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Guideline on data requirements for vaccine antigen master files (VAMF)

Draft

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Executive summary

The main aim of the guideline is to address the data to be included in a vaccine antigen master file (VAMF) for veterinary vaccines.

1. Introduction (background)

The concept of a VAMF was firstly introduced through Directive 2001/82/EC as amended, Annex I, Title IV, as a stand-alone part of the marketing authorisation (MA) application dossier, which contains all relevant information on quality concerning each of the active substances, which are part of this vaccine.

While the concept of a VAMF was already presented, it was never implemented and neither scientific guidelines concerning data requirements nor procedural guidance for submission and evaluation of a VAMF for veterinary vaccines were developed so far.

For human vaccines, the concept of VAMF was introduced with Directive 2001/83/EC as amended, Annex I, and guidance on scientific data requirements as well as requirements for VAMF certification were published. So far, no VAMF certification has yet been applied for in the human field.

The Commission Delegated Regulation (EU) 2021/805 of March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council, introduced in section V.2. 'Vaccine antigen master file' a more detailed concept of a VAMF with a focus on principles, content, evaluation and certification. It establishes the responsibility of the European Medicines Agency (Agency) for dealing with applications, carrying out the scientific evaluation and certification, and developing relevant guidance for the submission and approval of VAMFs.

The objective of a VAMF is to reduce the administrative and regulatory burden for industry and competent authorities for authorisation of vaccines, to offer greater consistency and predictability for the assessment of antigens with VAMFs included in applications for MAs and to contribute to an increased availability of veterinary vaccines in the EU thereby benefiting public and animal health.

The assessment of a VAMF application (or variation) dossier of the applicant will result in a certificate of compliance to Community legislation, issued by the Agency. This certificate, accompanied by the evaluation report, shall be valid throughout the Community. This certificate, if submitted by the applicant, shall be taken into account by competent authorities that will grant or have granted MAs for concerned veterinary vaccine(s).

2. Scope

Guidance is provided on the data for active substances (antigens) to be included in a VAMF. The guideline includes scientific requirements for the submission, the evaluation and certification of VAMFs.

Procedural guidance for the submission, evaluation and certification of VAMFs will be provided separately in documents to be published by the Agency and is out of the scope of the present guideline.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the Commission Delegated Regulation EU) 2021/805 amending Annex II to Regulation (EU) 2019/6, section I (General principles and requirements), section

IIIb (Requirements for immunological veterinary medicinal products (IVMPs)) and section V.2 (Vaccine antigen master file). Furthermore, other relevant EU and VICH guidelines as well as European Pharmacopoeia applicable texts and monographs to IVMPs shall be considered.

The submission and approval of a VAMF shall comply with the relevant guidance published by the Agency.

4. Principles

Vaccines may contain one or several active substances. The same active substance may be common to several vaccines.

A VAMF means a stand-alone part of the MA application dossier concerning an active substance for a vaccine. This stand-alone part contains all relevant information on the starting materials and reagents, the production process, specifications and routine controls, the stability and the extraneous agents safety aspects of a vaccine antigen and will not include information on the formulation process or further downstream production steps. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or MAH. Where the same vaccine antigen is included in vaccines of different MAHs, each MAH will apply for a VAMF certificate.

The use of a VAMF is optional meaning that the VAMF procedure is not mandatory for the MAH or MA applicant. However, the use of a VAMF provides clear advantages, as the VAMF remains common to all the linked MAs. The main benefit is that once a VAMF is 'approved' there should be no re-assessment when presented in the context of a subsequent application for MA. Further benefits concern variations to modify a VAMF and the introduction of the updated VAMF in the respective MAs.

For combined vaccines, the active substance(s) intended to be included in a VAMF shall be specified and a separate VAMF shall be required for each of them. Within the same combined vaccine application, it is allowed to have active substances covered by a VAMF and active substances not covered by a VAMF. A MA or a MA application may contain one or more VAMF certificates and respective VAMF data.

For vaccines containing new active substance(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 active substance for which the use of a VAMF is intended.

In the case of existing MAs, MAHs may initiate the VAMF certification process. The data submitted for certification should correspond to the quality data already approved for the relevant antigen in the linked MA. Further details will be provided in the procedural guideline.

A certificate of compliance of the VAMF is a document summarising the parts of the dossier that are assessed and accepted, and that will not be re-assessed for a vaccine, which contains the same active substance. This certificate accompanied by the evaluation report should be included in the MA application dossier for which the use of a VAMF is intended.

Once approved and certified, the VAMF can be used for the authorisation of "fall-out" or "build-up" vaccines (i.e. further monovalent or combined vaccines containing the antigen included in the VAMF).

A VAMF can only be used in the authorisation of vaccines intended for target species already described/ included in the VAMF. If the VAMF is to be used for a new target species, the VAMF must be updated to include the information missing for the new target species (e.g. TSE/EAs risk assessment).

The VAMF is applicable to vaccines registered by any procedure (centralised, mutual recognition, decentralised and national procedures) and can also be used in applications for multi-strain dossiers.

The inclusion of an already certified VAMF in the marketing authorisation dossier of an authorised vaccine when changes do not affect the properties of the finished product is included in the list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 (Commission Implementing Regulation (EU) 2021/17).

The inclusion of a new VAMF or an updated or amended VAMF (when changes affect the properties of the finished product) in the marketing authorisation dossier of an already authorised vaccine is included in the Agency/CMDv guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations (draft available).

The decision as to whether a particular VAMF is to be used in a MA rests with the MAH, who may decide that even though the same antigen is contained in several MAs, the MAH may only wish to link the certificate to some, not all such MAs.

5. Content of a VAMF

The general principles and requirements set out in Section I (correspond to Part 1 of Section IIIb - Summary of the dossier) of Annex II to Regulation (EU) 2019/6 are valid also for VAMF, if applicable.

