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The Rules Governing Medicinal Products in the European Union

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EU Guidelines for

Good Manufacturing Practice for

Medicinal Products for Human and Veterinary Use

Annex 14

Manufacture of Medicinal Products Derived from Human Blood or Plasma

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision 1

Reasons for changes: the Annex has been revised in the light of Directive 2002/98/EC and relevant implementing directives setting standards of quality and safety for the collection and testing of human blood and blood components for all uses, including the manufacture of medicinal products.

Deadline for coming into operation: 30 November 2011

Manufacture of medicinal products derived from human blood or plasma

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Glossary

Blood

Blood, as referred to in Directive 2002/98/EC (Art. 3a), means whole blood collected from a donor and processed either for transfusion or for further manufacturing.

Blood component

A blood component, as referred to in Directive 2002/98/EC (Art. 3b), means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods.

Blood establishment

A blood establishment, as referred to in Directive 2002/98/EC (Art. 3e), is any structure or body that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. While this definition does not include hospital blood banks, it is understood to include centres where apheresis of plasma is performed.

Blood products

A blood product, as referred to in Directive 2002/98/EC (Art. 3c), means any therapeutic product derived from human blood or plasma.

Fractionation, fractionation plant

Fractionation is the manufacturing process in a plant (fractionation plant) during which plasma components are separated/purified by various physical and chemical methods such as e.g. precipitation, chromatography.

Good Practice guidelines

Good practice guidelines give interpretation on the Community standards and specifications defined for quality systems in blood establishments established in the Annex of Directive 2005/62/EC.¹

Medicinal products derived from human blood or human plasma

Medicinal products derived from human blood or human plasma, as referred to in Directive 2001/83/EC (Art. 1 No. 10), are medicinal products based on blood constituents which are prepared industrially by public or private establishments.

Plasma for fractionation

Plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration or centrifugation of anti-coagulated blood in an apheresis procedure; it is intended for the manufacture of plasma derived medicinal products, in particular albumin, coagulation factors and immunoglobulins of human origin and specified in the European Pharmacopoeia (Ph. Eur.) monograph “Human Plasma for fractionation” (0853).

Plasma Master File (PMF)

A Plasma Master File, as referred to in Directive 2001/83/EC (Annex I, Part III, No. 1.1.a), is a stand-alone document, which is separate from the dossier for marketing authorisation. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipients and active substances, which are part of plasma, derived medicinal products or medical devices.

Processing

According to the terminology of directive 2005/62/EC, “processing means any step in the preparation of blood component that is carried out between the collection of blood and the issuing of a blood component”, e.g. separation and freezing of blood components. In this Annex, processing in addition refers to those operations performed at the blood establishment that are specific to plasma to be used for fractionation.

Qualified Person (QP)

The qualified person is the person referred to in Directive 2001/83/EC (Art. 48).

Responsible Person (RP)

The responsible person is the person referred to in Directive 2002/98/EC (Art. 9).

Third countries contract fractionation program

This is a contract fractionation in a plant of a fractionator/manufacturer in the EU/EEA, using starting material from third countries and manufacturing products not intended for the EU/EEA market.

¹ At the time of publication of this Annex adoption of the Good Practice guidelines by the European Commission was still pending

1. Scope

1.1 The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the EU/EEA. The Annex applies also to the starting material (e.g. human plasma) for these products. In line with the conditions set out in Directive 2003/63/EC, the requirements apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.

1.2 This Annex defines specific Good Manufacturing Practices (GMP) requirements for processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.

1.3 The Annex addresses specific provisions for when starting material is imported from third countries and for contract fractionation programs for third countries.

