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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for the development of a guideline on data requirements for vaccine antigen master files (VAMF)

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Start of public consultation	29 January 2021
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Comments should be provided using this template. The completed comments form should be sent to Vet-guidelines@ema.europa.eu

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1. Introduction

In 2019, the European Commission requested EMA to provide scientific advice regarding technical data to be provided by applicants for marketing authorisations (MA) of veterinary medicinal products, which are outlined in Annex II of Regulation 2019/6 (replacing Annex I of current Dir. 2001/82). The request from the Commission advised that "*Where possible, when elaborating on the above, the conclusions of the work conducted by the Task Force on availability for vaccines, and particularly specific requirements for Vaccine Antigen Master File (VAMF) or technological Platforms, should be taken into account.*"

While the concept of a VAMF was already introduced through Directive 2001/82/EC as amended (Annex I, Title IV), neither scientific guidelines nor procedural guidance for submission and evaluation of a VAMF for veterinary vaccines have been elaborated or published so far. For human vaccines, the VAMF concept was introduced with Directive 2001/83/EC, Annex I, and guidance on scientific data requirements as well as requirements for VAMF certification have been published. Nevertheless, no VAMF certification has yet been applied for in the human field.

The draft Annex to the Commission Delegated Regulation amending Annex II to Regulation (EC) No 2019/6 (still to be adopted or endorsed by the European Commission), introduces in section 'V.2. Vaccine antigen master file' a more detailed concept of a VAMF and outlines the basic principles, requirements in terms of dossier content and the approach to evaluation and certification.

The Immunologicals Working Party has been tasked with reflecting on the need for additional guidance on the technical/scientific data requirements to be submitted in support of a VAMF and, if considered needed, the preparation of this guidance.

2. Problem statement

In the draft Annex to the Commission Delegated Regulation amending Annex II to Regulation (EC) No 2019/6, the following is indicated:

Vaccine antigen master file

For particular immunological veterinary medicinal products and by derogation from Section IIIb, Part 2, the concept of a Vaccine Antigen Master File is introduced.

Principles

For the purpose of this Annex, a Vaccine Antigen Master File means a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances, which are part of the veterinary medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

The use of Vaccine Antigen Master Files is optional. For combined vaccines, the vaccine antigen(s) to be included in Vaccine Antigen Master File(s) shall be specified and a separate Vaccine Antigen Master File shall be required for each of them.

The submission and approval of a Vaccine Antigen Master File shall comply with the relevant guidance published by the Agency.

Content

The Vaccine Antigen Master File dossier shall contain the information in Parts V.2.2.1 to V.2.3.3 extracted from the relevant sections of Part 1 (Summary of the dossier) and Part 2 (Quality documentation) as set out in Section IIIb of this Annex:

Summary of the dossier (Part 1)

The name and address of the manufacturer(s) and the site(s) involved in the different stages of manufacture and control of the active substance, accompanied by copies of the corresponding manufacturing authorisations, shall be given.

Qualitative and quantitative particulars of the constituents (Part 2.A)

The complete and exact name of the active substance (for example, virus or bacteria strain, antigen) shall be provided, in the same way as mentioned in any finished product. Information on product development relevant to the active substance shall be provided.

Description of the manufacturing method (Part 2.B)

The description of the manufacturing method for the active substance shall be provided including validation of the key stages of production and justification, if relevant, of any intermediate storage proposed. For inactivated active substances, data relevant to the inactivation step, including the validation of the inactivation process shall be provided.

Production and control of starting materials (Part 2.C)

The standard requirements described in Section IIIb.2C and relevant to the active substance shall apply.

Information on the active substance (for example, virus/bacteria strain), the substrate/s (cells, culture medium) and all the raw materials (pharmacopoeia or non-pharmacopoeia, biological or non-biological) used in the production of the active substance shall be provided.

The dossier shall include the specifications, information on the processes implemented and on the tests to be conducted for the quality control of all batches of starting materials and results for a batch for all components used.

TSE and extraneous agents (EA) risk assessment shall be provided, where applicable. It is to be noted that the target species retained for the finished products making reference to the Vaccine Antigen Master File shall be considered for the TSE and EA risk assessment. Warnings or restrictions of use may be brought in at the Vaccine Antigen Master File level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product.

If the active substance is obtained by recombinant techniques, all corresponding relevant data on the genetically modified virus/bacteria shall be provided.

