Benefits of Plasma Quality Programs in Blood Establishments

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Director of Scientific and Regulatory Affairs

International Plasma Fractionation Association

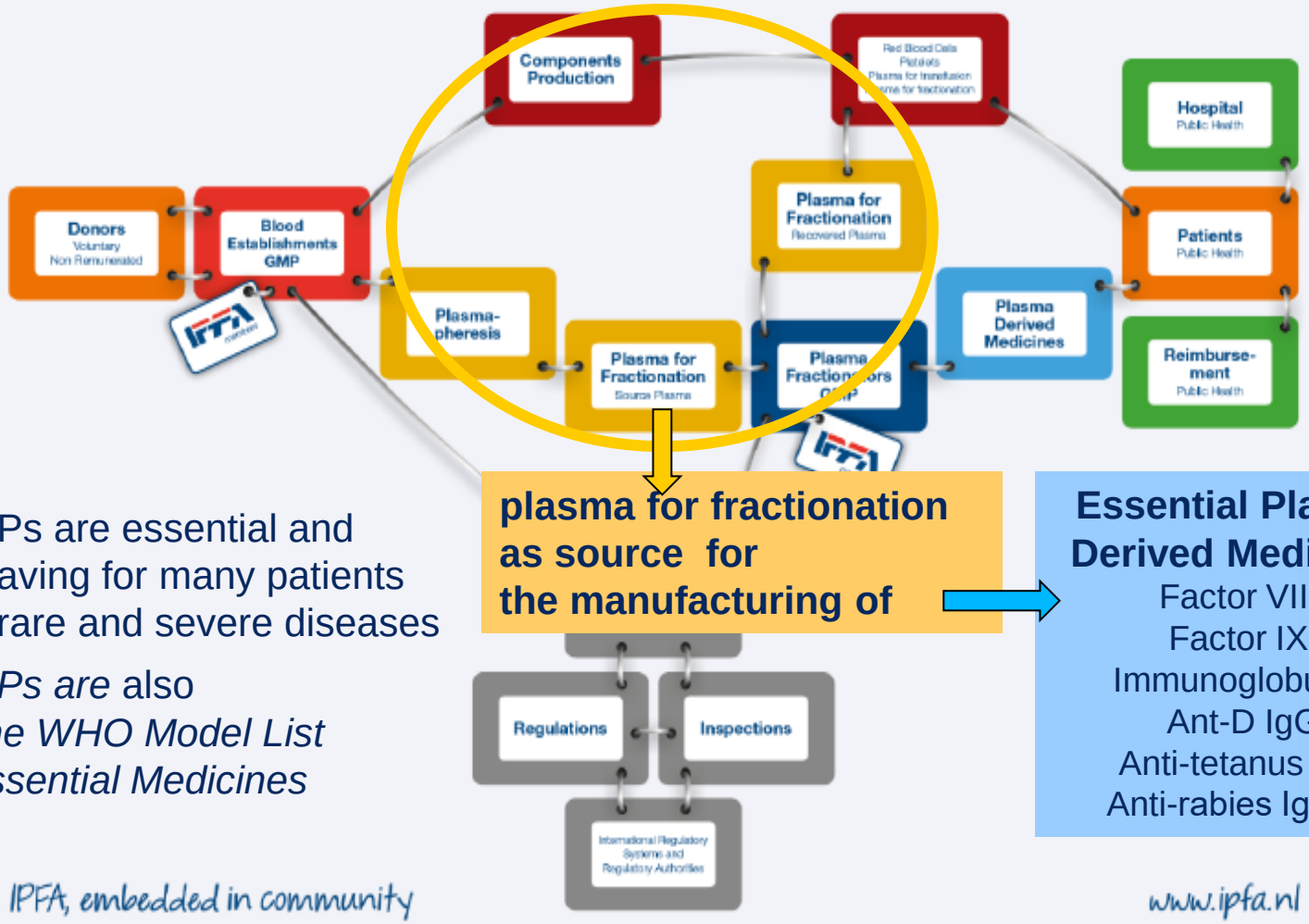
IPFA/EBA Workshop on Plasma Collection, Amsterdam, the Netherlands
14 - 15 January 2020