1.4 The Annex does not apply to blood components intended for transfusion.

2. Principles

2.1 Medicinal products derived from human blood or plasma (and their active substances which are used as starting materials) must comply with the principles and guidelines of Good Manufacturing Practice (as laid down in Commission Directive 2003/94/EC and the EU Guidelines on GMP published by the European Commission) as well as the relevant marketing authorisation (Directive 2001/83/EC, Art. 46, 51). They are considered to be biological medicinal products and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin (Directive 2001/83/EC Annex I Part I, No.3.2.1.1.b). Certain special features arise from the biological nature of the source material. For example, disease-transmitting agents, especially viruses, may contaminate the source material. The quality and safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including infectious marker testing, virus removal and virus inactivation.

2.2 In principle active substances used as starting material for medicinal products must comply with the principles and guidelines of Good Manufacturing Practice (see 2.1). For starting materials derived from human blood and plasma the requirements for the collection and testing defined in Directive 2002/98/EC are to be followed. Collection and testing must be performed in accordance with an appropriate quality system for which standards and specifications are defined in the Annex of Directive 2005/62/EC and interpreted in the Good Practice guidelines referred to in Article 2 (2) of Directive 2005/62/EC. Furthermore, the requirements of Directive 2005/61/EC on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient apply. In addition the monographs of the European Pharmacopoeia are to be observed (Directive 2001/83/EC, Annex 1, Part III No. 1.1.b).

2.3 Starting material for the manufacture of medicinal products derived from human blood or plasma imported from third countries and intended for use or distribution in the EU/EEA must meet standards which are equivalent to Community Standards and specifications relating to a quality system for blood establishments as set out in Commission Directive 2005/62/EC (Recital 6; Article 2(3)), the traceability and serious adverse reaction and serious adverse event notification requirements as set out in Commission Directive 2005/61/EC (Recital 5; Article 7), and the technical requirements for blood and blood components as set out in Commission Directive 2004/33/EC (Recital 4; point 2.3 of Annex V)

2.4 In the case of third country contract fractionation programs the starting material imported from third countries must be in compliance with the quality and safety requirements as laid down in Directive 2002/98/EC and in Annex V of Directive 2004/33/EC. The activities conducted within the EU/EEA must fully comply with GMP. Consideration should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Commission Directive 2005/62/EC, the traceability requirements and notification of serious adverse reactions and events set out in Commission Directive 2005/61/EC and the relevant WHO guidelines and recommendations as listed in the addendum

2.5 For all subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) the requirements of Directive 2001/83/EC apply and must therefore be done in accordance with the principles and guidelines of Good Manufacturing Practice. Normally, these activities would be carried out under the responsibility of a Qualified Person in an establishment with a manufacturing authorisation. Where specific processing steps in relation to plasma for fractionation take place in a blood establishment, the specific appointment of a Qualified Person may, however, not be proportionate given the presence and responsibility of a Responsible Person. To address this particular situation and to ensure the legal responsibilities of the Qualified Person are properly addressed, the fractionation plant/manufacturer should establish a contract in accordance with Chapter 7 of the GMP Guide with the blood establishment that defines respective responsibilities and the detailed requirements in order to ensure compliance. The Responsible Person of the blood establishment and the Qualified Person of the fractionation/manufacturer plant (see 3.5) should be involved in drawing up this contract. The Qualified Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

2.6 Specific requirements for documentation and other arrangements relating to the starting material of plasma-derived medicinal products are defined in the Plasma Master File.

3. Quality Management

3.1 Quality management should govern all stages from donor selection to delivery of the finished product. Reference is made to Directive 2005/61/EC for traceability up to and including the delivery of plasma to the fractionation plant, and to Directive 2005/62/EC for all stages concerning collection and testing of human blood and human plasma to be used for the manufacture of medicinal products.

3.2 Blood or plasma used as source material for the manufacture of medicinal products must be collected by blood establishments and be tested in laboratories which apply quality systems in accordance with Directive 2005/62/EC, are authorised by a national competent authority and are subject to regular inspections as referred to in Directive 2002/98/EC. Third country contract fractionation programs have to be notified to the competent EU authority by the manufacturer as

referred to in Directive 2001/83/EC.

