The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

GUIDELINE ON REQUIREMENTS FOR VACCINE ANTIGEN MASTER FILE (VAMF) CERTIFICATION

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Note: This document contains a number of abbreviations, a list of which is provided here below:

BWP	Biotech Working Party
CP	Centralised procedure
CPMP	Committee for Proprietary Medicinal Products
MAA	Marketing Authorisation Application
MA	Marketing Authorisation
MAH(s)	Marketing Authorisation Holder(s)
MRFG	Mutual Recognition Facilitation Group
MR	Mutual Recognition
MS	Member State
VAMF	Vaccine Antigen Master File

1. INTRODUCTION

This document is intended to provide guidance to Marketing Authorisation (MA) Applicants and Marketing Authorisation Holders (MAHs) on issues associated with the submission, evaluation and certification of the VAMF by the EMEA. This guidance may be reviewed after experience. The detailed scientific requirements for an application for VAMF certification are described in the '*Guideline on the Scientific Data Requirements for a Vaccine Antigen Master File*'[1].

2. LEGAL FRAMEWORK

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use introduces the concept of the Vaccine Antigen Master File. Part III, section 1.2 of Annex I lays down specific requirements related to VAMF[2].

3. PRINCIPLES OF THE VAMF CERTIFICATION

The use of the VAMF certification system is optional.

The VAMF is a stand-alone part of the marketing authorisation application dossier (MAA) for a vaccine. One given VAMF contains all relevant information of biological, pharmaceutical and chemical nature for one given vaccine antigen, which is common to several vaccines from the same MA applicant or MAH.

The VAMF system is aimed at simplifying the tasks of both applicants and competent authorities by:

- Reducing the number of dossier submissions and data evaluations carried out for the same vaccine antigen.
- Harmonising the data for a given antigen present in several vaccines.
- Ensuring consistency throughout the European Community.

The VAMF certification consists of a centralised assessment of the VAMF application dossier submitted by the MA Applicant/MAH, which results in a certificate of compliance to Community legislation, issued by the EMEA. This certificate shall be valid throughout the European Community.

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 on the concerned medicinal product(s) (Figure 1). This document only deals with the first step; details on the 'second step' procedure will be given in a separate guidance document.

[1] EMEA/CPMP/BWP/3734/03
[2] Commission Directive 2003/63/EC, O.J. L159/82, vol.46, 27.6.2003