IPFA Objectives and Focus

- **Plasma Availability and Quality of Plasma**
  - Supply of plasma from whole blood and plasmapheresis donors as source for plasma products
  - Strong collaboration between suppliers of plasma (blood establishments) and fractionators
  - ➢ Focus on high quality of plasma for fractionation
    - Safe, robust supply of plasma
    - Avoid wasting of Recovered plasma
    - Increase plasmapheresis plasma in developed countries
    - Voluntary Non Remunerated Donors

- **Plasma fractionation and patients**
  - High need and demand for plasma products for patients and hospitals

The Source material for Plasma-Derived Medicinal Products (PdMPs)



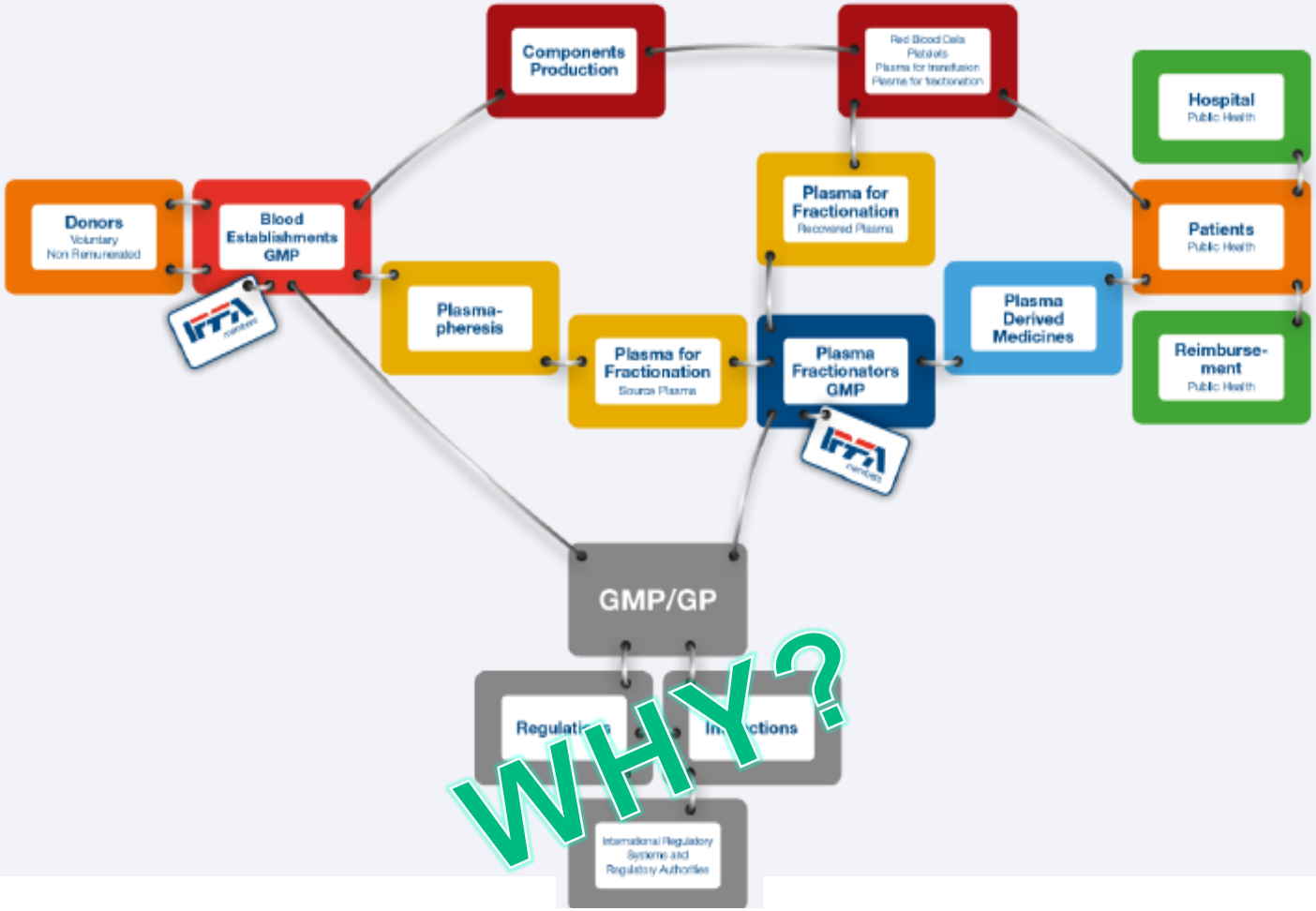
- PdMPs are essential and life saving for many patients with rare and severe diseases
- *PdMPs are* also *on the WHO Model List of Essential Medicines*

plasma for fractionation as source for the manufacturing of

Essential Plasma-Derived Medicines

Factor VIII,
Factor IX,
Immunoglobulins
Ant-D IgG
Anti-tetanus IgG
Anti-rabies IgG …

Plasma Chain



Quality of Plasma for Fractionation?

