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GUIDELINE ON THE SCIENTIFIC DATA REQUIREMENTS FOR A PLASMA MASTER FILE (PMF) Revision 1

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- *This document provides guidance on the structure and requirements for presentation of data on starting material in a Plasma Master File (PMF). This guidance shall also apply when the PMF certification scheme is not followed.*
- *The PMF structure follows Part III of Annex I of Commission Directive 2001/83/EC[1] as amended. This Guideline supersedes EC III/5272/94 "Contribution to Part II of the Structure of the Dossier for Applications for Marketing Authorisation - Control of Starting Materials for the Production of Blood Derivatives" and takes into account the consultation on the draft document released for consultation in July*

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2001 Ref. CPMP/BWP/2053/01 draft (III/5272/94 rev 1)[2]."

- *Directive 2002/98/EC[3] amending Directive 2001/83/EC, entered into force on 8 February 2003. From 8 February 2005, Directive 2002/98/EC applies for the collection and testing of human blood and blood components used in the manufacture of medicinal products and these scientific data requirements have been updated accordingly. Furthermore, for the implementation of this directive, the following Commission directives have been issued:*
  a. *Commission Directive 2004/33/EC[4]*
  b. *Commission Directive 2005/61/EC[5]*
  c. *Commission Directive 2005/62/EC[6]*

GUIDELINE ON THE SCIENTIFIC DATA REQUIREMENTS FOR A PLASMA MASTER FILE (PMF)

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INTRODUCTION AND PRINCIPLE OF A PMF

All starting materials for medicinal products should comply with the requirements as laid down in Directive 2001/83/EC. This includes compliance with Ph. Eur. and GMP.
Annex I of Directive 2001/83/EC, amended by Directive 2003/63/EC[7], lays down specific requirements for the starting material of plasma-derived medicinal products. The concept of Plasma Master File has been introduced and the principles, content, evaluation and certification are described.

In Directive 2003/63/EC reference is made to Article 109 of Directive 2001/83/EC, as amended by Directive 2002/98/EC ("Blood directive"), concerning the requirements for donors and the testing of donations. Directive 2002/98/EC shall apply to the collection and testing of human blood and blood components whatever their intended purpose.

Every blood establishment has to be approved by a Competent authority according to the Directive 2002/98/EC. Inspection and approval according to GMP is, in addition, required for processing, storage and transport of blood and blood components, including plasma, to be used for manufacture of medicinal products.

The PMF contains common information on plasma, from collection to plasma pool, relevant to the manufacture of all intermediate fractions including cryoprecipitate, all constituents of the excipient and all active substance(s), which are part of medicinal products or medical devices, for which this PMF is applicable.

Cryoprecipitate or any other intermediates are not covered by the PMF certification procedure. The manufacturing process starting from the pooled plasma is not part of the PMF dossier, this should be described in the relevant sections of the dossier for each individual medicinal product, medical device or investigational medicinal product.

The PMF should contain complete information in accordance with this guideline. There should be no cross-reference to data held in other PMFs.

This Guideline describes the structure and scientific data required on plasma, from collection to plasma pool, to be submitted in a PMF or included in the marketing authorisation dossier whenever the PMF certification scheme is not followed[a].

Applicants or MAHs using the PMF certification system need to clearly identify and make reference to the PMF(s) in the dossier of each medicinal product. Reference to more than one PMF is possible but this must be clearly indicated. Where information is specific to a particular product (e.g. immunisation scheme used for specific immunoglobulins) this should be included in section 2. 3 S of the dossier for the relevant product and not in the PMF, unless otherwise stated in this guideline.

The procedure for the submission, evaluation and certification is described in the Guideline on Requirements for Plasma Master File (PMF) certification, EMEA/CPMP/BWP/4663/03[8].

Annual update

The PMF information shall be updated and re-submitted for approval on an annual basis. The scientific documentation for the annual update should include the following:

- Summary of all changes and updates applied for with the annual update
- Annex I “check list on annual update”, including all the changes already approved during the year, on-going variations and changes applied for with the annual update. Precise cross reference (i.e. page/vol.) to the actual updated PMF dossier should be made.
- All outstanding commitments (follow up measures) and related data concerning previous evaluations.

[a] The term ‘PMF’ is now defined in legislation as stand alone documentation. Therefore, this term should no longer be used when documentation is provided within a product dossier.