3.3 If plasma is imported from third countries it should only be purchased from approved suppliers (e.g. blood establishments, including external warehouses). They should be named in the specifications for starting materials as defined by the fractionation plant/manufacturer, and be accepted by an EU/EEA competent authority (e.g. following an inspection) and by the Qualified Person of the fractionation plant in the EU/EEA. Certification and release of plasma (plasma for fractionation) as starting material is mentioned in section 6.8.

3.4 Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.

3.5 The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments. As a minimum the following key aspects should be addressed:

- definition of duties and respective responsibilities
- quality system and documentation requirements
- donor selection criteria and testing
- requirements for the separation of blood into blood components/plasma
- freezing of plasma
- storage and transport of plasma
- traceability and post donation / collection information (including adverse events).

The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer of the medicinal product. In addition, any fractionation step subcontracted should be defined in a written contract.

3.6 A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality or safety of the products, or traceability. The potential impact of proposed changes should be evaluated. The need for additional testing and validation, especially viral inactivation and removal steps, should be determined.

3.7 An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:

- defines an inventory holding time (internal quarantine time) before processing the plasma i.e. to remove look back units²
- considers all aspects of virus reduction and/or testing for infectious agents or surrogates.
- considers the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.

4. Traceability and Post Collection Measures

4.1 There must be a system in place that enables each donation to be traced, from the donor and the donation via the blood establishment through to the batch of medicinal product and vice versa.

4.2 Responsibilities for traceability of the product should be defined (there should be no gaps):

² Plasma units donated by donors during a defined period (as defined on a national / EU basis) before it is found that a donation from a high-risk donor should have been excluded from processing, e.g. due to a positive test result.

- from the donor and the donation in the blood establishment to the fractionation plant (this is the responsibility of the RP at the blood establishment),
- from the fractionation plant to the manufacturer of the medicinal product and any secondary facility, whether a manufacturer of a medicinal product or of a medical device (this is the responsibility of the QP).

4.3 Data needed for full traceability must be stored for at least 30 years, according to Article 4 of Directive 2005/61/EC and Article 14 of Directive 2002/98/EC³.

4.4 The contracts (as mentioned in 3.5) between the blood establishments (including testing laboratories) and the fractionation plant/manufacturer should ensure that traceability and post collection measures cover the complete chain from the collection of the plasma to all manufacturers responsible for release of the final products.

4.5 The blood establishments should notify the fractionating plant/manufacturer of any event which may affect the quality or safety of the product including events listed in Annex II part A and Annex III part A of Directive 2005/61/EC, and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information⁴ (post-collection information). Where the fractionation plant/manufacturer is located in a third country, the information should be forwarded to the manufacturer responsible for release in the EU/EEA of any product manufactured from the plasma concerned. In both cases, if relevant for the quality or safety of the final product, this information should be forwarded to the competent authority⁵ responsible for the fractionation plant/manufacturer.

4.6 The notification procedure as described in 4.5 also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing licence/certificate/approval.

4.7 The management of post-collection information should be described in standard operating procedures and taking into account obligations and procedures for informing the competent authorities. Post-collection measures should be available as defined in the "Note for Guidance on Plasma Derived Medicinal Products" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency.⁶

5. Premises and Equipment

5.1 In order to minimise microbiological contamination or the introduction of foreign material into the plasma pool, thawing and pooling of plasma units should be performed in an area conforming at least to the Grade D requirements defined in Annex 1 of the EU-GMP Guide. Appropriate clothing should be worn including face masks and gloves. All other open manipulations during the manufacturing process should be done under conditions conforming to the appropriate requirements of Annex 1 of the EU-GMP Guide.

5.2 Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with

³ Both Directives are linked to Article 109 of Directive 2001/83/EC by defining specific rules for medicinal products derived from human blood or plasma

⁴ Information that appears if a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers or any other risk factors which may induce a viral infection

⁵ as referred to in Directive 2001/83/EC

⁶ Current version at date of publication: CPMP/BWP/269/95

Annex 1 of the EU-GMP Guide. Acceptance limits should be specified.