The VAMF dossier shall contain the information extracted from the relevant sections of Part 2 (Quality documentation) as set out in Section IIIb of Annex II to Regulation (EU) 2019/6.

It may be useful if, in the MA dossier, the parts concerned are marked as belonging to a VAMF.

The following structure should be followed:

- Part 1: Summary of the dossier
- Part 2: Quality documentation (physicochemical, biological and microbiological information)
    - 2.A. Product description
        - 2A1. Qualitative and quantitative composition
        - 2A2. Product development
    - 2B. Description of the manufacturing method
    - 2C. Production and control of starting materials
        - 2C1. Starting materials listed in pharmacopoeias
        - 2C2. Starting materials not listed in a pharmacopoeia
            - 2C2.1. Starting materials of biological origin
            - 2C2.2. Starting materials of non-biological origin
    - 2D. Control tests during the manufacturing process
    - 2F. Batch-to-batch consistency (active substance)
    - 2G. Stability tests (active substance)
    - 2H. Other information, if applicable

5.1. 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.

The manufacturing processes for the active substance(s) shall comply with Good Manufacturing Practice (GMP). Corresponding GMP certificates shall be provided.

Information on the target species for which the active substance has been developed (and certification is applied for) should be given.

5.2. Product description (Part 2.A.)

Qualitative and quantitative particulars of the constituents

The qualitative composition of all the constituents of the active substance shall be given. 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.

The nature of the antigen should be described (inactivated, live, recombinant, …).

Any information on titre/potency specifications at specific production steps should be addressed in the corresponding sections of antigen production.

Product development

Information on product development relevant to the active substance shall be provided. The choice of the active substance and the choice of the constituents of the active substance, in particular relative to their intended functions, shall be described.

The justification of the antigen/strain relevance should cover the situation in the EU, as the VAMF will be certified by the EMA, regardless of the authorisation procedure of the corresponding vaccine(s).

The selection of the manufacturing process of the active substance shall be explained.

5.3. Description of the manufacturing method (Part 2B.)

An adequate description of the various stages of manufacture of the active substance, including purification procedures, shall be provided, accompanied by a process flow chart and a list of in-process controls indicating the stage of manufacture of the active substance at which they are conducted.

The key stages of the production process of the active substance should be identified and validated. For inactivated active substances, data relevant to the inactivation step, including the validation of the inactivation process shall be provided.

Validation of the key methods of control used in the manufacturing process of the active substance shall be described, documented and the results provided, unless otherwise justified. Results of three consecutive active substance batches produced using the method of production described should be provided.

Any information on antigen quantities to be used in finished product blending would be addressed in the finished product sections of the corresponding vaccine MA dossier.

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

The standard requirements described in Section IIIb.2C of Annex II to Regulation (EU) 2019/6 and relevant to the active substance shall apply. For the purposes of this Part, 'starting materials' means all components used in the production of the active substance.

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.

Certificates of analysis shall be presented for the starting materials in order to demonstrate compliance with the defined specification.

If materials of animal origin are used for preparation of culture media, the animal species and the tissue used have to be included and compliance with the relevant monographs including general monographs and general chapters of the European Pharmacopoeia shall be demonstrated.

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

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 VAMF shall be considered for the TSE and EA risk assessment. Warnings or restrictions of use may be brought in at the VAMF level depending on the information presented, which may be mitigated during the risk analysis at the level of the finished product.

The use of antibiotics during production of the active substance shall be justified and in compliance with the European Pharmacopoeia.

If the active substance is obtained by recombinant techniques, all corresponding relevant data on history, selection, construction, genetic stability and characteristics of the genetically modified organism shall be provided.

For genetically engineered starting materials, details shall be included such as the description of the starting cells or strains, the construction of the expression vector (name, origin, function of the replicon, promoter enhancer and other regulator elements), control of the sequence of DNA or RNA effectively inserted, oligonucleotide sequences of plasmid vector in cells, plasmid used for co-transfection, added or deleted genes, biological properties of the final construct and the genes expressed, copy number and genetic stability.

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

The standard requirements described in Section IIIb.2D of Annex II to Regulation (EU) 2019/6 shall apply for the in-process control tests carried out during the manufacture of the active substance, including validations of key control tests.

Specifications shall be set for each control test and the analytical methods shall be described.

For inactivated or detoxified active substances, inactivation or detoxification shall be tested during each production run as soon as possible after the end of the inactivation or detoxification process and after neutralisation if this occurs, but before the next step of production.

In accordance with the provisions of Directive 2010/63/EU and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests shall be carried out in such a way as to use the minimum number of animals and to cause the least pain,

suffering, distress or lasting harm. If available, an alternative in vitro test shall be used when this leads to replacement or reduction of animal use or reduction of suffering.

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

The standard requirements described in Section IIIb.2F of Annex II to Regulation (EU) 2019/6 shall apply for the demonstration of consistency in the manufacture of the active substance.

5.7. Stability (Part 2G.)

The standard requirements described in Section IIIb.2G of Annex II to Regulation (EU) 2019/6 to demonstrate the stability of the active substance and, where relevant any intermediate storage, shall apply.

If the active substance is stored, the intended conditions and duration of storage shall be defined based on stability data. Those data may be obtained either through testing of the active substances themselves or through appropriate testing of the finished product.

A description shall be given of the tests undertaken to support the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed for the active substance.

5.8. Other information, if applicable (Part 2H.)

Information relating to the quality of the active substance not covered by the previous sections may be included here.

6. Evaluation and certification

A scientific and technical evaluation of each VAMF shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for each VAMF, 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 VAMF 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 VAMF. The certificate issued shall apply throughout the Union.