- An integrated PMF dossier. This annual update should include all changes and updated information since the last certification (initial or annual). (Note: changes to all lists and annexes should be submitted with track changes.)
  - Updated epidemiological data i.e. newly available data together with its scientific evaluation.
  - Updated sections 1.1[b], 2.1.3 and 2.3[c]. In section 1.3, updated flow chart when applicable. In addition, when relevant, update on deletions of country(ies) and/or centres(s)/establishment(s) used for blood/plasma collection, or in which testing of donation and plasma pools is carried out, and deletion of blood bag(s) may be submitted at the annual update. The reason for the deletion should be specified.
  - Update of inspection/audit status of blood establishments (see Annexes II, III, IV and V).
  - Update on the participation in proficiency studies for plasma pool testing (viral marker and NAT testing, see section 2.2.2).
- List including:
  - Cases, over the previous year, for which it was retrospectively found there were indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A, B or C[d].
  - The number of positive donations that have been identified per viral marker by NAT (Nucleic Acid Amplification Technique) testing at the fractionator level including minipool testing. If NAT testing of minipools is performed by the PMF holder, results of the NAT testing should be provided, including the number of minipools tested and positive donations identified.

Specify historic information where this is still relevant for batches that may be on the market e.g. information on the period when an establishment or centre was actively supplying plasma.

1. GENERAL INFORMATION (SUMMARY)

1.1 Plasma-derived products' list (see annex A)

The Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, with the relevant Competent Authority(ies) for each plasma-derived product. This list should also include medical devices incorporating stable derivatives of human blood or human plasma (Council Directive 93/42/EEC[9] as amended) and investigational medicinal products referred to in Article 2 of Directive 2001/20/EC[10].
Separate listings for these different categories of products should be submitted.
A list of cryoprecipitates and intermediates in relation to this PMF should also be available stating their destination.
In addition, a list of medicinal products incorporating stable derivatives of human blood or human plasma (e.g. active substances, excipients, stabilisers) should be also submitted whenever contracts and/or agreements exist between the PMF holder and third companies. When the final product is not known to the PMF holder, because intermediates are sold to other companies, a list of these cryoprecipitates and intermediates should be submitted.

[b] This product-list is also part of the PMF application form and valid PMF certificate. This list should be kept up-to-date to allow a link between finished products and the plasma source. The updates to this list are not considered variations. Independently, all MAHs incorporating a new plasma source, with consequent changes to the manufacturing process starting from the pooled plasma, will need to apply for a variation to the Marketing Authorisation in accordance with the Commission Regulation (EC) No 1085/2003.[20] In other cases where a new plasma source is incorporated, the need for a variation to the MA will depend on the impact on the finished product.
[c] Changes to these sections are not considered variations but updated information to the previous PMF (initial/annual update).
[d] This is in addition to the requirement that Marketing Authorisation Holders inform relevant Medicines Competent Authority(ies) without delay of any cases where there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis in accordance with the Note for Guidance on Plasma-derived medicinal products, EMEA/CPMP/BWP/269/95 (current version, section 2.3).

1.2 Overall safety strategy

A critical evaluation of the contribution of each of the significant steps, from collection of blood/plasma to preparation of the plasma pool, to the overall safety of the plasma pool should be provided. It should demonstrate how different aspects of the PMF interrelate and contribute to the overall safety of the plasma. This critical evaluation should incorporate all aspects of the PMF and draw together the following information: the epidemiological data on blood transmissible infections known for the donor population, criteria for the use of donations from first time donors (when applicable), the system of donor selection criteria including measures that reduce the risk of (v)CJD, screening of donations, minipool strategy if relevant, the testing of the plasma pools, viral load limits for plasma pools and normal size of plasma pool, inventory hold and "look-back" procedures. The critical evaluation should be supported by diagrams, e.g. to describe the plasma donation test system and strategy of (mini/plasma) pool testing. The aim should be to demonstrate how the company's strategy integrates to robustly ensure that all measures taken throughout the collection, processing, testing, storage and transport of the plasma work together to provide a safe plasma pool.
The estimated residual risk of missing viraemic donations that may enter the production pool should be described[11].

1.3. General logistics

A flow-chart, describing the complete supply-chain for plasma from collection to the manufacture of the plasma pool, should be provided. This should include all relevant establishments involved in the collection, testing, processing, storage and transport of blood or plasma and the relation between them. The flow chart should describe the complete transport chain including details of international transport and customs. If applicable indicate the country of import into the EU.

