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Procedural advice for veterinary vaccine antigen master file (VAMF) certification

Draft

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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

This document is intended to provide advice to marketing authorisation (MA) applicants and marketing authorisation holders (MAHs) on issues associated with the submission, evaluation, certification and use of a veterinary vaccine antigen master file (VAMF) by the European Medicines Agency (EMA). The detailed scientific requirements for an application for veterinary VAMF certification are described in Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council.

2. Legal framework

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC sets out the concept of VAMF. Section V.2 of Annex II lays down specific requirements related to the VAMF.

3. Principles of the VAMF certification

A VAMF is a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information on quality for one given vaccine antigen or active substance. 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 the VAMF certification system is optional. For combined vaccines, the vaccine antigen(s) to be included in VAMF(s) shall be specified and a separate VAMF shall be required for each of them.

The VAMF certification (1st step) consists of a centralised assessment of the VAMF application dossier submitted by the applicant/MAH, which results in a certificate of compliance to Union legislation, issued by the EMA. This certificate is valid throughout the European Union.

As a second step, the competent authority that will grant or has granted the MA shall take into account the certification, re-certification or variation of the VAMF for the concerned medicinal product(s) (Figure 1).

This document focusses on the first step. For the second step, changes to existing marketing authorisations resulting from VAMF certification procedures (i.e. inclusion of a new, updated or amended VAMF) will be introduced via variation following the relevant guidance (see References).

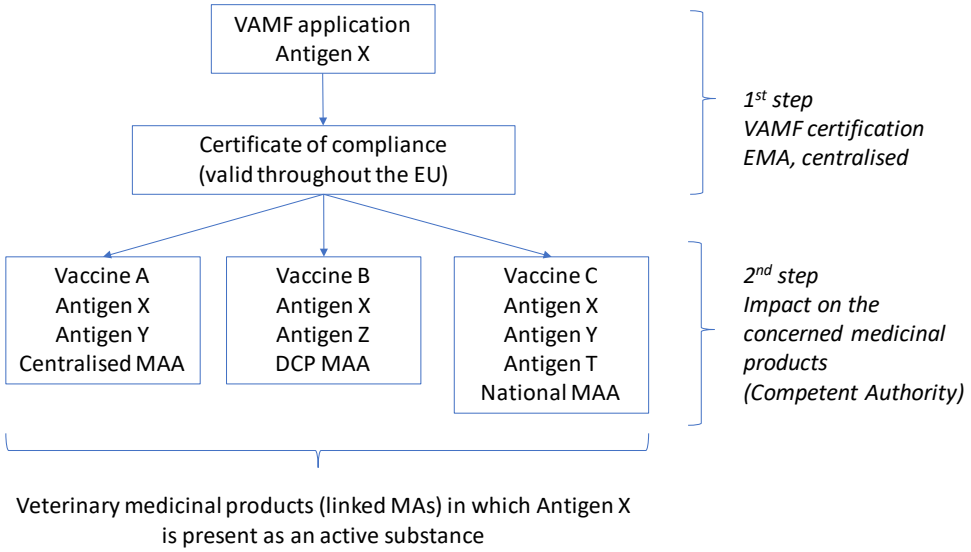


Figure 1: General principles of a VAMF

A marketing authorisation (MA) or a marketing authorisation application (MAA) may contain one or more VAMF certificates and respective VAMF data.

Two different scenarios referred to as 'triggers' are possible for the initial certification of a VAMF (see Annex 1):

- Trigger 1: For new vaccine antigens which have not been already authorised in the Union, the evaluation of VAMF(s) will be carried out as part of the evaluation of the full marketing authorisation dossier of the vaccine in which they are included. To this end, a full marketing authorisation application dossier should be submitted to the Agency, including all the VAMFs corresponding to each single vaccine antigen for which the use of a VAMF is intended. The same will also apply to vaccine antigens included in a new vaccine in a novel combination, irrespective of whether or not one or more of those vaccine antigens are part of vaccines already authorised in the Union.

