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Plasma Master File (PMF) requirements. Questions and Answers for PMF Holders

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[1] Last day of relevant Committee meeting.

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1. Introduction

Introduction to the Q&A
This guidance in the format of a Q&A supplements the data requirements in the published guidelines on PMF scientific requirements (EMEA/CHMP/BWP/3794/03) and dossier requirements on PMF epidemiological data (EMA/CHMP/BWP/548524/2008) on topics related to information on blood establishments and blood/plasma centres (BE/BCs) to be included in the PMF as well as listing of prospective BE/BCs in Annex II of the PMF.

The inclusion in the PMF of prospective BE/BCs which are not actively supplying plasma or closed centres which with no plasma in stock does not accurately provide the information related to the blood collected starting and raw material of the PDMP (plasma derived medicinal products) which is important for traceability purposes and part of the PM definition, content and principle. Traceability, in accordance with Regulation, should be guaranteed in all cases. In PMF it is essential to link the products manufactured (Annex A) out of the collected plasma and covered by the listed BEs/BCs (Annex II). There are/have been cases where BE/BCs from which no plasma is collected or in stock are/were, however, listed in the PMF (as operational or non-operational in Annex II). preventing a fully valid traceability link[2].

In 2023-24, the PMF expert group therefore engaged in discussions on simplification and harmonisation regarding inclusion and listing of centres in the PMF dossier in general and in the context of fulfilling requirements for tender processes at national level. PMF-Holders (PMF-Hs) were also consulted via a survey.

For this Q&A, all the above has been considered together with some important points reported by PMF-Hs concerning practical difficulties in deleting and reapplying for BE/BCs in PMF on a yearly basis for tender purposes.

This Q&A describes the approach to be applied in the evaluation of the compliance of BE/BCs registered in PMF applications, with the aim to improve and harmonise the PMF content at submission and consequently to streamline the PMF certification and evaluation timelines.

2. Questions and answers

PMF harmonised submission. Submission and listing of BE/BCs[3] (New 2025)

1. What BE/BCs can the PMF Holder apply for inclusion in the PMF dossier as prospective centres[4] for collection of blood and plasma?

At the time of the submission for a PMF (re-)certification, the PMF-Hs can apply for all prospective BE/BCs that fulfil legal and regulatory requirements as per Directive 2001/83/EC and scientific PMF guidelines[5] and that have been awarded with a contract for blood and/or plasma supply for that particular PMF holder. This also includes BE/BCs in case a national tender is won by the PMF holder.

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[2] Pharmaceutical legislation also requests to ensure traceability of human blood and plasma. For this reason, PMFs can keep "non-operational" BE/BCs in their PMFs. The *Annexes to Guideline on the scientific data requirements for a plasma master file* defines "*non-operational*" BE/BCs as "*permanently closed or temporarily suspended but from which plasma is still available*". Ref. is also given to Directive 2002/98 Article 14 which obliges Member States to take all necessary measures in order to ensure that blood and blood components collected, tested, processed, stored, released and/or distributed on their territory can be traced from donor to recipient and vice versa.

[3] Annex I, Part III, par.1.1, of Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC: the PMF must provide information on human blood or plasma used for manufacturing medicinal products which may replace the "*information related to the starting and raw material*" in Module 3.

[4] An establishment /centre that has been awarded with an active blood/plasma collection contract with PMF-H and is expected to be collecting blood/plasma for plasma manufacturing in that PMF.

[5] Ref. EMEA/CHMP/BWP/3794/03 Scientific data requirements for plasma master file - Scientific guideline | European Medicines Agency (EMA) and EMA/CHMP/BWP/548524/2008 Epidemiological data on blood transmissible infections - Scientific guideline | European Medicines Agency (EMA), current versions.

Such PMF prospective BE and/or BCs applied for in the PMF should be listed in the annex II under operational list of centres in the PMF dossier.

2. **Can new prospective BE/BCs without signed contract for blood/plasma supply be applied for and included in an EU-PMF?**

No. BE/BCs that do not have in place a valid signed contract for blood/plasma supply cannot be applied for inclusion in an EU PMF.

3. **What should the PMF holder do if blood/plasma collection contract(s) with the BE/BCs have been discontinued?**

If the contract between the PMF and the BE/BCs has been discontinued, and there is plasma from those BE/BCs in stock[6], the BE/BCs should remain to be listed in the PMF, and they should be moved from the list of operational to non-operational centres. Without plasma in stock, the BE/BCs should be removed and deleted from the PMF.

4. **What to do if the PMF has currently listed potential prospective BE/BCs that have no signed contract in place for the supply of plasma to the PMF?**

Potential prospective BE/BCs without active supply of plasma to that PMF (i.e. no signed contract in place for the supply of blood/plasma) should not be listed in the PMF dossier and should be removed[7] from the respective PMF annex at the time of the next Annual Update, in case they are listed.