2. TECHNICAL INFORMATION ON STARTING MATERIALS

The quality and safety of products derived from human plasma rely both on the source plasma material and the further manufacturing processes. Therefore, the collection, testing, processing, storage and transport of human plasma are major factors in the quality assurance of the manufacture of plasma-derived products. Blood establishments and centres should fulfil the requirements and be inspected and approved in accordance with the Blood Directive (2002/98/EC) and corresponding Commission directives (2004/33/EC, 2005/61/EC and 2005/62/EC) for collection and testing and in accordance with GMP Directive 2003/94/EC[12], Annex 14 of the EU Guide to GMP, and Ph. Eur. for all other activities.

If a blood establishment uses mobile or temporary equipped centres to collect blood or plasma, these centres should operate under the same quality system as the establishment they are connected to.

An exhaustive list of names and addresses of blood establishments and centres[e] in which collection and/or testing, storage and transport of donations and testing of plasma pools is carried out, including any sub contractors should be provided using the tabular format given in the annexes II, III, IV and V.

2.1 Plasma origin

2.1.1 Information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

a. Information on blood establishments and centres in which blood/plasma collection and/or processing is carried out

See Annex II.

[e] Centres which include permanent and full equipment.

An exhaustive list of names and addresses of blood establishments and centres, from which plasma is still available, should be provided using the tabular format given in annex II.
If mobile or temporary equipped centres are used, the relationship with their respective blood establishments should be briefly described in the PMF. A statement should be provided that these mobile and temporary centres operate under the same quality system as the blood establishment they are related to.

The suppliers of plasma, for which special criteria[f] are applicable (such as anti-D), should also be identified.
The collection and processing operations of the blood establishments and centres should be described and summarised in this section.
To show that plasma is sourced from establishments approved in accordance with the previously mentioned legislation, indicate date and final outcome of last inspection.
If establishments or centres are no longer used, or are temporarily not used, they should be listed in a stand-alone table indicating the date when use of the centre or establishment has ceased and the reason[g]. The information should be kept in the list as long as the plasma is in stock.
If there is a separate look back department, the address, duties, and approval status by EU competent authorities should be mentioned.

b. Characteristics of donations

For any establishment responsible for collection it should be specified whether the donors are non-remunerated or remunerated. The nature of any compensation for donation should be described if applicable. "A donation is considered voluntary and non-remunerated if the person gives blood, plasma or cellular components of his/her own free will and receives no payment of it, either in the form of cash or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donations."

c. Epidemiological data on blood transmissible infections should be submitted in accordance with

Guideline on Epidemiological Data on Blood Transmissible Infections, EMEA/CPMP/BWP/125/04.

2.1.2 Information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.

See Annex III.
The test laboratory used for each establishment or centre should be specified.
If certain tests, such as confirmatory tests are performed at separate laboratories these should be included in Annex III.
If test laboratories are no longer used, or are temporarily not used, they should be listed in a stand-alone table indicating the date when use of the laboratory ceased and the reason[h]. This information should be kept in the list as long as the tested plasma is in stock.

2.1.3 Selection/exclusion criteria for blood/plasma donors.

Confirm for each establishment or centre the compliance with the selection/exclusion criteria for blood/plasma donors in Directive 2001/83/EC, Directive 2002/98/EC, Directive 2004/33/EC and the requirements of the European Pharmacopoeia Monographs. Where appropriate, indicate compliance with CHMP guidance documents, WHO and Council of Europe recommendations. With regard to Creutzfeldt-Jakob disease, the exclusion criteria should be stated explicitly in compliance with CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal

[f] The immunisation of donors should be described in the specific dossier of the product.
[g] It is sufficient to indicate that the closure was for commercial reasons. However, if the closure was for safety reasons, then details are required.
[h] It is sufficient to indicate that the closure was for commercial reasons. However, if the closure was for safety reasons, then details are required.

product (EMEA/CPMP/BWP/2879/02)[13]. In addition, specify any requirements versus emerging infectious agents in a specific country of collection and confirm that selection/exclusion criteria for blood/plasma donors are in compliance with such requirements.