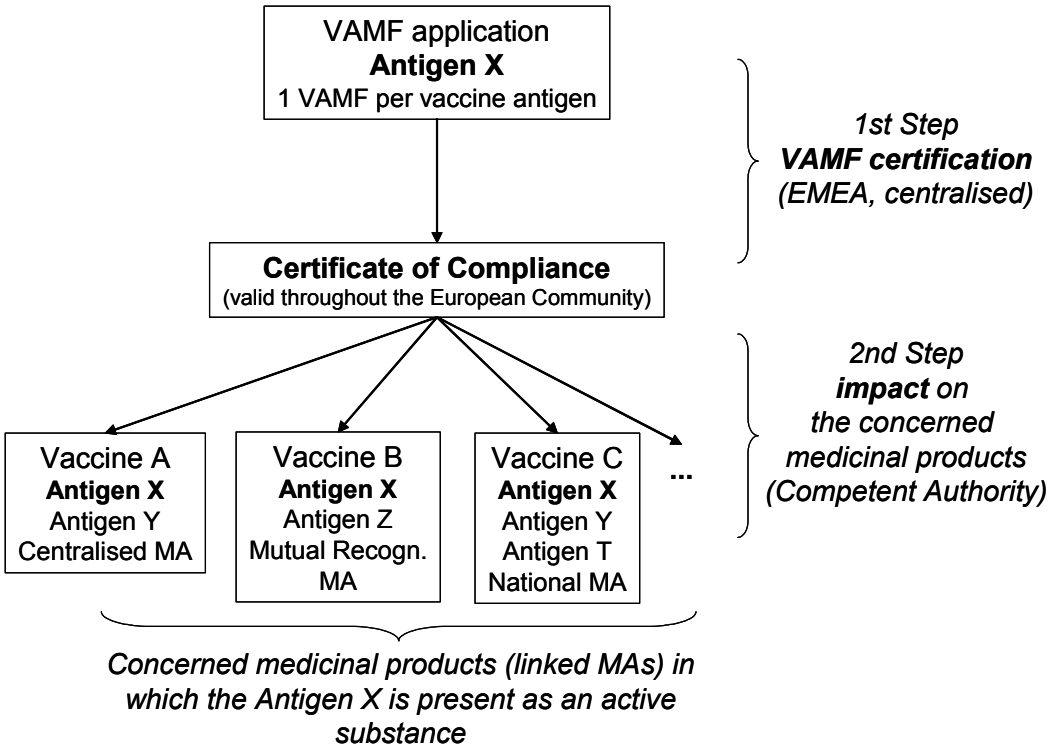


Figure 1: General principles of a VAMF.

A Marketing Authorisation (MA) or a Marketing Authorisation Application (MAA) may contain one or more VAMF certificates and respective VAMF data.

If, when submitting a new MAA, the MA Applicant decides to opt for vaccine antigen master files, the VAMFs must be submitted for all vaccine antigens in the respective MAA. As a rule, one VAMF should be submitted per vaccine antigen (see figure 2). In the case of a group of antigens aimed at preventing a single infectious disease (e.g. Inactivated poliovirus Serotypes 1, 2 and 3), a VAMF should be submitted for each antigen in the group.

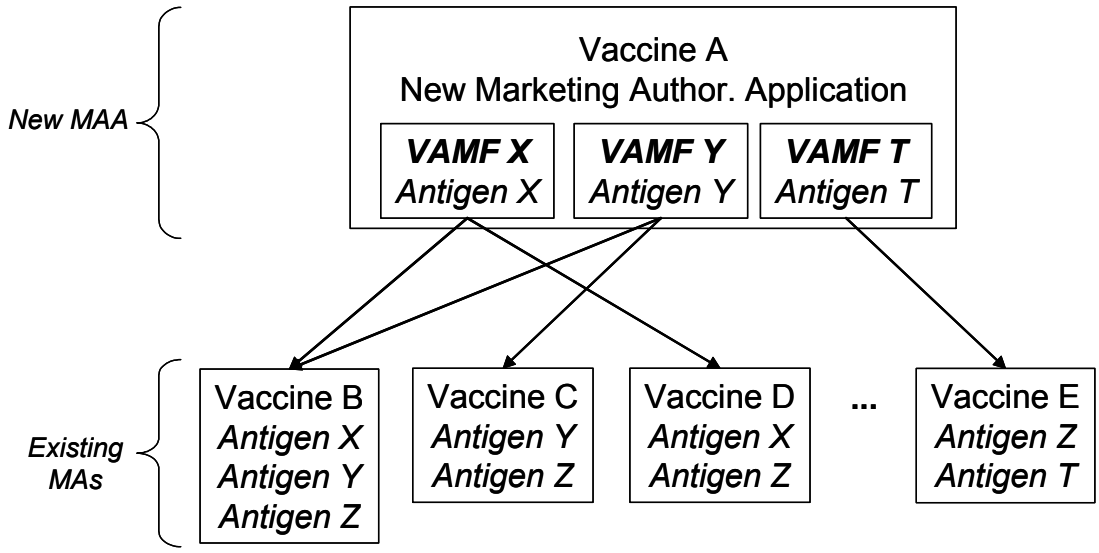


Figure 2: Example of a new MAA for a Vaccine (Vaccine A), which has 3 antigens as active substances (Antigen X, Y and T). For existing vaccines (Vaccines B, C, D, E), VAMF certificates will not be available for all antigens (e.g. Vaccine B has VAMF certificates for antigens X and Y, but not for antigen Z).

A VAMF application can only be submitted to the EMEA for antigens that form part of at least one MA or MAA, which has been, or will be evaluated via a Community procedure (Mutual Recognition (MR) or Centralised Procedure (CP)). If this not the case, the evaluation shall be carried out by the national competent authority that has granted the marketing authorisation. This guidance document does not cover a purely national VAMF certification process.