- PdMPs need to be registered by Competent Authorities to be available to patients
- PdMPs do satisfy GMPs
- PdMPs registration includes documentation of Starting Material
- Starting material for PdMPs **is** the Plasma

✓ Documentation of Plasma as Starting Material:
Scientific Data on Plasma (e.g. European PMF)

✓ Scientific Data on Plasma includes documentation of quality of plasma

➢ Plasma PfF needs to be at high quality level

Quality

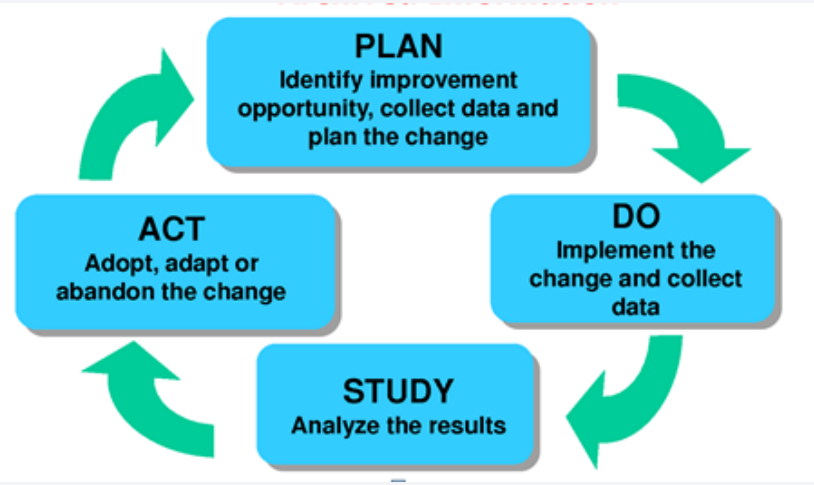
In production, a state of being free from defects, deficiencies and significant variations.

Strict and consistent commitment to certain standards
that **achieve uniformity of a product**
within countries, regions, even cities
in order **to satisfy specific customer or user requirements**.

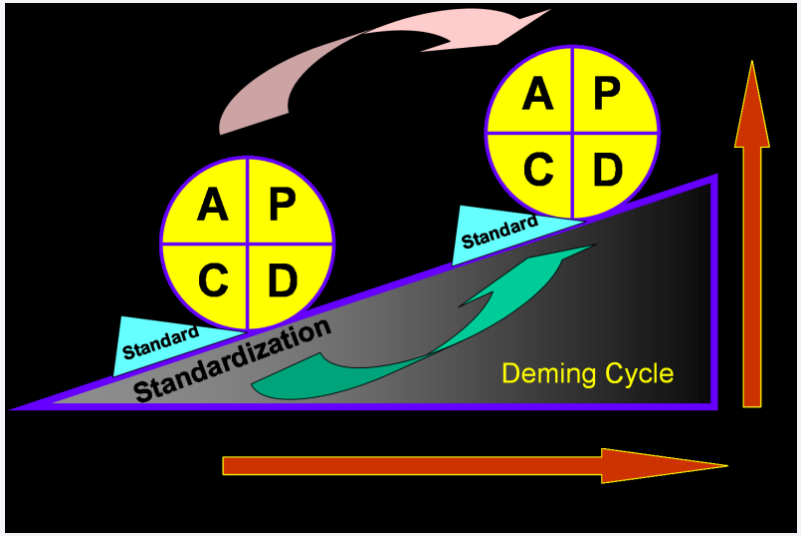
ISO 8402-1986/ ISO 9000:2015 standard defines quality as
"*the totality of **features and characteristics of a product …***
*that bears its ability **to satisfy stated or implied needs**.*"

Quality, a virtuous Process

PDSA/PDCA is a process through which new standards are set; to be challenged; revised and replaced by newer and better standards