2.1.4 System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.

Summarize the system in place, which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products, including testing facility and vice versa. Confirm compliance with Directives 2002/98/EC, 2005/61/EC, 2005/62/EC and GMP Directive 2003/94/EC and Annex 14 of the EU Guide to Good Manufacturing Practice[14] especially concerning traceability including the identification procedures, labelling and record keeping. If several establishments/countries are involved, the information is given for each system. Include information on how traceability is maintained for closed collection establishments or centres, and/or establishments or centres that are temporarily closed and/or have stopped delivering plasma. Traceability, in accordance with the Blood Directive and corresponding Commission Directives, should be guaranteed in all cases. Indicate, for closed blood establishments, who is the holder of records.
Give information on steps that would be taken if it was found retrospectively that donation(s) should have been excluded from processing ("look-back procedure", any system in place to retain samples) and justify the system in accordance with section 2.3.6 of the Guideline on Plasma-derived medicinal products, EMEA/CPMP/BWP/269/95[15] (current version).

2.2 Plasma quality and safety

2.2.1 Compliance with European Pharmacopoeia Monographs.

Confirm compliance with the Ph. Eur. Monograph for Human Plasma for Fractionation and with any requirements for particular products for which Ph. Eur. Monographs exist.
Describe the conditions for processing including freezing, and for storage of plasma for every establishment or centre responsible for collecting blood/plasma. Compliance with the Ph. Eur. requirements for freezing and storage should be included in Annex II, with an indication of whether requirements for recovery of proteins that are labile or not labile in plasma are met.
Confirm validation of the freezing conditions.

2.2.2 Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

Information should be provided:

- on screening tests for markers of infection required according to Directive 2001/83/EC, as amended, Directive 2002/98/EC and the European Pharmacopoeia Monographs,
- on any other screening tests carried out.

Test	**Test Performed on:**		
	Individual Donation	**Minipool (size)** ***(if relevant)***	**Plasma Pool**
HBsAg			
HIV 1 and 2 Antibody			
HCV Antibody			
HCV RNA			
B19 DNA			
Other tests			

When minipools of donations are tested, the rationale and full details of this testing should be provided, including the size of the minipools.

It should be clarified whether all minipools/pools are tested in the same way (e.g. size of minipool, types of viruses). If this is not the case, the different strategies should be described.

Criteria for acceptance or rejection of donation/pool and re-testing policy should be described (see also Council Recommendation 98/463/EC[16] annex V).

List of kits used for each test, including NAT testing.

Parameter	**Test method**	**Brand name of the kit**	**Manufacturer**	**CE mark (yes/no)**	**Used for**		**Testing site**
					Individual donations	**Minipool /Plasma pool**	
HBsAg							
HIV 1 and 2 Antibody							
HCV Antibody							
NAT for HCV RNA							
B19 DNA							
Other tests							

Validation of testing methods

a. Testing of donations

a.1 Serology markers

Confirm that tests on single donations are carried out in accordance with the manufacturers' directions for use. Copies of the instructions for use of commercial kits are not needed.
For CE-marked test kits submission of validation data is not required.
For non-CE-marked test kits, the applicant should demonstrate that they comply with equivalent standards and can be considered "state of the art" according to the Common Technical Specifications for *in vitro*-diagnostic medical devices, 2002/364/EC[17], with particular attention to evidence for seroconversion sensitivity and sub-type sensitivity in comparison with a CE-marked test kit.

a.2 NAT

In case of mini pool testing by NAT as part of the screening of individual donations, a brief description of the analytical procedures for NAT methods should be provided if non-CE-marked tests are used (in-house methods or commercial kits). A summary of the validation reports should also be provided and should include specificity, detection limit and robustness. The description of the analytical procedures and the summary of the validation are not required for mini pools testing by NAT if the test is CE marked for this purpose. However, information on the detection limit, as related to the single donation, should be provided.

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)[18]
- Guideline on Validation of Immunoassay for the Detection of Hepatitis B Virus Surface Antigen (HBsAg) in Plasma Pools, (EMEA/CHMP/BWP/298390/2005)[19].

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

c. NAT testing of the plasma pool(s)

All NAT methods used for plasma pool testing should comply with the requirements in Ph Eur General Methods 2.6.21 Nucleic acid amplification techniques. For every laboratory that carries out plasma pool testing by NAT, provide a description of each NAT test method and the respective validation report.
NAT for HCV RNA is required by the Ph. Eur. Monograph "Human Plasma for Fractionation". Validation 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). As recommended in this guideline, the ability of the analytical procedure to detect all HCV genotypes is demonstrated.