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 chooses to use the Community VAMF certification system, all variations to the corresponding MAs 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 for submission of a VAMF application.

An application for a VAMF may be submitted as follows (see also the diagram in Annex 1):

Trigger 1:

In the framework of a new MAA assessment via the centralised procedure. In this case, the certification of the VAMF is an intrinsic part of the assessment of the MAA dossier submitted to the EMEA.

Trigger 2:

In the framework of a new MAA via the Mutual Recognition (MR) procedure.

Trigger 3:

In the framework of a new MAA via a purely national procedure, provided at least one of the antigens has already been evaluated through a Community procedure.

Trigger 4:

In the case of existing MAs, MAHs may initiate the VAMF certification at any time, e.g.:

(i) The data submitted for certification are identical to the corresponding data approved in all proposed linked MAs, and no changes are proposed during the certification.

(ii) A change to the data approved in all linked MAs is proposed by the Applicant.

(iii) The Applicant may intend to harmonise differences between the data package as currently approved for a given antigen in all proposed linked MAs, e.g. differences in approved storage times of intermediates.

Note for Applicants: 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, the Applicants should not submit variations related to the content of the VAMF until the VAMF is certified.

4.2 Pre-submission activities

Prior the submission of the VAMF application (see section 4.1), the MA Applicant/MAH should inform the relevant Competent Authority(ies) that they intend to use the Community VAMF certification system (see also Annex 2).

4.2.1 Letter of intent to EMEA

MA Applicants and MAHs should ideally inform the EMEA of their intention to submit VAMF applications approximately 2-3 months before submission, specifying the intended submission date and the appropriate trigger for submission (see section 4.1).

A list of MAs, to which the respective VAMF will apply, with the corresponding Member States (MS) of authorisation should also be provided at this time. In addition, the name(s) and address(es) of the manufacturing site(s) of the vaccine antigen, with the corresponding inspection information and supportive information, should be provided. For any application, other than that made in the framework of a new centralised MAA, the MA Applicant/MAH should also propose co-ordinators in their letter of intent. The co-ordinator(s) will be responsible for the evaluation of the VAMF certification application on behalf of the EMEA.

4.2.2 Appointment of co-ordinator(s)

Two co-ordinators will be appointed by the CPMP in consultation with the BWP and the appointment will be notified to the MA Applicant/MAH, and where appropriate to the Mutual Recognition Facilitation Group (MRFG) and the National Authority.

The EMEA will publish a list of VAMF co-ordinators.

4.3 Submission and validation

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

The MA Applicant/MAH shall submit the application and accompanying documentation to the EMEA, to the co-ordinator(s), and to all Member States (MS). All documentation requirements for the EMEA, co-ordinators and MS will be published on the EMEA website.

The validation of the submission will be performed by the EMEA and the outcome communicated to the MA Applicant/MAH, the co-ordinators and the MS with the evaluation timetable.

4.4 Evaluation

In all cases, an evaluation report will be prepared by the appointed co-ordinator(s) and circulated for review by the BWP. The BWP will then make appropriate recommendations on the outcome of the evaluation, to the CPMP.

In the case a VAMF certification application is submitted within a new centralised MAA (trigger 1, section 4.1), the assessment will by definition be embedded in the centralised evaluation procedure. The timetable will follow that of the respective MAA. Certification may occur at any stage prior to or at the stage of the CPMP opinion on the MAA.

The timetable for all VAMF certification applications following triggers 2, 3 and 4 (see section 4.1) will be as follows (see also Annex 3):

Day -10	EMEA validation of the VAMF application
Day 0	Clock start (at official CPMP start date)
Day 30	CPMP adoption of inspection request(s) for the vaccine antigen manufacturing site(s), if necessary. (see section 4.5)
Day 45	Circulation of co-ordinators' evaluation report to the BWP. Subsequent transmission of this report, by the EMEA, to the Applicant.
Day 75	Comments BWP members
Day 83	BWP discussion/recommendation
Day 90	CPMP adoption of the evaluation report & certification/List of Questions (clock stop)(*)

(*)A response timetable may be arranged as necessary.