For **Continual Improvement**



Quality in Blood Chain

Quality management; Develop a culture of quality

In BEs

Strict and consistent commitment to certain standards
that achieve uniformity of a donation
to satisfy specific customer (patients; fractionators) requirements

- **Support from government is needed**
  - **Action plan with clear milestones**
  - **Dedicated key people working in coordination**
- **Regulatory needs**
  - **Implementation of National Regulatory Authority (NRA) for blood products**
  - **National blood policy and directives of plasma donations** in order to set guidelines and assure homogeneity in the quality of the raw material, plasma
- **Sufficient Inspection resources** of National Competent Authorities for regular inspections of local collection centres

Quality Reference Documents

World Health Organization

NATIONAL STANDARDS FOR BLOOD TRANSFUSION SERVICE

Edition 1-2013

WHO Technical Report Series, No. 961, 2011

Annex 4

WHO guidelines on good manufacturing practices for blood establishments

Blood Safety Program, Health Care and Diagnostic Division
Department of Medical Services
Ministry of Health
Thimphu: Bhutan

The Rules Governing Medicinal Products in the European Union
Volume 4

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

Good Practices Guidelines

for Blood Establishment Required to comply with Directive 2005/62/EC
Per Commission **Directive (EU) 2016/1214** (in force 15/02/2018)

Human Plasma for Fractionation

Plasma Humanum Ad Separationem

Eur. Pharmacopeia Monograph 01/2014:0853

FDA e-CFR data is current as of November 24, 2015
Title 21 → Chapter I → Subchapter F → Part 606
Title 21: Food and Drugs

PART 606— **Current Good Manufacturing Practice for Blood and Blood Components**

© World Health Organization WHO Technical Report Series, No. 961, 2011

https://apps.whoExpert Committee on Biological Standardization Sixty-second report 2011

https://www.who.int/bloodproducts/publications/GMP_Bloodestablishments.pdf.Annex 4


World Health Organization

NATIONAL STANDARDS FOR BLOOD TRANSFUSION SERVICE

Edition 1-2013

Blood Safety Program, Health Care and Diagnostic Division
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World Health Organization
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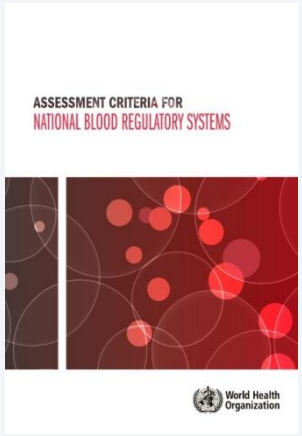

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Annex 4

WHO guidelines on good manufacturing practices for blood establishments

Annex 7

Assessment criteria for national blood regulatory systems

Assessment Criteria for National Blood Regulatory Systems. WHO Expert Committee on Biological Standardization, Sixty-second Report; WHO Technical Report Series No. 979, 2013, Annex 7

WHO Expert Committee on Biological Standardization Sixty-second report

Annex 7

Assessment criteria for national blood regulatory systems

6. Approval of plasma-derived medicinal products *Applicable to plasma-derived medicinal products*			
Main criteria related to the function	Rating*		Indicators related to the main criteria
	Main criteria	Indi-cator	

[Assessment Criteria for National Blood Regulatory Systems. WHO Expert Committee on Biological Standardization, Sixty-second Report; WHO Technical Report Series No. 979, 2013, Annex 7]

R	6.2.2	There is a requirement for the applicant to include a list of all the blood establishments that collected the plasma used in the product.
R	6.2.3	Specifications related to the quality and safety of plasma for fractionation are defined and under the supervision of the NRA.
R	6.2.4	Selection, deferral and transmissible disease testing requirements for plasma donors are established (see criteria 5.3 and 5.4).

Part B. Core functions

3. Licensing and/or registration of blood establishments *Applicable to blood and blood components including plasma for fractionation*			
Main criteria related to the function	Rating*		Indicators related to the main criteria
	Main criteria	Indi-cator	

R	3.2.3	A list of all licensed and/or registered blood establishments is maintained and made available where needed.