- Trigger 2: For antigens included in currently authorised vaccines, via the centralised (CP), decentralised (DCP), or mutual recognition procedure (MRP), the evaluation and certification of a VAMF will be performed through a separate procedure. In this case, an application for a VAMF will be submitted to the Agency containing all the quality data corresponding to the antigen for which a VAMF is intended. The use of the VAMF certification system is not foreseen for antigens that form part of vaccines authorised solely via the national route.

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

Once the applicant/MAH chooses to use the VAMF certification system, all variations to the corresponding MAs concerning antigens included in approved VAMFs will have to be submitted through the same certification system. Either the same change is made to all linked MAs or the particular MA in question is removed from the system.

4. Initial certification of a VAMF

4.1. Trigger 1 – New MAA for a vaccine via CP

In the framework of a new MAA assessment via the centralised procedure for a vaccine with a new antigen or an existing antigen in a novel combination of antigens. In this case, the certification of the VAMF is an intrinsic part of the assessment of the MAA dossier submitted to the Agency.

4.1.1. Pre-submission activities

The MA applicant should inform the Agency that they intend to use the EU VAMF certification system (see Annex 2). Applicants may ask for a pre-submission meeting to obtain further procedural and regulatory advice from the Agency.

4.1.1.1. Letter of intent to the Agency

For applications for VAMFs linked to the submission of an initial MAA, the intention to use VAMF shall be confirmed in the pre-submission request form (i.e. to confirm eligibility for the centralised procedure) to be submitted four months prior to the submission of the MAA or, in any case, via notification to the Agency submitted no later than 2-3 months prior to the submission of the MAA. Information that should be provided:

- Intent to use the EU VAMF certification system.
- The name(s) and address(es) of the manufacturing site(s) of the vaccine antigen, with the corresponding inspection information and supportive information (e.g. manufacturing authorisations).

4.1.1.2. Appointment of rapporteurs

The rapporteur and co-rapporteur appointed by the CVMP for the evaluation of the MAA will also be responsible for the evaluation of the corresponding VAMF(s). The appointment of rapporteurs will be notified to the MA applicant.

4.1.2. Submission activities

The submission dates for VAMF(s) will follow the standard submission deadlines for MAAs published by the Agency and available on the EMA website. The final submission date will be agreed by the applicant and the Agency.

The MA applicant shall submit the application and accompanying documentation to the Agency. All submission requirements for the Agency are published on the EMA website. The VAMF data package should arrive simultaneously with the marketing authorisation application.

The validation of the submission will be performed by the Agency and the outcome communicated to the MA applicant with the evaluation timetable. Applicants should ensure that a technically valid submission is received by the Agency before the submission deadline. Any technically invalid applications will result in non-acceptance, which may cause a delay in the start of MAA the procedure.

4.1.3. Evaluation

For VAMF certification applications submitted within a new centralised MAA, the assessment will by definition be embedded in the centralised evaluation procedure. The timetable will follow that of the

respective MAA. An evaluation report of the VAMF will be prepared in addition to the MA evaluation report. The VAMF certification will occur at the stage of the CVMP opinion on the MAA.

4.1.4. Inspections

When considered necessary to complete the assessment of the submitted VAMF, (an) inspection(s) of vaccine antigen manufacturing site(s) may be requested by the CVMP.

4.1.5. Certification

Within 15 working days of the adoption by the CVMP of a positive evaluation report, the Agency will issue a VAMF certificate. The VAMF evaluation report will accompany the certificate.

Within 15 working days of the adoption by the CVMP of a negative evaluation report, the Agency will issue a letter refusing the grant of a certificate for a VAMF to the applicant. The VAMF evaluation report will be attached to the refusal letter.

4.2. Trigger 2 – New VAMF for an antigen in authorised vaccine(s) via CP, MRP, DCP

In the case of antigens contained in vaccines authorised via CP, MRP or DCP, the MAH may initiate the VAMF certification at any time.

It is encouraged that the data submitted for certification are identical to the corresponding data approved in one linked MA, and no changes are proposed during the certification. In the case of a VAMF application for an antigen included in different authorised vaccines where differences in the quality data packages exist, the MAH may consider harmonising the respective dossiers before applying for a VAMF.