Control tests during the manufacturing process (Part 2.D)

The standard requirements described in Section IIIb.2D shall apply for the in-process control tests carried out during the manufacture of the active substance, including validations of key control tests and, if relevant, any intermediate storage proposed (prior to blending).

Batch-to-batch consistency (Part 2.F)

The standard requirements described in Section IIIb.2F shall apply for the demonstration of consistency in the manufacture of the antigen.

Stability (Part 2.G)

The standard requirements described in Section IIIb.2G to demonstrate the stability of the antigen and, where relevant any intermediate storage, shall apply.

Evaluation and certification

For vaccines containing new vaccine antigen(s) where no Vaccine Antigen Master File already exists, the applicant shall submit to the Agency a full marketing authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

The above paragraph shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of those vaccine antigens are part of vaccines already authorised in the Union.

Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency. In the case of a positive evaluation, the Agency shall issue a certificate of compliance with Union legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Union.

The basic principles of VAMF are set out in the Annex II. A summary of the content is provided and scientific data requirements to support a VAMF are defined, focussing on Part 1 (Summary of the dossier) and Part 2 (Quality documentation). In preparation for the implementation of Regulation (EU) 2019/6, the development of a guideline on the detailed scientific data requirements for a VAMF is under discussion.

Procedural guidance for the submission, evaluation and certification of VAMF will be developed in parallel by the Agency. This task is out of the scope of this concept paper.

3. Discussion (on the problem statement)

For the development of the guideline, the new legal basis and the provisions in Regulation (EU) 2019/6 will be considered.

The draft Annex II introduces the concept of a VAMF. A VAMF is intended to be a stand-alone part of a MA application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances that are part of the product.

The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or MA holder. The use of a VAMF is optional.

For vaccines containing new vaccine antigen(s) where no VAMF already exists, the applicant shall submit to the Agency a full MA application dossier including all the VAMFs corresponding to each single vaccine antigen for which the use of a VAMF is intended.

IWP discussed if the text in the Annex II would provide sufficient detail about the data requirements to be submitted in support of a VAMF. Information in a VAMF is requested on Part 1 (Summary of the dossier) and Part 2 (Quality documentation), except for Part 2.E (Control tests on the finished product). References are included to standard requirements described in Section IIIb of Annex II.

While the requirements as presented in Annex II are clear, it has been suggested that a more detailed guidance may be beneficial to the applicants to give the necessary predictability for the submission of a VAMF.

Therefore, stakeholders are requested to provide feedback on the proposed content of a VAMF as described in Annex II, specifically if it provides sufficient detail for submission of a VAMF. If it is considered that the information provided in the Annex is not an adequate basis for compiling a dossier for regulatory submission, stakeholders are requested to comment on which aspects would benefit from additional technical guidance.

4. Recommendation

The Committee for Medicinal Products for Veterinary Use (CVMP) recommends the Immunologicals Working Party (IWP) to discuss the drafting of a guideline on more detailed data requirements to support a VAMF in order to take into account the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products. As a starting point, the IWP has been requested to consider if the data requirements already described in Annex II are an adequate basis for compiling a dossier for regulatory submission.

5. Proposed timetable

29 January 2021	Concept paper released for consultation
31 March 2021	Deadline for comments from stakeholders
May 2021	Discussion in IWP
July 2021	Adoption of 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 guideline

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

6. Resource requirements for preparation

The development of the new guideline will involve the IWP (including a drafting group composed of rapporteur, co-rapporteur and 1-2 IWP members).

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

7. Impact assessment (anticipated)

The elaboration of any guidance is expected to benefit industry. The objective of the VAMF is to reduce the administrative and regulatory burdens on industry and authorities for authorisation of certain categories of veterinary vaccines and offer greater consistency and predictability for the assessment of antigens with VAMFs included in applications for marketing authorisations.

Overall, it is anticipated that the guideline will have a positive impact on the development of veterinary vaccines. The use of a VAMF is expected to facilitate and speed up the submission and authorisation of

veterinary vaccines and to contribute to increased availability of veterinary vaccines, 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.

9. References to literature, guidelines, etc.

Directive 2001/82/EC of the European Parliament and the Council of 6 November 2001 on the Community Code relating to Veterinary Medicinal Products as amended.

Advice implementing measures under Article 146(2) of Regulation (EU) 2019/6 on veterinary medicinal products – Scientific recommendation on the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products (EMA/CVMP/351417/2019).

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