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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**GUIDELINE ON REQUIREMENTS FOR
PLASMA MASTER FILE (PMF) CERTIFICATION**

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

BWP Biotechnology Working Party
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
PMF Plasma Master File

1. INTRODUCTION

This document is intended to provide guidance on issues associated with the submission, evaluation and certification of the Plasma Master File (PMF) by the EMEA. This guidance may be reviewed as experience is gained.

The detailed scientific requirements for an application for PMF certification are described in the 'Guideline on the Scientific Data Requirements for a Plasma Master File'¹.

Where a PMF corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State (MS), the scientific and technical evaluation of the said PMF shall be carried out by the national competent authority of that MS. This guidance document does not cover this situation.

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 PMF. Part III, section 1.1 of Annex I lays down specific requirements related to PMF and states that "For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in "Information related to the starting and raw materials", for starting materials made of human blood/plasma may be replaced by a PMF certified in accordance with this Part."²

3. PRINCIPLES OF THE PMF CERTIFICATION

The use of the PMF certification system is optional.

The PMF is a stand-alone documentation, which is separate from the dossier for marketing authorisation, which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices incorporating stable derivatives of human blood or human plasma.³.

The PMF certification system is aimed at simplifying the tasks of both MA applicants/MAHs and Competent Authorities by:

- Reducing the number of dossiers submissions and data evaluations carried out for the same plasma.
- Ensuring consistency throughout the European Community.

The PMF certification consists of an assessment of the PMF application dossier submitted by the Applicant in a system analogous to the centralised procedure, 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 effect of the certification or re-certification of the PMF on the concerned medicinal product(s) (Figure 1). PMF certification can also be used for medical devices

¹ EMEA/CPMP/BWP/3794/03

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

³ Referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma (OJ L 313, 13.12.2000, p. 22).

incorporating stable derivatives of human blood or human plasma. In the case of medical devices, the EMEA shall take into account the effect of the certification or re-certification of the PMF on the concerned stable derivative of human blood or plasma. This document only deals with the first step; details on the ‘second step’ procedure will be given in a separate guidance document

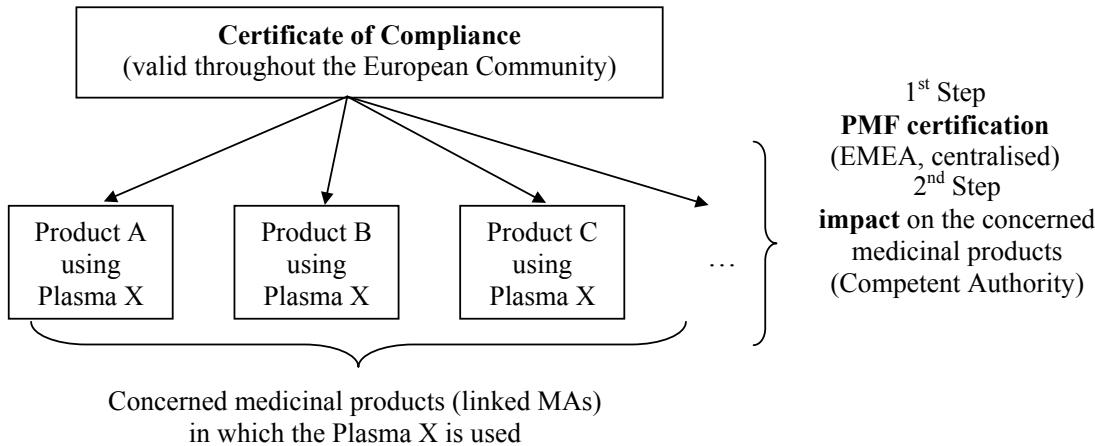


Figure 1: General principles of a PMF.

A Marketing Authorisation (MA) or a Marketing Authorisation Application (MAA) may refer to one or more PMFs or respective certificates.

Once the applicant chooses to use the Community PMF certification system, all variations to the corresponding plasma for all the linked MAs will have to be submitted through the same certification system.

4. INITIAL CERTIFICATION OF A PMF

4.1 Trigger for submission of a PMF application.

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

1. In the framework of a new MAA via the centralised procedure. In this case, the certification of the PMF is an intrinsic part of the assessment of the MAA dossier done at the EMEA.
2. In the framework of a new MAA via Mutual Recognition (MR) procedure.
3. In the framework of a new purely national MAA, provided the PMF corresponds to blood/plasma-derived medicinal products with marketing authorisations in more than one MS.
4. In the case of existing MAs, the PMF certification application may be initiated at any time, e.g. when:
 - (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 (variation) to the data approved in all linked MAs is proposed by the Applicant
 - (iii) Annual update is due.