5.3 In the production of plasma-derived medicinal products, appropriate viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products. Dedicated and distinct premises and equipment should be used for manufacturing steps after viral inactivation treatment.

5.4 To avoid placing routine manufacture at risk of contamination from viruses used during validation studies, the validation of methods for virus reduction should not be conducted in production facilities. Validation should be performed according to the "Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency⁷.

6. Manufacturing

Starting material

6.1 The starting material should comply with the requirements of all relevant monographs of the European Pharmacopoeia and of the conditions laid down in the respective marketing authorisation dossier including the Plasma Master File. These requirements should be defined in the written contract (see 3.5) between the blood establishment and the fractionating plant/manufacturer and controlled through the quality system.

6.2. Starting material for third country contract fractionation programs should comply with the requirements as specified in 2.4.

6.3 Depending on the type of collection (i.e. either whole blood collection or automated apheresis) different processing steps may be required. All processing steps (e.g. centrifugation and/or separation, sampling, labelling, freezing) should be defined in written procedures.

6.4 Any mix-ups of units and of samples, especially during labelling, as well as any contamination, e.g. when cutting the tube segments/sealing the containers, must be avoided.

6.5 Freezing is a critical step for the recovery of proteins that are labile in plasma, e.g. clotting factors. Freezing should therefore be performed as soon as possible after collection (see the European Pharmacopoeia monograph No 0853 "*Human Plasma for Fractionation*" and where relevant, monograph No 1646 "*Human Plasma pooled and treated for virus inactivation*"), following a validated method.

6.6 The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded. Any deviation from the defined temperature should be notified to the fractionation plant. Qualified equipment and validated procedures should be used.

Certification/release of plasma for fractionation as starting material

6.7 Plasma for fractionation should only be released, i.e. from a quarantine status, through systems

⁷ Current version at date of publication: CHMP/BWP/268/95

and procedures that assure the quality needed for the manufacture of the finished product. It should only be distributed to the plasma fractionation plant/manufacturer after it has been documented by the Responsible Person (or in case of blood/plasma collection in third countries by a person with equivalent responsibilities and qualifications) that the plasma for fractionation does comply with the requirements and specifications defined in the respective written contracts and that all steps have been performed in accordance with Good Practice and GMP Guidelines, as appropriate.

6.8 On entering the fractionation plant, the plasma units should be released for fractionation under the responsibility of the Qualified Person. The Qualified Person should confirm that the plasma complies with the requirements of all relevant monographs and the conditions laid down in the respective marketing authorisation dossier including the Plasma Master File or, in case of plasma to be used for third country contract fractionation programs, with the requirements as specified in 2.4.

Processing of plasma for fractionation

6.9 The steps used in the fractionation process vary according to product and manufacturer and usually include several fractionation/purification procedures, some of which may contribute to the inactivation and/or removal of potential contamination.

6.10 Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.

6.11 The methods used in the viral inactivation process should be undertaken with strict adherence to validated procedures and in compliance with the methods used in the virus validation studies. Detailed investigation of failures in virus inactivation procedures should be performed. Adherence to the validated production process is especially important in the virus reduction procedures as any deviation could result in a safety risk for the final product. Procedures should be in place, that take this risk into consideration.

6.12 Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant marketing authorisation.

6.13 A system for clearly segregating/distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

6.14 Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on the recommendations of the Guideline on Epidemiological Data on Blood Transmissible Infections⁸. The risk management process should consider whether it is necessary to use dedicated equipment in the case of third country contract fractionation programs.

6.15 For intermediate products intended to be stored, a shelf-life should be defined based on stability data.

⁸ EMEA/CPMP/BWP/125/04

6.16 The storage and transport of intermediate and finished medicinal products at any stage of the transport chain should be specified and recorded. Qualified equipment and validated procedures should be used.

