dossier as follows:

For certain immunological veterinary medicinal products and by derogation from the provisions of Section IIIb, Part 2, the concept of the use of a multi-strain dossier is introduced.

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.

Each multi-strain dossier is applicable only to one virus species, bacteria genus or 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. For new applications to multi-strain dossier marketing authorisations where no authorised multi-strain vaccine already exists for a particular virus/bacterium/disease, eligibility for the multi-strain dossier approach shall be confirmed by the Agency before submission of the application.

Indeed, for a specific viral disease, the underlying cause is always a specific virus species. For instance, Foot-and-Mouth disease (FMD) is always caused by the Foot-and-mouth disease virus, but this virus species includes a large variety of strains (also encapsulating differences in serotypes), such as O Manisa, SAT2 Ery or A22 Iraq. From an epidemiological point of view, viruses might sometimes be endemic, but the different strains are often circulating/spreading rather quickly over large areas, with high mutation rates, and the vaccines need to be adapted accordingly to remain efficacious.

To the contrary, bacteria do not exhibit high mutation rates in comparison to RNA viruses or even to DNA viruses, allowing the latter to rapidly evolve; typically, there is slow change over time at a local level, but the epidemiological situation can vary greatly amongst regions at the EU level (please refer to the example provided on *Leptospira* described below). In such circumstances, it may not be economically practicable/feasible to develop vaccines with a fixed composition covering all the field requirements. Therefore, the final vaccines should be blended to include strains according to need based on the current epidemiological data.

To illustrate this, some bacteria like *Haemophilus parasuis*, *Mannheimia haemolytica* or *Leptospira* inducing respectively similar diseases may be good examples. AhE presented the canine leptospirosis bacteria example to explain the relevance of the multi-strain dossier concept for bacteria. Leptospirosis is one such disease that requires careful choice of vaccine strains due to the lack of cross-protection between serogroups. The recommended vaccine strains have evolved over the course of time as new strains have emerged. Today prevalence of the various *Leptospira* serogroups is variable among EU countries, showing classical ones, including *Canicola* or *Icterohaemorragiae* but also more recent ones, such as *Grippotyphosa*, *Pomona* or *Australis*, showing that an efficient vaccination of dogs against *Leptospira* requires components variable according to geography. *Leptospira* geographical situation echoes AI, FMD or BTV's where vaccine adaptation to geography or timing is necessary, despite its potential slower spread as a bacterial infection. If one wants to have a single vaccine to best match all epidemiological situations, this may not be achievable or may require the incorporation of (too) many strains at a risk of decreased safety. The multi-strain dossier concept is a regulatory mechanism that may address this issue and allow appropriate protection of dogs according to needs.

In conclusion, it appears that the multi-strain dossier concept could be useful for the authorisation of vaccines against both viral and bacterial diseases, although the underlying reasons for applying this approach might be different in both cases.

3. Discussion (on the problem statement)

Due to the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products, it is necessary to review the current guideline on data requirements for multi-strain dossiers that is currently restricted to AI, BT and FMD.

From the outcome of previous discussions with industry concerning the interpretation of the existing guideline and from the proposal of some member states, it is clear that there is a need to clarify the terms of applicability of the guideline in order to facilitate the development of multi-strain dossiers.

When revising the existing guidance document, the following issues will be addressed:

- Extension of the multi-strain approach to viruses (RNA or DNA) other than FMD, AI and BT.
- Extension of the multi-strain approach to bacteria.
- Definition of the criteria for inclusion of viruses and bacteria under the scope of the guideline; in particular, special attention should be given to the extent to which the concept should be opened to bacteria, up to the genera or restricted to the species.

- Review the validity of the current requirements with regard to the extension of the scope to other viruses and bacteria, keeping in mind that the current requirements must be met with regard to FMD, AI and BT, in order to avoid discrepancies between dossiers submitted in support of existing marketing authorisations based on the multi-strain dossier concept and dossier requirements for future applications.

4. Recommendation

The Committee for Medicinal Products for Veterinary Use (CVMP) recommends the Immunologicals Working Party (IWP) to revise the CVMP guideline on data requirements for multi-strain dossiers for inactivated vaccines against AI, BT and FMD in order to take into account the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products.

5. Proposed timetable

29 January 2021	Concept paper released for consultation
31 March 2021	Deadline for comments
May 2021	Discussion in IWP
July 2021	Adoption the draft guideline by CVMP and release for consultation
October 2021	Expected end of consultation
January 2022	Expected date for adoption by CVMP and publication of the revised guideline

It is expected that the guideline will come into operation earlier than six months after adoption, coinciding with the date of application of Regulation (EU) 2019/6 (28 January 2022).

6. Resource requirements for preparation

The revision of the guideline will involve the IWP (including a drafting group composed of rapporteur, co-rapporteur and 2 IWP members).

The IWP drafting group will meet virtually as required (e.g. 3-4 virtual meetings). Discussion is foreseen at 2 IWP plenary meetings.

7. Impact assessment (anticipated)

It is anticipated that the guidance would benefit both industry and regulators due to the need to maintain only one marketing authorisation dossier, which can cover a wide range of vaccine strains. It will result in a more consistent assessment of products by regulators. This will contribute to increase veterinary vaccine availability by authorising each possible combination of vaccine strains that might be envisaged or needed to deal with a particular disease situation in the field, and thereby benefit public and animal health.

8. Interested parties

Veterinary pharmaceutical industry and consultants.

EU Regulatory authorities involved in assessment of marketing authorisation applications for veterinary vaccines.

147 EU competent authorities responsible for animal disease control.

148 9. References to literature, guidelines, etc.

149 Revised guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian
150 influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)
151 (EMA/CVMP/IWP/105506/2007Rev.1).

152 Annex to the Commission Delegated Regulation amending Annex II to Regulation (EC) No 2019/6 of
153 the European Parliament and of the Council (draft published for feedback, 10 November 2020).