In the case a VAMF certification application submitted within a national MAA, which may be going for MR (trigger 2 and 3, section 4.1), the assessment should be instigated before or at the beginning of the national authorisation process, so that the Certificate is available before the end of the initial 210 day review process.

In some circumstances (e.g. in the case of initial VAMF certification for already existing MAs when VAMF data have been previously assessed and authorised via a centralised MA), there may be no need for scientific re-evaluation of the data and the timetable will be shortened.

4.5 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 CPMP.

4.6. Certification

Within 5 working days of the adoption of a positive evaluation report by the CPMP, the EMEA will issue a VAMF certificate. The evaluation report will accompany the certificate.

Within 5 working days of the adoption of a negative evaluation report by the CPMP, the EMEA 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.

In both cases, MA applicant/MAH and MS will be notified by the EMEA.

5. DOSSIER REQUIREMENTS FOR INITIAL APPLICATION FOR CERTIFICATION

5.1 Administrative information

The following documentation should be provided in the initial application for certification:

An application form for each EMEA VAMF certification submission, which will contain:

- A list of medicinal products to which the VAMF will apply, with corresponding MAs/reference numbers if relevant, countries of authorisation if relevant (MS) and approval dates. Information on pending approvals should also be given. For information**,** third country approvals of MAs containing the same data should also be listed.
- For VAMF linked MAs, if a particular MAH name and address are not identical to the name and address of the proposed VAMF certificate holder, a relevant declaration should be provided attached to the application form, stating that the MA Applicant and the MAH belong to the same mother group of companies, which share the same data package.

5.2 Expert statement

The Applicant should provide an Expert statement on the data submitted for certification. This should also include an overview/summary of the Applicant's view of the possible impact of the VAMF to each linked MA. In case of submission under trigger 4(i) (see section 4.1), the submission of an expert statement is not required.

5.3. Scientific data

Refer to the "*Guideline on the Scientific Data Requirements for a Vaccine Antigen Master File*" (EMEA/CPMP/BWP/3734/03).

5.4. Specific dossier requirements

In the case of trigger 4 (ii) and (iii), the change(s) and/or harmonisation introduced should be clearly highlighted in the VAMF dossier. Where a harmonisation of any differences between respective MAs is proposed (trigger 4 (iii), see section 4.1), it should be indicated in the

submission what is exactly approved in the various dossiers (specify country of authorisation and MA number). Where there is already a VAMF data package approved via a centralised MA, then the content of this VAMF data package should normally be the reference file. If there is no centralised MA, then the most recent MR MA should normally be the reference file.

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 Article 1 (2) of Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93[3].

6.2 Procedure for Variations to the terms of a VAMF certificate

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 EMEA, to the co-ordinator(s), and to Member States (MS) . All documentation requirements for the EMEA, co-ordinators and MS will be published on the EMEA website.

By analogy to the original submission for certification, for type II variations, an expert statement including the Certificate Holder's view of the possible impact of the VAMF to each linked MA should be provided.

Once approved, the EMEA will deliver a certificate of compliance to Community legislation with the variation evaluation report attached, if applicable.