It is not possible to certify a VAMF that might change during the procedure. Therefore, it is strongly advised not to initiate a VAMF certification when there are ongoing variations related to the content of the VAMF in the individual MA(s). Additionally, MAHs should not submit variations related to the content of the VAMF until the VAMF is certified.

For any application other than that made in the framework of a new centralised MAA, rapporteur(s) will be appointed by the CVMP. The rapporteur(s) will be responsible for the evaluation of the VAMF certification application on behalf of the EMA.

4.2.1. Pre-submission activities

Prior to the submission of the VAMF application, the MAH should inform the Agency that they intend to use the EU VAMF certification system (see Annex 2). MAHs may ask for a pre-submission meeting to obtain further procedural and regulatory advice from the Agency.

4.2.1.1. Letter of intent to the Agency

MAHs should ideally inform the Agency of their intention to submit VAMF applications approximately 2-3 months before submission, specifying the intended submission date. Information that should be provided:

- A list of MAs, to which the respective VAMF will apply, with the corresponding Member States (MS) of authorisation.

- The name(s) and address(es) of the manufacturing site(s) of the vaccine antigen, with the corresponding inspection information and supportive information (e.g. manufacturing authorisations).

4.2.1.2. Appointment of rapporteur(s)

For the evaluation of the VAMF, one rapporteur and one co-rapporteur will be appointed by the CVMP. The appointment of rapporteur(s) will be notified to the MAH. For antigens contained in a centrally authorised vaccine, the rapporteur(s) responsible for the authorised product will be appointed as rapporteur(s) for the evaluation of the VAMF application.

4.2.2. Submission and validation

The monthly deadlines for submission of applications for VAMF certification will be published on the EMA website.

The MAH shall submit the application and accompanying documentation to the Agency. All submission requirements for the Agency are published on the EMA website.

The validation of the submission will be performed by the Agency and the outcome communicated to the MAH.

4.2.3. Evaluation

An evaluation report will be prepared by the appointed rapporteur(s) and circulated for review by the CVMP. The CVMP will then make appropriate recommendations on the outcome of the evaluation.

The timetable for VAMF certification applications for Trigger 2 will be as follows (see Annex 3):

Day -15	Submission of VAMF application
Day 0	Validation of the VAMF application
Day 1	Start of the procedure
Day 45	Rapporteur's evaluation report
Day 52	Co-rapporteur's comments
Day 66	CVMP comments
Day 70	Revised rapporteur's evaluation report
Day 90	**Adoption of VAMF certificate and evaluation report** *or* adoption of list of questions and clock stop
Day 91	Re-start after submission of responses
Day 108	Rapporteur's assessment of responses and evaluation report
Day 115	Co-rapporteur's comments
Day 119	CVMP comments
Day 129	Revised rapporteur's evaluation report
Day 150	Adoption of VAMF certificate and evaluation report

4.2.4. Inspections

When considered necessary to complete the assessment of the submitted VAMF, (an) inspection(s) of vaccine antigen manufacturing site(s) may be requested by the CVMP.

4.2.5. Certification

Within 15 working days of the adoption of a positive evaluation report by the CVMP, the Agency will issue a VAMF certificate. The evaluation report will accompany the certificate.

Within 15 working days of the adoption of a negative evaluation report by the CVMP, the Agency will issue a letter refusing the grant of a certificate for a VAMF to the Applicant. The evaluation report will be attached to the refusal letter.

The VAMF certificate holder will need to introduce the VAMF certificate in the corresponding MA(s) via the relevant variation.

5. Data requirements for initial application for certification

The content of a VAMF to be submitted for initial certification is described in Annex II (section V.2.2) to Regulation (EU) 2019/6. Further guidance on technical data requirements for VAMF is provided in the 'Guideline on data requirements for vaccine antigen master files (VAMF)' (EMA/CVMP/IWP/258755/2021).

6. Changes to the content of a VAMF (Variations)

6.1. Legal framework

A variation to the terms of a VAMF certificate must be submitted in accordance with Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 and with the EMA/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 (EMA/CMDv/7381/2021; see Chapter H).

