

EPIDEMIOLOGY REGULATORY LANDSCAPE

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The Plasma Master File (PMF) concept

Historically, licensing of plasma-derived therapeutics required submission of identical information about the plasma starting material with each Marketing Authorization (MA) for a plasma-derived medicinal product. This required manufacturers to submit duplicate details on each of several products derived from the same starting material. Ideally, reference to one document containing all information on the starting material would be more efficient for the manufacturer: the concept of a Plasma Master File (PMF) was born.

In support of its member fractionators, PPTA began advocating in the 1990s for the introduction of a PMF as a stand-alone dossier as part of the MA for a plasma-derived medicinal product. A stand-alone PMF could be independently administered from the other elements of the MA dossier and would better accommodate the specific requirements related to human plasma as starting material.

In June 2003 Commission Directive 2003/63/EC provided the legal basis for a PMF by amending Directive 2001/83/EC for medicinal products derived from human blood or plasma. The amendment allowed replacing the dossier requirements related to the starting and raw materials by a PMF certified in accordance of the provisions of the Directive.

As proposed by PPTA, the PMF was designed to be a stand-alone dossier, which would be reviewed and certified by the European Medicines Agency (EMA). The PMF Certificate would then be submitted to the European National Competent Authorities for acceptance into the marketing authorization dossiers for the products licensed in those countries. A number of different guidelines of the EMA were developed to provide guidance on procedural and content details for the PMF.

Epidemiology and the International Quality Plasma Program (IQPP)

An important common goal of our industry and regulatory bodies is to ensure that plasma for fractionation is obtained from donors who do not have an elevated risk of having infectious disease. In this light, emphasis is being focused on donor or donor center quality, as measured by epidemiological data on infectious disease risk. While donor selection is important, it must be acknowledged that steps such as sensitive infectious disease testing and viral removal and inactivation are crucial to ensuring the safety of

plasma protein therapies. Identification of collection centers with high infectious disease rates is valuable for quality control. Interpretation of epidemiological data for identifying “outliers” is like navigating a field of quicksand. False steps can lead to dire consequences that negatively impact plasma availability needlessly. It is important to note that no known viruses have been transmitted by plasma protein therapies in almost two decades.

Since the late 1990s, PPTA has had a viral marker standard to assess donor center quality as a central component of the International Quality Plasma Program (IQPP). This standard has been an effective measure for quality improvement by the source plasma industry.



The EMA Guideline on epidemiological data on blood transmissible infections

The requirement to collect epidemiological data on blood transmissible infections is intended to provide information on the theoretical infection risk in a specific donor population and is seen as an important part of the measures to ensure an adequate selection of donors of blood and plasma. Recently, a revised version of the 2005 Guideline on epidemiological data on blood transmissible infections came into force. Regulators felt that a revision of the guideline will benefit and improve the PMF dossiers with better submission of data and consistency across evaluation. To comply with the provisions of the guideline the PMF holder must

1. Report and analyze individual plasma center epidemiology data;
2. Facilitate tracking and time trending of these data; and
3. Establish a range of limits for acceptability of donor centers based on epidemiology data.

PPTA's International Quality Plasma Program (IQPP) and the PPTA Viral Marker Standard address issues of donor quality and limits of acceptability for source plasma. The EMA approach also includes recovered plasma as starting material for the production of medicinal products under the supervision of the agency. The most significant difference is that the PPTA standards are based on the donations actually fractionated, while the EMA guideline is based on donors.

IQPP classifies donors as either Applicant or Qualified do-

nors and calculates positivity rates based on the number of Qualified donations. The PPTA Qualified Donor Standard treats every person who has not donated in the last six months as an Applicant donor. EMA categorizes donors as either first-time tested (FTD) or repeat tested (RTD) and defines positivity rates for each based on the number of donors. RTDs are classified as persons, whose plasma or blood has been previously tested for infectious disease markers in a given collection system. This definition difference has resulted in two different systems for quality assessment and data reporting. The definitions of the measures are shown below.

		IQPP	EMA
Donor definitions	A1	Applicant donors	FTD
	A2		RTD
	Ar		
	Q	Qualified donors	
Rate calculation	Numerator	Positives	Positives
	Denominator	# donations	# donors

- A1:** 1st Applicant donation
- A2:** 2nd applicant donation
- Ar:** Qualified donor returning after more than 6 months
- Q:** Donor who has successfully completed two health screenings and is negative on the two qualifying donations for all infectious diseases


The consequence of the different approaches for calculating the positivity rates is an increased data collection burden for collectors and fractionators. However, it helps ensure the end goal of product safety. The need for EMA to include the two different plasma types that contribute to the quality and safety of the final plasma-derived medicinal product they regulate is obvious. To help member fractionators identify outlier donor centers with higher than expected viral marker rates so that corrective action steps can be taken, PPTA, through its Epidemiology Data Task

Force, has developed a metric for assessing center donor quality that can be applied to all donor centers. This has been presented and discussed with the EMA on several occasions, the most recently in June, 2011 and can be used by member companies for their 2011 PMF assessments.

However, donor selection is only one of the multiple safety measures in place. Measures like inventory hold, NAT testing of donations as well as manufacturing pools, and the virus inactivation/and removal during the manufacturing process, provide the most important contribution to the overall safety of the

plasma-derived products. But these safety measures, mostly part of PPTA's voluntary industry initiatives are not taken into account in the guideline. The current revised guideline appears strongly linked to the supervision and the practices in blood collection centers, transfusion needs and more broadly to public health surveillance. It seems to neglect the efforts the

plasma collection industry has made to provide patients with plasma-derived medicinal products with high margins of safety.

The source plasma industry is committed to providing an adequate supply of safe products to those who depend on them for their health. Working with regulatory agencies to have meaningful steps to help maintain product safety is crucial and a process to which industry is committed. 

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