7. USE OF VAMF CERTIFICATES WHEN SUBMITTING NEW MAAS

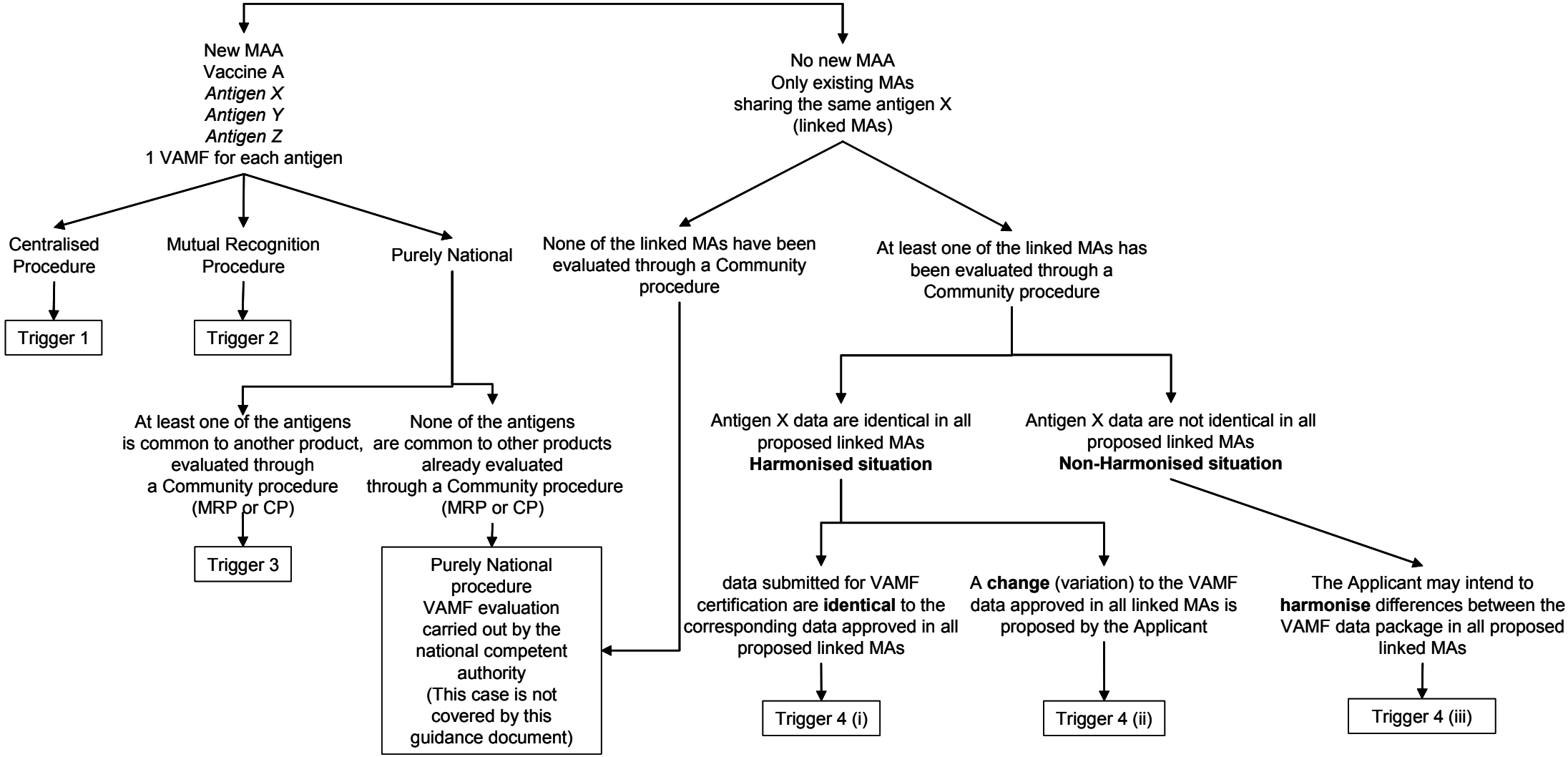
When submitting an application for a new MA, the MA Applicant should notify the EMEA or the National Competent Authority, if appropriate, of the use of VAMF certificates in the application.

The Applicant will be required to provide, to the relevant competent authority, all valid VAMF certificates of compliance to Community legislation and accompanying evaluation reports together with the respective VAMF data.

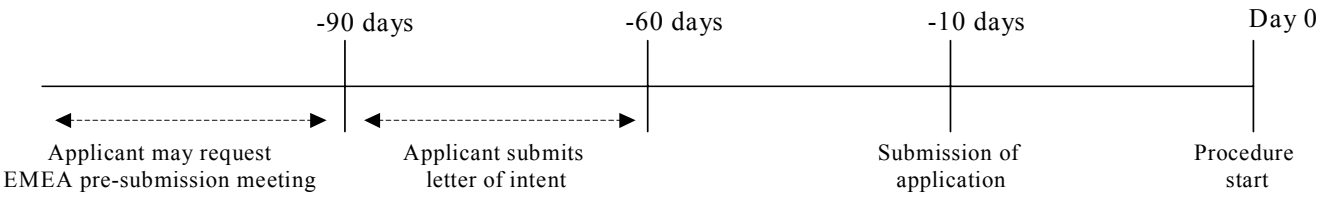
The list of relevant medicinal products to which the VAMF applies forms part of the VAMF application form. This list should be updated by the MAH after the new MA has been granted. In addition, a signed declaration stating that the VAMF certificates are fully applicable to the attached updated list of all linked MAs, highlighting the new MA additions should be provided. The updated list and declaration should be sent to the EMEA, all co-ordinators and MS.