7. Quality Control

7.1 Testing requirements for viruses or other infectious agents should be considered in the light of knowledge emerging on infectious agents and on the availability of appropriate, validated test methods.

7.2 The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate from the plasma pool) should be tested using validated test methods of suitable sensitivity and specificity, according to the relevant European Pharmacopoeia monographs (e.g. No. 0853).

8. Release of intermediate and finished products

8.1 Only batches derived from plasma pools tested and found negative for virus markers/antibodies and found in compliance with the relevant European Pharmacopoeia monographs, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File), should be released.

8.2 The release of intermediates intended for further in-house processing or delivery to a different site, and, the release of finished products should be performed by the Qualified Person and in accordance with the approved marketing authorisation.

8.3. The release of intermediates and final products used in third country contract fractionation programs should be performed by the Qualified Person on the basis of standards agreed with the contract giver, and compliance with EU GMP standards. Compliance with relevant European Pharmacopoeia monographs may not be applicable, as these products are not intended for the use on the European market.

9. Retention of plasma pool samples

One plasma pool may be used to manufacture more than one batch and/or product. Retention samples and corresponding records from every pool should be kept for at least one year after the expiry date of the finished medicinal product with the longest shelf-life derived from the pool.

10. Disposal of waste

There should be written procedures for the safe and documented storage and disposal of waste, disposable and rejected items (e.g. contaminated units, units from infected donors, out of date blood, plasma, intermediate or finished products).

Addendum

A) Member States should implement the following Directives and guidelines:

1. for collection and testing of blood and blood components:

Directive/Guidelines	Title	Scope
Directive 2002/98/EC of the European Parliament and of the Council	Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, amending Directive 2001/83/EC.	Art.2 Defines standards of quality and safety for the collection and testing of human blood and blood components, whatever their intended purpose, and for their processing, storage and distribution when intended for transfusion.
Commission Directive 2004/33/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components	Defines the provision of information to prospective donors and information required from donors (Part A and B, Annex II), eligibility of donors (Annex III), storage, transport and distribution conditions for blood and blood components (Annex IV), as well as quality and safety requirements for blood and blood components (Annex V).
Commission Directive 2005/61/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.	Defines traceability requirements for blood establishments, donors, blood and blood components, and for the final destination of each unit, whatever the intended purpose. It further defines the reporting requirements in the event of serious adverse events and reactions.

Commission Directive 2005/62/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.	Defines the implementation of quality system standards and specifications as referred to in article 47 of Directive 2001/83/EC.
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2. for collection and regulatory submission of data/information for plasma for fractionation:

Directive/ Guidelines	Title	Scope
Directive 2001/83/EC of the European Parliament and the Council	On the Community Code relating to medicinal products for human use.	Art. 2 Medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, covering medicinal products derived from human blood or human plasma.
Commission Directive 2003/63/EC	Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Amending the Annex on documentation of medicinal products	
Commission Directive 2003/94/EC	Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	Art. 1 Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
EU Guidelines on Good Manufacturing Practice	Giving interpretation on the principles and guidelines on GMP	
EMA/CHMP/BWP /3794/03 Rev.1, 15. Nov. 2006	Guideline on the Scientific data requirements for a Plasma Master File (PMF) Revision 1	
EMA/CHMP/BWP /548524/2008 EMA Guideline	Guideline on Epidemiological Data on Blood Transmissible Infections	

B). Other relevant documents:

Document	Title	Scope
Recommendation No. R (95) 15 (Council of Europe)	Guide to the Preparation, use and quality assurance of blood components	
WHO Recommendations for the production, control and regulation of human plasma for fractionation. Annex 4 in: WHO Expert Committee on Biological Standardization. Fifty-sixth report. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 941)	WHO Recommendations for the production, control and regulation of human plasma for fractionation	Guidance on the production, control and regulation of human plasma for fractionation
WHO guidelines on Good Manufacturing Practices for blood establishments		

Reference should be made to the latest revisions of these documents for current guidance.