6.2. Procedure for variations to the terms of a VAMF certificate

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. The variation submission, data requirements and evaluation will follow the current established procedure for variations to centralised MAs.

The Certificate Holder shall submit the VAMF variation application and accompanying documentation to the EMA. For variations requiring assessment, an expert statement including the Certificate Holder's view of the possible impact of the VAMF to each linked MA should be provided.

In the case of a positive evaluation, the Agency shall re-issue the certificate of compliance with Union legislation for the VAMF with the variation evaluation report attached, if applicable.

The VAMF certificate holder will need to introduce the updated VAMF certificate in the corresponding MA(s) via the relevant variation.

7. Use of VAMF certificates when submitting new MAAs

When submitting an application for a new MA, the applicant should notify the EMA or the National Competent Authority, if appropriate, of the use of VAMF certificates in the application.

The applicant will be required to provide to the relevant competent authority all valid VAMF certificates of compliance to Union legislation and accompanying evaluation reports.

The list of relevant medicinal products to which the VAMF applies should be updated by the MAH after the new MA has been granted. The MAH should have a record of the MAs to which the VAMF applies and should provide it to competent authorities upon request.

8. References

Regulation (EU) 2019/6 of the European Parliament and the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC

Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council.

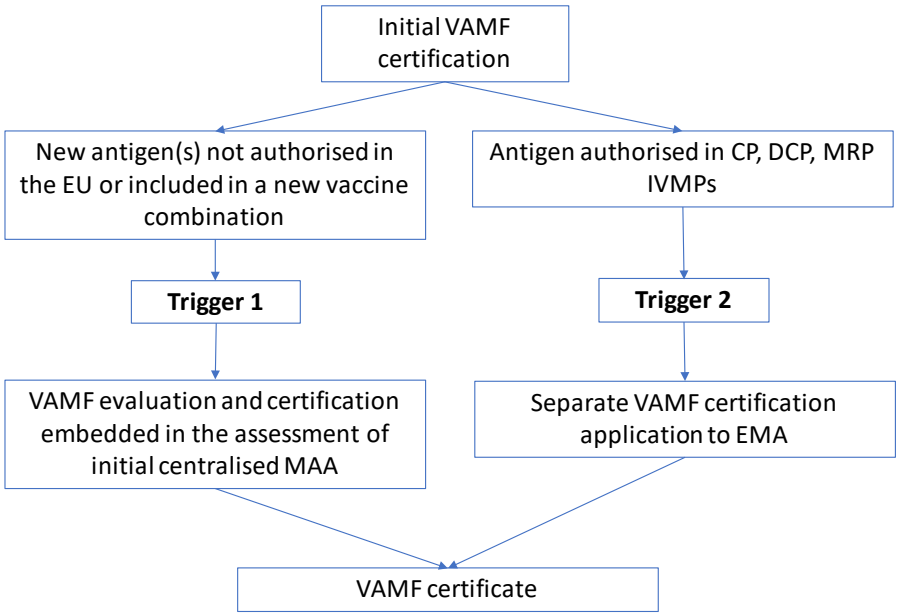
Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council

EMA/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 (EMA/CMDv/7381/2021)

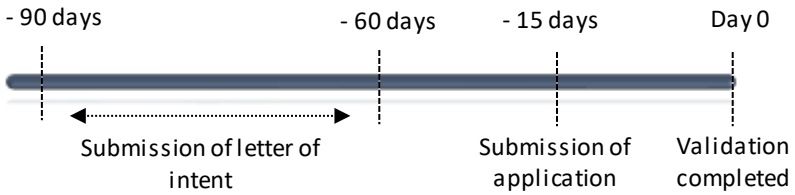
CVMP guideline on data requirements for vaccine antigen master files (VAMF) (EMA/CVMP/IWP/258755/2021)

9. Annexes

Annex 1 - Triggers for VAMF certification



Annex 2 - Pre-submission activities for initial certification of a VAMF



Annex 3 – Timetable for certification of a VAMF – Trigger 2