5. Alternatively, a new PMF can be submitted for certification separately, at anytime in advance of any application for a MA, or for a consultation on a blood derivative incorporated in a medical device.

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

4.2 Pre-submission activities

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

4.2.1 Letter of intent to EMEA

Applicants should ideally inform the EMEA of their intention to submit PMF applications approximately 2-3 months before submission, specifying the intended submission date and the appropriate trigger for submission (see section 4.1, and Annex 1 & 2).

A list of MAs/MAAs, to which the respective PMF will apply, with the corresponding MS of authorisation, should also be provided at this time. In addition, a list of establishments⁴ in which blood/plasma collection, testing, storage and transportation is carried out, with the corresponding inspection and approval information, should also be provided, where applicable. The Applicant should also propose co-ordinator(s) in their letter of intent. The co-ordinator(s) will be responsible for the evaluation of the PMF certification application on behalf of the EMEA.

4.2.2 Appointment of co-ordinators

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

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

4.3 Submission and validation

The monthly deadline for submission of applications for PMF certification will be published on the EMEA website.

The Applicant shall submit the application and accompanying documentation to the EMEA, to the co-ordinators, and to the MS according to their requirements. 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 Applicant together 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.

⁴ Blood establishment' means any structure or body that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution, as defined in Article 3 of Directive 2002/98/EC.

In the case of a PMF certification application submitted within a centralised MAA, 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 other PMF certification applications following triggers 2, 3, 4 and 5 will be as follows (see annex 2):

Day -10	EMEA validation of the PMF application
Day 0	Clock start (at official CPMP start date)
Day 30	CPMP adoption of inspections of blood establishments, if necessary.
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 of a PMF 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 PMF certification for already existing MAs when PMF data have been previously assessed & 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 Inspection(s)

When considered necessary to complete the assessment of the submitted PMF, (an) inspection(s) may be requested by the CPMP. Inspection(s) requested must be carried out and the final report(s) sent to the EMEA and submitted to the CPMP in accordance with the 90-day time limit for the evaluation of the PMF. Due to the time constraints, MA applicants/MAHs should inform the EMEA of their intention to submit the PMF application 2-3 months before submission and include a list of blood establishments, with the corresponding inspection information and supportive documentation, as described in chapter 3.1 of the 'Guideline on the Scientific Data Requirements for PMF'.

4.6 Certification

Within 5 working days of the adoption of a positive evaluation report by the CPMP, the EMEA will issue a PMF 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 PMF. The evaluation report will be attached to the refusal letter.

In both cases, the Applicant and MS will be notified.

5. 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 PMF certification submission.

- A list of medicinal products to which the PMF will apply, with corresponding MAs/reference numbers, countries of authorisation (MS and Third Countries) and approval dates. Information on pending approvals should also be given (e.g. pending MA or pending application for use of a medicinal product in clinical trials, or use in medical devices).
- The period of data collection should be specified. The data lock point (i.e. the date designated as the cut-off date for data to be included in the PMF) should also be specified.

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 PMF to each linked MA.

5.3 Scientific data

Refer to the '*Guideline on the scientific data requirements for a Plasma Master File (PMF)*' (EMEA/CPMP/BWP/3794/03).

5.4 Specific dossier requirements

Specific dossier requirements are as follows:

- For triggers 4 (ii) and 4 (iii), the change(s) introduced should be clearly highlighted in the PMF dossier.
- Where the PMF data has been already approved as part of a centrally-authorised MA, reference to the EMEA procedure number should be given in the dossier submission. In the event that there is no centralised MA, then reference should be given to the most recent MR MA.

6. CHANGES TO THE CONTENT OF A PMF (VARIATIONS)

6.1 Legal framework

A variation to the terms of a PMF 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.

6.2 Procedure for Variations to the terms of a PMF 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 PMF variation application and supporting documentation to the EMEA, to the co-ordinators, and to the 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 PMF 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.

7. RE-CERTIFICATION OF PMF

Following the initial certification at the EMEA, the PMF shall be updated and re-certified on an annual basis. The existing certificate remains valid until the evaluation of the re-certification is determined.

The PMF Holder shall ensure that it submits the re-certification PMF annual update application and supporting documentation to the EMEA, to the co-ordinators, and to the MS according to their requirements. All documentation requirements for the EMEA, co-ordinators and MS will be published on the EMEA website.

The application for this re-certification of the PMF shall be submitted at the agreed “birth date” of the PMF and yearly thereafter.

The assessment of the PMF submission for re-certification will be carried out as a 60-day procedure, similar to the current established procedure for Type II variations to centralised MAs. Changes to the PMF may be submitted with the application for re-certification.

7.1 Documentation

7.1.1 Administrative information

See section 5.1.

7.1.2 Scientific Data

See section 5.2.

