EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Guideline on

Plasma Master File (PMF)

And

Vaccine Antigen Master File (VAMF)

“Second Step”

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1. INTRODUCTION

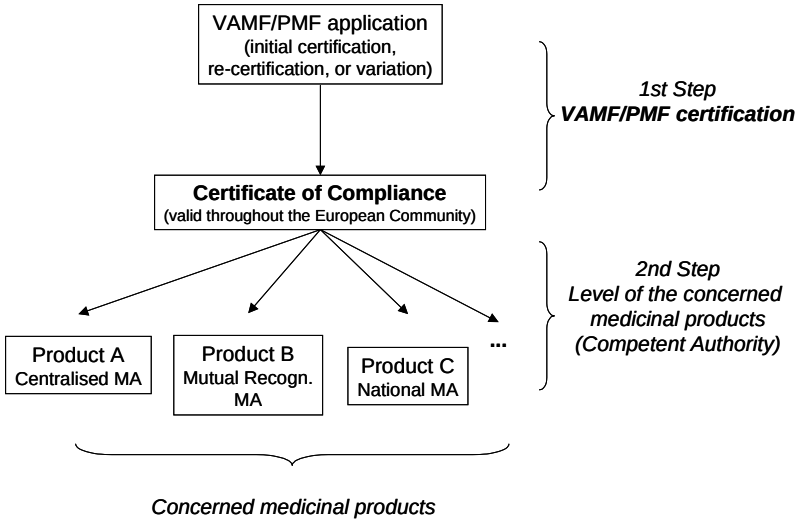
This document is intended to provide guidance to Competent Authorities, Marketing Authorisation (MA) Applicants and Marketing Authorisation Holders (MAHs) on the "2nd step" of the VAMF and PMF certification. Detailed guidance on scientific and procedural requirements for the "1st step" of the PMF/VAMF certification can be found on the European Medicines Agency (EMEA, hereafter referred to as "the Agency") website.[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[2], introduces the concepts of Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF). Specific requirements related to PMF and VAMF are laid down in Part III, sections 1.1 and 1.2 of Annex I. Both concepts aim at simplifying procedures for the approval of and subsequent changes (variations) to human plasma-derived medicinal products and vaccines, respectively.

As a first step in the procedure, the scientific evaluation of the PMF/VAMF is conducted. In most cases, this evaluation is carried out at Community level, *i.e.* by the Agency. A positive evaluation results in a certificate of compliance with Community legislation, which applies throughout the Community. As stated in Recitals (5) and (7) of Commission Directive 2003/63/EC, this certificate prevents from any subsequent reassessment of the corresponding PMF/VAMF data.

As a second step (following the PMF/VAMF evaluation and certification), "*the Competent Authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the [PMF/VAMF] on the concerned medicinal product(s)*" [2]



VAMF and PMF 'two-steps' systems.

[1] See notably CPMP/BWP/3734/03, CPMP/BWP/4663/03, CPMP/BWP/4548/03 and CPMP/BWP/3794/03

[2] Commission Directive 2003/63/EC, O.J. L159/80, vol.46, 27.6.2003

In the case of centrally authorised medicinal products, the distinction between the 'first step' and 'second step' is rather theoretical, since the Agency is both responsible for the PMF/VAMF certification and for the assessment of the concerned medicinal product(s). In such cases, both steps will be carried out within one single administrative procedure.

Thus, sections 3 and 4 of this document are of particular relevance when the 'second step' is carried out at a national level.

3. '2ND STEP' FOR THE PMF

3.1 Documents

Following the issuing of a PMF certificate, the PMF holder shall without delay forward the following documents to each of the Competent Authorities that will grant or have granted the marketing authorisation for the concerned medicinal product(s):

- The PMF certificate of compliance with Community legislation, together with the evaluation report attached.
- The respective PMF data package, if it differs from the one that is already in the dossier(s) of the concerned medicinal product(s)[3].
- An Expert statement, outlining the applicant's view of the impact (or non-impact) of the PMF to each concerned medicinal product(s).
- A signed declaration stating that the PMF data package and certificate of compliance are fully applicable to the concerned medicinal product(s).

