# WORKSHOP
# QUALIFICATION OF NEW BLOOD DONORS BEFORE DONATION

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# Blood donor selection and testing for plasma-derived medicinal products



Karen Cristiano

# PLASMA POOLS FOR FRACTIONATION

- Ever since 1 July 1999, the Ph. Eur. monograph for "Human Plasma for Fractionation" has required plasma pools to be tested for HBsAg, HIV antibodies and HCV RNA by NAT
- Additional testing for other viral markers (i.e. HCV antibodies, HIV RNA, HBV DNA, HAV RNA or Parvovirus B19 DNA) is carried out by blood products manufacturers on a voluntary basis

# PLASMA POOLS FOR FRACTIONATION (cont.)

- Testing for HAV RNA is required by the Ph. Eur. monograph for "Human Plasma (Pooled and Treated for Virus Inactivation)" in addition to testing for B19V DNA that is also a requirement for "Human anti-D immunoglobulin"
- If normal immunoglobulin for intramuscular/intravenous administration and/or albumin are used in the manufacture of anti-D immunoglobulin, the plasma pools from which they are derived should comply with the requirement of the respective Ph. Eur. monograph on anti-D immunoglobulin
- Testing for HEV introduced in the Ph. Eur. monograph for "Human Plasma (Pooled and Treated for Virus Inactivation)"

# PLASMA POOLS FOR FRACTIONATION (cont.)

For validation of all testing methods, the “Guideline on plasma-derived medicinal products” (EMA/CHMP/BWP/706271/2010) - replacing “Note for Guidance on plasma-derived medicinal products” (CPMP/BWP/269/95) - makes reference to the “Guideline on scientific data requirements for a Plasma Master File” (EMEA/CHMP/BWP/3794/03)

# What is the Plasma Master File (PMF)?

- The PMF is a collection of the relevant information covering collection, testing, storage and processing of human plasma up to and including its pooling for the manufacture of blood products
- The PMF relates to products derived from plasma used as excipients (e.g. albumin), in manufacturing processes (e.g. component of cell culture) or in devices
- The PMF does not include information on intermediates after the plasma pool (e.g. cryprecipitate, intermediate fractions)

# PMF historical background

- ✓ December 1994: the concept of PMF is born to provide an additional measure to improve quality and safety of blood products
- ✓ Introduced in the quality part of the MA dossier
- ✓ June 2003: a legal basis is established for the PMF (Directive 2003/63/EC amending Directive 2001/83/EC)
- ✓ Stand-alone document, separate from the MA dossier, to achieve a harmonised control of the relevant information regarding starting material used for the manufacture of blood products
- ✓ Subject to certification and annual update for re-certification

# PMF Certification *via* the Centralized Procedure (EMA)

- The use of this procedure is optional
- Not to be used if the PMF corresponds only to blood/plasma-derived medicinal products the MA of which is restricted to a single MS
- Administrative guidance provided in *Guideline on requirements for Plasma Master File (PMF) certification (EMEA/CPMP/BWP/4663/03)*
- Scientific guidance provided in *Guideline on the scientific requirements for a Plasma Master File (PMF) (EMEA/CHMP/BWP/3794/03 Rev.1)*

# 2.2.2 Testing of blood/plasma donations and pools for infectious agents… (EMEA/CPMP/BWP/3794/03)

Information should be provided:

- on any screening tests for markers of infection required according to Directive 2001/83/EC as amended and the Ph. Eur. Monographs
- on any other screening tests carried out.

A list of kits used for each test, including NAT testing, should be provided.

# 2.2.2 Testing of blood/plasma donations and pools for infectious agents… (EMEA/CPMP/BWP/3794/03) (Cont.)

**Validation of testing methods**

- b. Viral marker testing of the plasma pool(s)

For every laboratory that carries out plasma pool testing for viral markers, provide a description of each test method and the respective validation report according to the following guidelines:

- Guideline on Validation of Immunoassay for the Detection of Antibody to human Immunodeficiency Virus (Anti-HIV) in Plasma Pools, (EMEA/CHMP/BWP/298388/2005)
- Guideline on Validation of Immunoassay for the Detection of Hepatitis B Virus Surface Antigen (HBsAg) in Plasma Pools, (EMEA/CHMP/BWP/298390/2005).

Information on the sensitivity of the test for each marker as a function of the pool size should also be included.

# 2.2.2 Testing of blood/plasma donations and pools for infectious agents… (EMEA/CPMP/BWP/3794/03) (Cont.)

**Validation of testing methods**

c. NAT testing of the plasma pool(s)

For every testing laboratory, provide a report on the validation of the NAT tests performed. Validation of NAT for HCV is carried out according to the Ph. Eur. "Guidelines for validation of NAT for the detection of HCV RNA in plasma pools" (PA/PH/OMCL (98) 22, DEF).* Validation of NAT for B19V is performed according to the "Guideline for validation of NAT for quantitation of B19 virus DNA in plasma pools" (PA/PH/OMCL (03) 38, DEF).

*Published in Ph. Eur. General method 2.6.21 "Nucleic acid amplification techniques"

# 2.2.2 Testing of blood/plasma donations and pools for infectious agents… (EMEA/CPMP/BWP/3794/03) (Cont.)

**Validation of testing methods**

c. NAT testing of the plasma pool(s) (cont.)