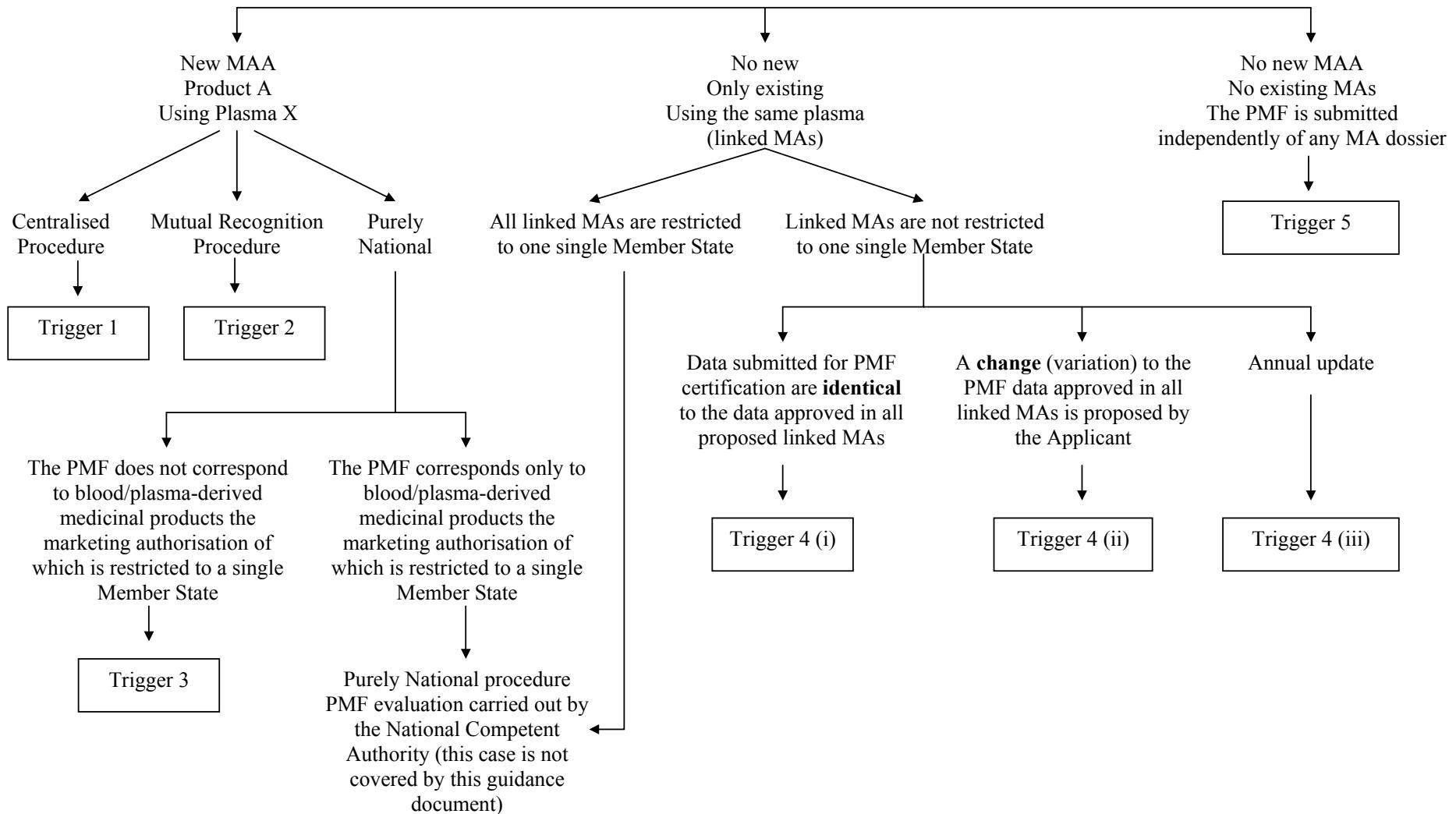
8. USE OF PMF CERTIFICATES WHEN SUBMITTING NEW MAAs

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

The MA Applicant will be required to provide, to the relevant competent authority, all valid PMF certificates of compliance to Community legislation and accompanying evaluation reports together with the respective PMF data package. In addition, a signed declaration that these certificates are fully applicable to the data contained in the respective MAA is required.

The list of relevant medicinal products, including pending MAAs, to which the PMF applies, forms part of the PMF application. This list should be updated by the Certificate holder after the new MA has been granted together with a signed declaration stating that the PMF data are fully applicable to the attached updated list of all linked MAs, highlighting the new MA additions. The updated list and declaration should be sent to the EMEA, all co-ordinators and MS.

ANNEX 1



ANNEX 2

Timetable for Initial Certification of PMF