Where the PMF holder differs from the MAH or from the MA Applicant for the concerned medicinal product(s), the PMF shall be made available to the MAH or MA Applicant for submission to the Competent Authority. In any case, the MAH or MA Applicant shall take responsibility for the medicinal product.

3.2 Amending the Marketing Authorisation dossiers

Upon receipt of these documents, the Competent Authority shall take into account the certification, re-certification or variation of the PMF on the concerned medicinal product(s). To this end, the following procedure is suggested:

If the certified PMF data package is identical to the one present in the existing concerned MA dossier(s), the PMF certificate should simply be added to the dossier(s). In this case, the '2nd step' should be of purely administrative nature.

[3]The PMF shall provide a list of the medicinal products for which the PMF is valid, whether these products have been granted a marketing authorisation or are in the process of being granted such an authorisation (including pending applications for products to be used in clinical trials).

If the certified PMF data package is not identical to the one present in the concerned MA dossier(s), the Competent Authority shall evaluate the impact of the changes on the concerned medicinal product(s). This evaluation:

- Shall not lead to any subsequent reassessment of the certified PMF data
- Should take into account the aforementioned Expert statement
- Should be carried out within a given timeframe (*e.g.* 30 days)

Usually, variations to a PMF should not have an impact at the level of the concerned medicinal product(s). In this case, the Competent Authority should amend the dossier(s), simply by including the updated PMF data package and the corresponding certificate of compliance. This should be of purely administrative nature.

Alternatively, variations to the PMF might have an impact, *i.e.* leading to consequential variations at the level of the concerned medicinal product(s) (*e.g.* revision of the summary of the product characteristics, labelling and package leaflet…). In such a case, applications for these consequential variations shall be submitted by the MAH to the concerned Competent Authority. The examination of these applications shall follow the standard procedures outlined in Commission Regulation (EC) 1084 & 1085/2003.

To avoid unnecessary delays, consequential variations that are already foreseen in the Expert statement should be submitted by the applicant as early as possible, *i.e.* together with the documents described in section 3.1.

4. '2ND STEP' FOR THE VAMF

4.1 Documents

Following the issuing of a VAMF certificate, the VAMF holder shall without delay forward the following documents to each of the Competent Authorities that will grant or have granted the marketing authorisation for the concerned medicinal product(s):

- The VAMF certificate of compliance with Community legislation, together with the evaluation report attached.
- The respective VAMF data package, if it differs from the one that is already in the dossier(s) of the concerned medicinal product(s)[4].
- An Expert statement, outlining the applicant's view of the impact (or non-impact) of the VAMF to each concerned medicinal product(s).
- A signed declaration stating that the VAMF data package and certificate of compliance are fully applicable to the concerned medicinal product(s).

[4]The VAMF shall provide a list of the medicinal products for which the VAMF is valid, whether these products have been granted a marketing authorisation or are in the process of being granted such an authorisation (including pending applications for products to be used in clinical trials).

4.2 Amending the Marketing Authorisation dossiers

Upon receipt of these documents, the Competent Authority shall take into account the certification, re-certification or variation of the VAMF on the concerned medicinal product(s). To this end, the following procedure is suggested:

If the certified VAMF data package is identical to the one present in the concerned MA dossier(s), the VAMF certificate should simply be added to the dossier(s). In this case, the '2nd step' should be of purely administrative nature.

If the certified VAMF data package is not identical to the one present in the concerned MA dossier(s), the Competent Authority shall evaluate the impact of the changes on the concerned medicinal product(s). This evaluation:

- Shall not lead to any subsequent reassessment of the certified VAMF data
- Should take into account the aforementioned Expert statement
- Should be carried out within a given timeframe (*e.g.* 30 days)

If there is no impact, the Competent Authority should amend the dossier(s), simply by including the updated VAMF data package and the corresponding certificate of compliance. This should be of purely administrative nature.

If there is an impact, separate, consequential variations shall be filed at the level of the concerned medicinal product(s). Applications for these consequential variations shall be submitted by the MAH to the Competent Authority. The examination of these applications shall follow the standard procedures outlined in Commission Regulation (EC) 1084 & 1085/2003.

To avoid unnecessary delays, consequential variations that are already foreseen in the Expert statement should be submitted by the applicant as early as possible, *i.e.* together with the documents described in section 4.1.

Annex: General flow-chart for the PMF/VAMF '2nd step'