If the list of plasma-derived products for which the PMF is valid includes anti-D immunoglobulin for intravenous and/or intramuscular administration and/or human plasma (pooled and treated for virus inactivation), NAT for B19 DNA is also carried out as required by the respective Ph. Eur. Monographs. The maximum B19 virus burden should be in accordance with the current version of the Ph. Eur. monograph. Validation 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). Included in this guideline is the recommendation that for the design of primers and probes the existence of the B19 variants A6 and V9 is taken into account. The International Committee on the Taxonomy of Viruses (ICTV) classifies these variants under B19 virus (Eighth report of the ICTV, Eds.: C.M. Fauquet, M.A. Mayo et al., Elsevier, page 361).

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".

For practical purposes, in the case of NAT qualitative methods, validation is carried out taking into consideration the above mentioned guideline Validation of NAT for the Detection of HCV RNA in Plasma Pools. (PA/PH/OMCL (98) 22, DEF).
Provide information on specificity, including the ability of the assays to detect different genotypes, on sensitivity and robustness.

Proficiency Studies

Participation in proficiency studies is strongly encouraged and should be reported (i.e. date, viral markers).

2.2.3 Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used.

Name of bag 1, 2, 3... etc	**Manufacturer**	**Anticoagulant Solution**[i]	**CE-Marked yes/no**

The sterile blood bag systems used for the collection of blood and blood components and their processing shall be CE-marked or be demonstrated to comply with equivalent standards.

Information about the non-CE marked bag system should include comprehensive data on the following:

- identity and quality of plastic material involved,
- any leachables like plasticisers and adhesives, demonstrating that they do not pose any undue risk,
- sterilization procedure and its validation. Proof of absence of residual toxic substances.
- composition, quality and Ph. Eur. compliance of the anticoagulant solution and
- results of a real time storage stability study of plasma in the container concerned.

2.2.4 Conditions of storage and transport of plasma[21].

See Annexes IV and V.

For establishments listed in Annex II, compliance with the Ph. Eur. requirements for freezing and storage should be included in Annex II, with an indication of whether requirements for recovery of proteins that are labile or not labile in plasma are met. See also Section 2.2.1.

Describe the conditions for storage of plasma for every establishment responsible for storage of plasma that is not listed in annex II, including the following:

- Confirm compliance with Ph. Eur. with respect to storage.
- Give a list of establishments/centres which are involved in this storage and indicate the date of last inspection by a Competent Authority (annex IV)
- Describe conditions of storage (temperature and maximum time)

Describe the conditions of transport of plasma including the following:

- Confirm compliance with requirements in the Ph. Eur. Monograph for Human Plasma for Fractionation.
- Describe transport flows from collection establishments/centres to interim storage sites including customs, if relevant, and further to fractionation sites (see also 1.3 General logistics).
- List organisations which are involved in the transport (own and contractors) and indicate the date of last inspection by a Competent Authority (annex V).
- Provide a summary of the system in place to ensure the transport is performed under appropriate conditions (time, temperature and GMP compliance). Confirm that transport conditions are validated.

2.2.5 Procedures for any inventory hold period.

Provide details of any inventory hold and quarantine procedure for plasma and provide the justification for the chosen period. Specify whether the procedure applies to all plasma or specify for which plasma it is applicable.

[i] Indicate nature and composition

2.2.6 Characterisation of the plasma pool.

Provide addresses of all sites at which the pooling of plasma is performed.
For each site provide the following information:

Plasma pool preparation.

Give a short description of all the relevant procedures in preparation of the plasma pool: thawing process, visual inspection of individual bags or bottles before pooling, opening and pooling.
Indicate the size of the plasma pool, in number of donations and in litres.
Clarify whether or not the plasma pool is the same for all products (e.g. anti-D Ig).

Sampling of plasma pool

Define the plasma pool (e.g. cryosupernatant or complete plasma pool) from which the samples for the viral marker testing are obtained.
Describe the sampling procedure, any manipulation (rapid freezing, special precautions, …) of samples and the storage conditions of the pool samples.
Testing of the plasma pools for all sites should be performed in accordance with the details provided in this plasma master file.

2.3 System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

Confirm that a contract exists between the blood establishments on one hand and the manufacturer and/or the PMF holder on the other hand to ensure the interaction between them and the fulfilment of the GMP/Good Practice requirements in accordance with GMP Directive 2003/94/EC (including Annex 14 of the EU Guide to GMP) and Commission Directive 2005/62/EC. Such a contract should also exist for intermediates and plasma-derived products supplied to third parties (e.g. albumin supplied for use as an excipient).

Concerning systems for notification, confirm compliance with Directive 2002/98/EC, amending Directive 2001/83/EC and Commission Directive 2005/61/EC.