WHO WHA58.13 Blood safety: proposal to establish World Blood

3. Recommendations

3.1 For Member States

1. **Establish/strengthen the national blood donor programme** to augment voluntary blood donations to meet the national requirements and allocate appropriate resources for its efficient implementation. Funding mechanisms available under Global Fund to fight AIDS, Tuberculosis and Malaria may be explored, if needed
2. Organize extensive public campaigns to mobilize communities for regular voluntary blood donations
3. **Forge sustainable partnerships among various partners**, especially NGOs operating at the community level, to educate, recruit and retain voluntary blood donors
4. **Build the capacity of blood transfusion services through infrastructure strengthening and training of staff to ensure the care of donors before, during and after blood donation**.
5. **Integrate the principles and practices of a quality system at all levels of the blood donation process**
6. Utilize modern **information technology tools in managing blood centres**, especially blood donor databases
7. Undertake operational research to improve the knowledge, attitude and behaviour of communities towards voluntary blood donations

3.2 For WHO

1. **Provide technical support** for developing and implementing national blood donor programmes as well as for their effective monitoring
2. **Develop generic standards for blood donor recruitment and disseminate the same to all Member States**
3. **Provide assistance in mobilizing resources** to strengthen national blood donor programmes.
4. **Assist in building the capacity of countries** for efficient management of blood donor programmes.
5. Facilitate intercountry information-sharing on advances and success stories in the area of blood donation

PIC: Pharmaceutical Inspection Convention

Founded by The European Free Trade Association (EFTA) in October 1970
Is a legal Treaty between countries

Original Goals (18 EU MS only)

- **Harmonised GMP requirements**
- **Mutual Recognition of Inspections**
- **Uniform Inspection Systems**
- **Training of Inspectors**
- **Mutual Confidence**

Only European Commission authorised to sign agreements with other countries

European Countries

AT, BE, CY, CZ, DE, DK, EE, FI, FR, GB, GR, HR, HU, IE, IT, LV, Lichtenstein, LT, MT, NL, NO, PL, PT, RO, SK, SE, CH, UA

PIC Scheme — Pharmaceutical Inspection Cooperation Scheme

- ✓ ~~PIC/S GMP Guide (similar to EU GMP Guide).~~
- ✓ PIC/S GMP Guide for Blood Establishments.
- ✓ PIC/S Guide to Good Practices for the Preparation o Medicinal Products in Healthcare Establishments.

PIC/S Goal

"To lead the **international development**,
Implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products".

Quality Reference Documents / Content

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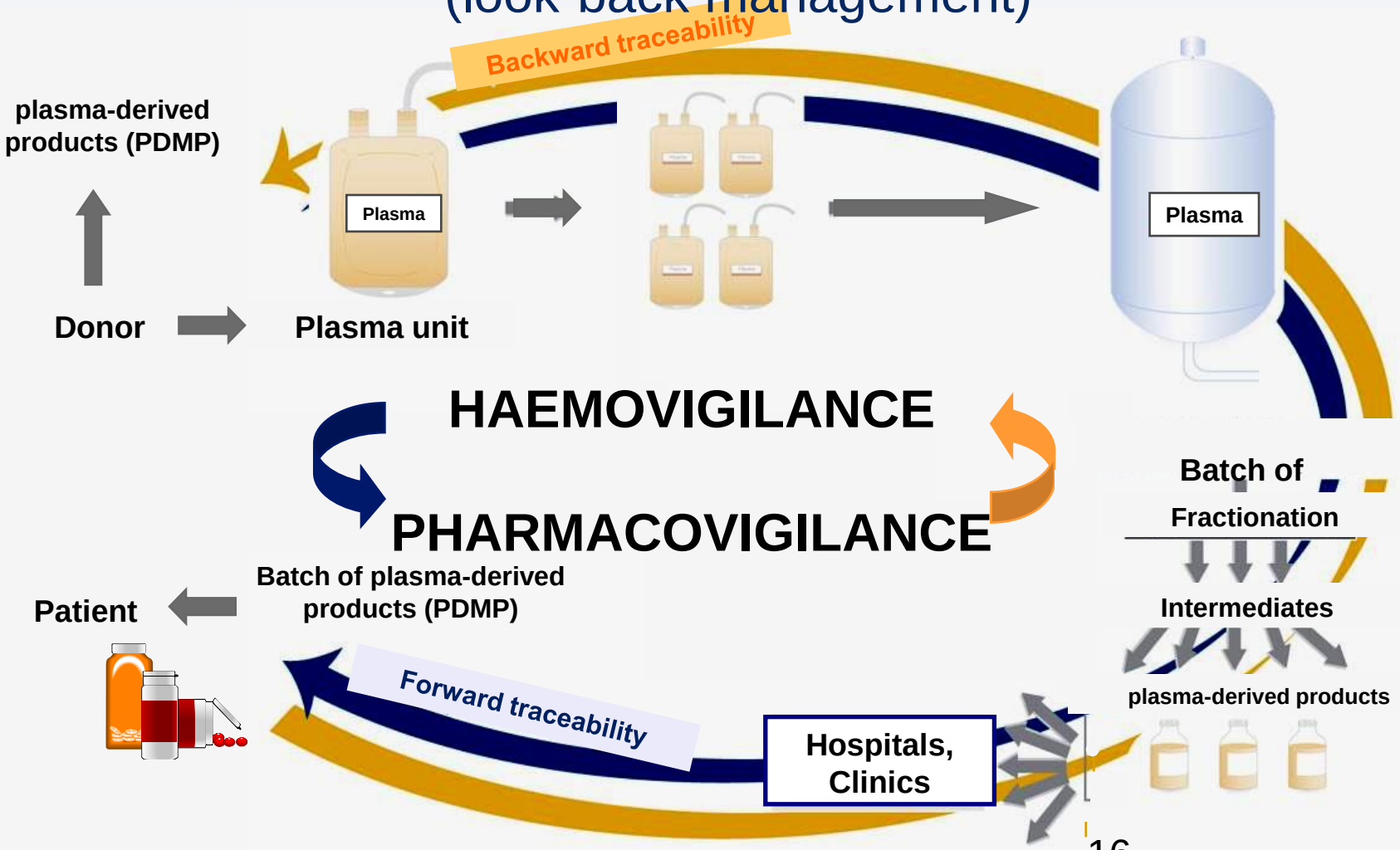
Title 21 → Chapter I → Subchapter F → Part 606
Title 21: Food and Drugs