5. **How to re-apply for a BE/BC that has been placed in non-operational or has been deleted from the PMF and has been awarded with a new signed contract?**

For both cases, a PMF variation is needed to re-apply for a centre that has been awarded with a new Blood/plasma collection contract. The type of change will be determined by Variation regulation and whether the centre has been previously assessed in the PMF certification.

Inspections by EU/EEA-competent authorities

6. **Can new centres/establishments without an acceptable inspection status be added to a PMF?**

No, a new centre/establishment cannot be added to a PMF in the absence of a satisfactory inspection. An acceptable inspection status (satisfactory outcome of an inspection by an EU/EEA competent authority) is a pre-requisite for the acceptance of a new centre/establishment to a PMF, and for the PMF dossier certification in line with current PMF regulation and respective PMF guidelines.

At the time of the PMF submission, in case that an EU/EEA-inspection is scheduled to take place during the evaluation or the EEA-inspection was already performed and the outcome is not yet available, but expected to be confirmed during the procedure, the PMF holder may include the respective new centre/establishment in the application. However, in both situations, a major objection will be raised during the first round of assessment and an acceptable outcome of the inspection needs to be confirmed during the procedure.

If an acceptable inspection outcome cannot be confirmed prior to the recommendation of the PMF certification procedure, the respective centre/establishment will have to be removed from the application, even if e.g. a new collection centre belongs to an already approved Blood Establishment.

Inspection at relocated sites.

[7] The PMF guideline states that non-operational centres should be in the Annex as long as plasma is on stock. See section 2.1.2.a) Guideline on the scientific data requirements for a Plasma Master File _PMF_ - Revision 1.doc (europa.eu)

[7] Ref. EMEA/CHMP/BWP/3794/03 Scientific data requirements for plasma master file - Scientific guideline | European Medicines Agency (EMA)

The same inspection approach as described above applies to relocated sites, as they are regarded as new sites and should therefore be treated in the same way.

Supplier audits

7. **Is it necessary that the PMF holder perform on-site audits for new or relocated centres/establishments before their inclusion in the PMF?**

Audits at new sites

Yes, on-site audits of new centres/establishments to be added to a PMF are required to verify compliance. This also applies for new centres/establishments already audited by another entity.

According to Annex 14 of the GMP guideline, supplier audits should be conducted by the fractionator/manufacturer according to established written procedures. These audits should be a systematic examination to determine compliance with regulatory requirements, and compliance with planned arrangements between PMF holder and establishments. It is the responsibility of the fractionator /manufacturer to qualify new suppliers as accurately as possible.

Therefore, where confirmation of a satisfactory audit for new centres/establishments is missing at the time of submission, a major objection will be raised during the PMF-(re)certification procedure.

This is applicable to collection, testing, storage, and transport facilities.

Unless justified, audits should be conducted on-site by the manufacturer or independent third-party auditors. Note that due to travel restrictions caused by the Covid-19 pandemic, the conducting of distant-audits instead of on-site audits was accepted during the 2020 and 2021 PMF annual assessments, when justified and agreed with EU/EEA inspectors.

Audits at relocated sites.

The same audit approach as described above applies to relocated sites, as they are regarded as new sites and should therefore be treated the same way.

Alert limits

8. **What statistical model should be applied to calculate the alert limits for viral marker rates?**

Alert limits are used to determine if a centre/establishment exceeds an allowed number of positive donors for each individual viral marker. The choice of statistical model is one of many important design aspects to establish these alert limits and should not be dealt with in isolation from other important factors such as the choice of the threshold to define outliers, or temporal/regional considerations to identify the data that will serve as a basis for modelling. Proper a priori planning of the experimental design and the corresponding statistical analyses are required to facilitate interpretation of the results of these analyses.

As the nature of the empirical data used to set alert limits is count data, the statistical model used needs to be suitable for modelling this type of data. Gamma, Poisson and Negative Binomial distributions should be considered, and the choice needs to be motivated based on the study design and data characteristics.

Assuming normally distributed data to calculate alert limits is not an appropriate approach, as viral marker rates are not normally distributed within a donor population. The use of a statistical model

based on Poisson distribution probability tables[8] with representative reference rates[9] of viral markers in the donor population is considered adequate to establish alert limits.

Other models might be acceptable, if sufficiently justified.

9. **Can alert limits be re-calculated? Under which circumstances is this acceptable?**

Yes, re-calculating alert limits based on a major change of the donor population, is considered acceptable in principle, however each re-calculation will need thorough justification to avoid widening of alert limits due to frequent re-calculation. It must be ensured that the prior standards of quality are maintained.

[8] These tables assess the relative probability of having a number of confirmed positive donors based on any given number of total donations.

[9] Average viral marker positivity rates that serve as the basis for establishing the viral markers Alert Limit tables