In the event of a serious failure of a centre being discovered, the manufacturer will be immediately informed.

It should be declared that all blood establishments have signed the contracts mentioned above.

DEFINITIONS

Approved (Directive 2002/98/EC): designated, authorised, accredited or licensed by the competent authority.

Audit (Council of Europe Recommendation No R (95) 15): systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled (ISO). This is a tool for checking that work is actually carried out according to the policies, protocols and procedures required (GMP).

Audit programme (Council of Europe Recommendation No R (95) 15): a systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

Blood establishment (Directive 2002/98/EC): shall mean any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended

purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks.

Centre: collection site or premise where blood or plasma is collected (and may also be processed and stored). Centre is also applicable to testing site.

Inspection: (by EU/EEA competent authority) (Directive 2002/98/EC): shall mean formal and objective control according to adopted standards to assess compliance with this Directive and other relevant legislation and to identify problems. The interval between two inspections and control measures shall not exceed two years.

GMP Inspection: (EMEA/INS/GMP/313513/2006[22]) On-Site assessment of the compliance with the Community GMP principles performed by officials of Community Competent Authorities.

Inventory hold: specified period of time (to be justified by the applicant), during which plasma units are held in storage allowing for the retrieval of any suspect donations before they are considered for use in plasma pools.

Look back: (EMEA/CPMP/BWP/269/95 Section 2.3.6) In the event that a plasma unit fails release due to any of the reasons listed below, a look-back should consist of tracing back and further testing of previous donations for at least six months prior to the last negative donation. The procedures to be followed should be documented in a standard operating procedure.

- it is found that the donor did not meet the relevant donor health criteria;
- a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
- it is discovered that testing for viral markers has not been carried out according to agreed procedures;
- the donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV and other non-A, non-B, non-C hepatitis viruses, HIV 1 and 2 and other agents in the light of current knowledge);
- the donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
- the recipient of blood or a blood component develops post-transfusion/infusion infection which implicates or can be traced back to the donor.

Mini-pool (EMEA/CPMP/BWP/269/95): the CHMP recommends that a strategy of pre-testing by manufacturers of mini-pools (of donations or of samples representative of donations) is encouraged in order to avoid loss of a complete manufacturing pool and to facilitate tracing back to the donor in the event of a positive test result.

Mobile site (Directive 2005/62/EC): means a temporary or movable place used for the collection of blood and blood components which is in a location outside of but under control of the blood establishment.

Plasma (Directive 2004/33/EC): the liquid portion of the blood in which the cells are suspended.

Plasma for fractionation (Ph. Eur. 0853): human plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a receptacle containing anticoagulant, or separated by continuous filtration or centrifugation; it is intended for the manufacture of plasma-derived products.

Plasma pool (Ph. Eur. 0853): first homogeneous pool of plasma (for example after removal of cryoprecipitate) tested for viral markers.

Post collection measures (Council of Europe Recommendation No R (95) 15): systems must be in place which allow the blood/plasma collection establishment and the manufacturing/fractionating establishments to communicate relevant post donation information.

Premises (Directive 2005/62/EC): including mobile sites shall be adapted and maintained to suit the activities to be carried out. They shall enable the work to proceed in a logical sequence so as to minimize the risk of errors, and shall allow for effective cleaning and maintenance in order to minimize the risk of contamination.

Proficiency testing (Council of Europe Recommendation No R (95) 15): a specific tool for monitoring the competency (performance) of laboratory personnel in carrying out their allocated tasks. This generally takes the form of analysis of blinded samples distributed by external source.

Quarantine (Directive 2005/62/EC): means the physical isolation of blood components or incoming materials/reagents over a variable period of time while awaiting acceptance, issuance or rejection of the blood components or incoming material/reagents.

Retention of samples and disposal of rejected products (Council of Europe Recommendation No R (95) 15): where possible, samples of each individual donation should be stored for the length of time specified by national authorities to enable any necessary further retrospective testing. For disposal of rejected blood, plasma and intermediates, there should be SOPs for the safe and effective disposal of blood and plasma and intermediates, with complete traceability.

Traceability (Directive 2005/61/EC): means the ability to trace individual unit of blood or blood components derived thereof from the donor to its final destination, whether this is a recipients, a manufacturer of medicinal products or disposal, and vice versa.

Validation (directive 2004/33/EC and 2005/62/EC): means the establishment of documented and objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

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