In case that the applicant performs NAT testing for viruses other than HCV and B19, the validation studies are carried out according to the following guidelines:

- ICH Topic Q2A Note for guidance on validation of analytical methods: definitions and terminology (CPMP/ICH/381/95)20
- Ph. Eur. General method 2.6.21 "Nucleic acid amplification techniques".

# 2.2.2 Testing of blood/plasma donations and pools for infectious agents… (EMEA/CPMP/BWP/3794/03) (Cont.)

**Validation of testing methods**

c. NAT testing of the plasma pool(s) (cont.)

For practical purposes, in the case of NAT qualitative methods, validation is carried out taking into consideration the above mentioned "Guidelines for validation of NAT for the detection of HCV RNA in plasma pools".

Provide information on specificity, including the ability of the assays to detect different genotypes, on sensitivity and robustness.

Results arising from participation in proficiency studies should be reported. (See also Section 7.4 External quality assessment of Ph. Eur. General method 2.6.21 "Nucleic acid amplification techniques")

# Ph. Eur. requirements for NAT for HCV RNA

- ✓ Validated nucleic acid amplification technique
- ✓ Include in the test: a positive control with 100 IU/ml (HCV RNA for NAT testing BRP is suitable for this use) and an internal control to test for inhibitors
- ✓ The test is invalid if the positive control is non-reactive or if there are inhibitors
- ✓ The plasma pool complies with the test if non-reactive for HCV RNA

# Ph. Eur. requirements for NAT FOR B19V DNA

- ✓ Validated nucleic acid amplification technique
- ✓ Include in the test: a positive control with 10,0 IU/µl (B19 DNA for NAT testing BRP is suitable for this use) and an internal control to test for inhibitors
- ✓ The test is invalid if the positive control is non-reactive or if there are inhibitors
- ✓ The maximum B19 virus burden is 10,0 IU/µl

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008*

- Formerly EMEA/CPMP/BWP/125/04
- Into effect since 1 March 2011
- The scope of the revision was to provide additional guidance to PMF holders on:
  - Submission of epidemiological data
  - Reporting critical analysis of epidemiological data (e.g. identification and reporting of trends)
  - Residual risk estimations and elements to be considered for the calculations.

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

For the purpose of the assessment of epidemiological data of donor populations, the following definitions are used in this document:

- First time tested donor - Person whose blood/plasma is tested for the first time for infectious disease markers (with or without donation) without evidence of prior testing in a given blood system.
- Repeat tested donor - Person whose blood/plasma has been tested previously for infectious disease markers in a given blood system.

A given blood system means a system that has records of whether a donor has donated before and the results of previous testing.

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

**Prevalence can be defined as :**

$$\frac{\text{No. of positive “first time tested donors” in a calendar year}}{\text{Total No. “first time tested donors” in the same calendar year}}$$

**Incidence can be defined as:**

$$\frac{\text{No. of positive “repeat tested donors” in a calendar year}}{\text{Total No. of “repeat tested donors” in the same calendar year}}$$

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

**Submission of epidemiological data**

Epidemiological data should be collected on those blood-borne infectious agents for which a potential transmission by blood products is well recognised and routine testing of blood and plasma donations is mandatory. These infectious agents currently include HIV, HBV and HCV.

Only confirmed infections should be reported using the following definitions:

- Confirmed seropositive - Repeatedly reactive (= 2 times reactive) in a screening test and positive in at least one supplementary test based on a different principle.
- NAT only positive - Positive in a NAT assay for a specific virus (HIV, HCV or HBV), not found seropositive for that virus in serological screening, and shown to be true positive by second NAT test or later serology.

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

Data should be reported per country, per organisation and per centre, using the tabular formats given in Tables 1* and 2# in the Appendix. If within a country both blood banks and plasma source centres (collecting whole blood recovered plasma and plasmapheresis plasma respectively) are used for the collection of blood/plasma, data should also be summarised separately for each of these two categories. The data should be reported for the calendar year (January-December). In order to facilitate a relative assessment of these data, the data should be presented in absolute numbers and calculated per 100,000 donors.

* "First time tested donor" population
# "Repeat tested donor" population

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

**Epidemiological assessment of donor populations, and trends over time**

A comparison should be made with the data provided over the three previous years of reporting for the individual collection centres, organisations and countries. Significant trends in individual collection centres should be discussed as well, highlighting centres exceeding the acceptable range. The purpose is to identify any overall trends in the rates of infectious markers in the donor population. In addition, the effectiveness of remedial actions for collection centres, which have previously been identified as above the acceptable range, should be discussed.

For a particular organisation/country demonstrating a significant higher prevalence/incidence than other organisations/countries in the PMF, a comparison with the general population might be valuable for the evaluation of the data.

# *Guideline on epidemiological data on blood transmissible infections EMA/CHMP/BWP/548524/2008* (cont.)

**Risk estimation of undetected infectious donations in routine testing**

The method used by the PMF Holder to estimate the risk of infectious donations passing undetected through routine testing at the time of donation collection should be fully described. Citing a reference describing the method used is not sufficient. Details should be described to enable the calculations to be reproduced by a reader of the PMF.

The reporting details in Table 3 in the Appendix should suffice to describe the PMF holders calculations when using the method recommended in this guideline. If PMF holders use an altered version of the standard recommended method, or a different method, this should be fully described and justified. The results of risk estimate(s) should be reported using the tabular format in Table 4 in the Appendix.

# Thank you for your attention!