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Biologics Working Party

PMF dossier requirements. Questions and Answers for PMF Holders

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Questions and Answers for PMF Holders

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1. Introduction

This guidance in the format of a Q&A supplements the data requirements in the published guidelines on Plasma Master File (PMF) Scientific requirements (EMEA/CHMP/BWP/3794/03) and dossier requirements on PMF epidemiological data (EMA/CHMP/BWP/548524/2008) on topics related to inspection approval status, information on audits and epidemiology alert limits.

This Q&A is complemented by the Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use During the Covid-19 Pandemic, published by the European Commission.[1]

Over the last years, the PMF-Drafting Group[2] has worked on a project targeting the harmonisation of the assessment of PMF applications. This PMF project has received the support of EU/EEA inspectors involved in inspection of PMF-listed sites and the Agency's Biostatistics[3] Working Party (BSWP). With the completion of this project in 2021, the need to publish further guidance to PMF holders was agreed.

This Q&A describes the approach applied in the evaluation of the compliance status of Blood establishments registered in PMF applications, with the aim to improve the PMF content at submission and consequently to streamline the PMF certification and evaluation timelines.

Blood establishments and centres should have inspection and approval status and fulfil the inspection and audit requirements in accordance with the Blood Directive (2002/98/EC) and corresponding Commission directives (2004/33/EC, 2005/61/EC, 2005/62/EC and 2016/1214), and the Good Practice Guidelines of the Blood Guide (EDQM), for collection and testing. Processing, storage and transport activities should be performed in accordance with GMP Directive 2003/94/EC, Annex 14 of the EU Guide to GMP and Ph. Eur. requirements.

Missing information on the inspection approval status is often raised as a major objection during PMF certification.

In accordance with Commission Directive 2003/63/EC[4] amending Directive 2001/83/EC, and the EMA Guideline on the Scientific Requirements for a Plasma Master File (EMEA/CHMP/BWP/3794/03), all centres/establishments are required to have undergone a successful inspection. The detailed epidemiology data requirements to be included in the PMF can be found in chapter 12 of the Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008.

2. Inspections by EU/EEA-competent authorities

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.

[1] Notice to stakeholders – Questions and answers on regulatory expectations for medicinal products for human use during the Covid-19 pandemics

[6] PMF Drafting group is the group of experts linked to the Biologic Working Party (BW) that supports with monthly meetings the BWP and CHMP scientific committees with the PMF dossier evaluation and certification recommendation.

[7] The BSWP (biostatistics working party https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/biostatistics-working-party), supports the PMF drafting group with the generation of evidence for the calculation of alert-limits in relation to evaluation of epidemiological data requested for the PMF

[8] 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 section Plasma origin b.1.i) lays down specific requirements related to PMF information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

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

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.

3. Supplier audits

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 fractionatort/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.

4. Alert limits

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[5] with representative reference rates[6] of viral markers in the donor population is considered adequate to establish alert limits.

Other models might be acceptable, if sufficiently justified.

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.

[5] These tables assess the relative probability of having a number of confirmed positive donors based on any given number of total donations
[6] Average viral marker positivity rates that serve as the basis for establishing the viral markers Alert Limit tables