PART 606— **Current Good Manufacturing Practice for Blood and Blood Components**

General Quality Points For Blood Products

- General principles: Quality system/ Good practices/Risk management
- Procedures and records
- Premises/Areas
- Maintenance of all equipment
- Blood collection, Testing and Processing/ Preparation
- Donor eligibility
- Labelling
- Release of Plasma for Fractionation
- Traceability and Post Collection Measures - Adverse reaction file.
- Non-conformance and recall

Traceability of plasma units and blood monitoring system (look-back management)



At EMA level: Plasma Master File

PMF : Certification Principe

Note Procedural Guidance on PMF (EMEA/CPMP/BWP/4663/03 – February 2004)

Guidelines

- Requirements for plasma master file certification
- Scientific data requirements for plasma master file
- Epidemiological data on blood transmissible infections
- Validation of immunoassay for the detection of antibody to human immunodeficiency virus in plasma pools
- Validation of immunoassay for the detection of hepatitis B virus surface antigen in plasma pools

Why valuing Plasma PfF?

- Plasma represents around 30% of the cost of PdMPs
- Plenty of plasma is thrown away, or not collected;
  let's fractionate it!
- The bill for importing PdMPs is costly and increasing;
  IVIG usage, Albumin, haemophilia care, etc.
- PdMPs will not be fully replaced by biotechnology substitutes in an affordable way

How to value Plasma PfF?

Once a country has invested a lot of resources
in its blood transfusion system, it is a shame not to value the plasma;
Indeed a major part of the effort has been achieved

Common core between Transfusion Products and Plasma for Fractionation

1. Vending/Yielding Plasma to Fractionators
2. Contract Fractionation with a Fractionator
3. Technology transfer from a Fractionator with the aim of …
4…. Owning your national fractionation(s) plant(s): Custom Fractionation

=> In all cases, the story starts the same way: Availability of quality PfF

1. Vending of Plasma to Fractionators

The foreseen impact would be an improvement of the national transfusion system (quality; safety; availability)

- Continuous improvement due to fractionator's quality audits in the BEs
- Examples of partnerships (gain in know-how)
- Potential negotiations for provision of foreign PdMPs

2. Contract Fractionation

Annex 4
WHO guidelines on good manufacturing practices for blood establishments

Contract plasma fractionation programme

EU GMP Annex 14: Manufacture of Products derived from Human Blood or Human Plasma (May 2011) third country contract fractionation dedicated paragraphs

Why perform contract manufacturing?