[3] O.J. L159, vol. 46, 27.6.2003

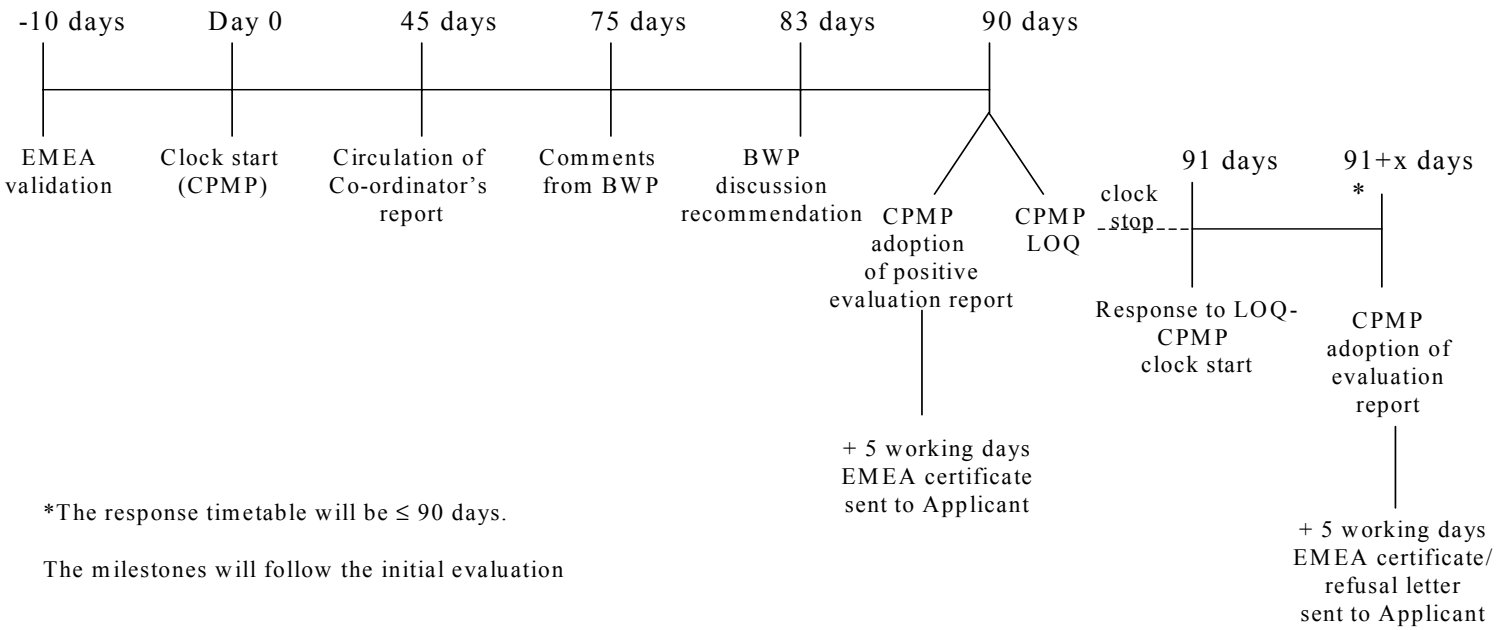
ANNEX 1 - TRIGGERS FOR A VAMF CERTIFICATION



ANNEX 2
PRESUBMISSION ACTIVITIES FOR INITIAL CERTIFICATION OF A VAMF



ANNEX 3
TIMETABLE FOR INITIAL CERTIFICATION OF VAMF



*The response timetable will be ≤ 90 days.

The milestones will follow the initial evaluation