- Avoid wasting quality PfF that is highly valuable
- Bill for importing plasma products costly and increasing (IgIV, etc…)
- Availability of key products is cyclical : when prices go up, manufacturers may be geographically selective
- Plasma represents around 30 % of the cost of blood products. The same proportion can be saved in the imports
- Plasmapheresis plasma improves this process
- Optimize the diversity of products. The more products got from a litre of plasma, the highest the cost saving

When perform contract manufacturing?

- The **chance to build** up a new profitable self-sufficiency fractionation plant is **limited**
- The country must not necessarily collect a large annual volume of plasma (from 40 10^3 litres)

How to value the Plasma PfF?

EU GMP Annex 14: Manufacture of Products derived from Human Blood or Human Plasma (May 2011)

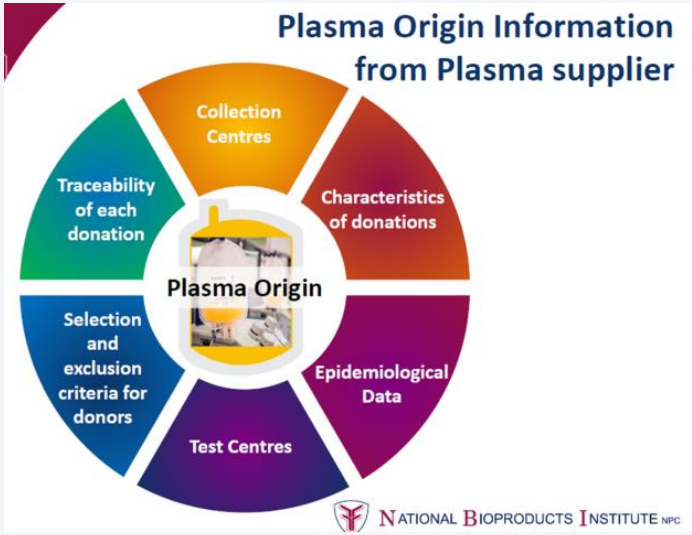
EU GMP Annex 14: Manufacture of Products derived from ...

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.

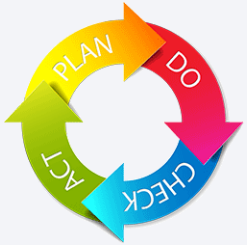
1.3 The Annex addresses specific provisions for when starting material is imported from third countries and for contract fractionation programs for third countries.

Critical parameters for insuring quality of Plasma PfF

= Acceptance Criteria by the Fractionator, whoever he is (you or them)



- Selection of Blood Donors
- Collection time of the whole blood
- Centrifugation of whole blood
- Plasma Processing
- Minimum volume of plasma (recommended 200ml)
- Basic requirements for Donor's testing
- Temperature
- Kinetics and time of plasma freezing
- Physico-chemical Composition: Total proteins level, FVIII level, pH, …
- Conservation/ Storage and Plasma Transport
- Traceability of plasma units and blood monitoring system (look-back management) (haemovigilance and pharmacovigilance)



The Fractionator will perform Audits => Benefits for the Blood Establishment

Written Agreements and Audits,
an opportunity to Develop a culture of quality,

a win-win situation
Definition of Roles and Responsibilities (BE - Fractionator)
Increase Safety of Blood products
Building expertise within the BE
Audits of donation centers are a regulatory requirement for fractionators
Anticipate impacts of regulatory changes
Readiness for Regulatory Competent Authority Regular Inspections

EDQM Blood Proficiency Testing Scheme (B-PTS),
a form of External Quality Assessment (EQA),
Important factor in Quality Assurance

Consequences observed in countries which have started plasma vending or contract fractionation

I**mproved efficiency in the transfusion system network**:
grouping of collection centres / of information systems / creation of centralized “state of the art” technical platforms for the qualification, creation of hubs for plasma freezing, increase of blood bag volumes / centralized quality starting material / Compliance with local Regulatory and quality in Documentation / Internal Formations

Harmonization of the safety level via the qualification procedure
in all the collection centres, which results
in the improvement of the Red Cells, Platelets and Plasma quality

Development of the look-back information system

Improvement in **virus epidemiology surveillance data monitoring**
and sensitization of the population to the blood safety issues

Conclusion

- Benefits of Improving Plasma Quality of Blood Establishments
  - Improves Quality and Safety of Blood and Plasma
  - Drastically upgrades transfusion safety and viral epidemiology management
  - Introduces Plasmapheresis
  - Allows less dependency on importations
  - Increases Availability of Blood and PdMPs for the Patients
  - Enhances Strategic Independence
- With a high positive impact on Public Health

Thank you for your attention

Back-up Slides

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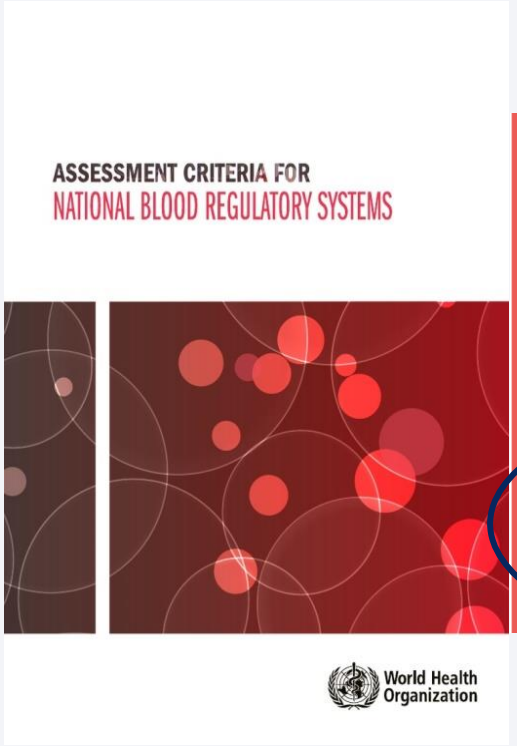
WHO Expert Committee on Specifications for Pharmaceutical Preparations - WHO Technical Report Series, No. 961 - Forty-fifth Report (Geneva, 18–22 October 2010)



The assessment criteria for national blood regulatory systems were adopted by the WHO Expert Committee on Biological Standardization at its sixty-second meeting, held in Geneva from 17 to 21 October 2011. The document contains the collective views of the WHO Blood Regulators Network. It was developed in response to a request from WHO and the International Conference of Drug Regulatory Authorities for an assessment tool to assist capacity building of national regulatory authorities for the regulation of blood and blood products.

The tool is intended to help Member States to identify gaps and priorities when developing capacity building programmes, and support the introduction of regulation of blood products. Establishment of such regulation was recommended in the 2010 World Health Assembly resolution (WHA63.12) on the availability, quality and safety of blood products.

General Quality Points For Blood Products

WHO

National Standards for Blood Transfusion Service | 2013

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5 | National Standards for Blood Transfusion Service/2013

FDA

e-CFR data is current as of November 24, 2015

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Title 21: Food and Drugs

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

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General Quality Points For Blood Products

EU

European Committee (Partial Agreement) on Blood Transfusion
&
European Commission

For Implementing Standards and Specifications for the Quality System in Blood Establishments

Good Practice Guidelines for Blood Establishment Required to Comply with Directive 2005/62/EC

This text in force by 15/02/2018
Per Commission Directive (EU) 2016/1214

Good practice guidelines 2016

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Pharmaceuticals

Brussels,
SANCO/C8/AM/an D(2010) 380358

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

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

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

01/2005:0853
corrected

HUMAN PLASMA FOR FRACTIONATION

Plasma humanum ad separationem

DEFINITION

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 an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure; it is intended for the manufacture of plasma-derived products.

PRODUCTION

DONORS

Only a carefully selected, healthy donor who, as far as can be ascertained after medical examination, laboratory blood tests and a study of the donor's medical history, is free from detectable agents of infection transmissible by plasma-derived products may be used. Recommendations in this field are made by the Council of Europe [*Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components*, or subsequent revision] and the European Union [*Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community* (98/463/EC)].

Immunisation of donors. Immunisation of donors to obtain immunoglobulins with specified activities may be carried out when sufficient supplies of material of suitable quality cannot be obtained from naturally immunised donors. Recommendations for such immunisation are formulated by the World Health Organisation (*Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives*, WHO Technical Report Series, No. 840, 1994 or subsequent revision).

Records. Records of donors and donations made are kept in such a way that, while maintaining the required degree of confidentiality concerning the donor's identity, the origin of each donation in a plasma pool and the results of the corresponding acceptance procedures and laboratory tests can be traced.

Laboratory tests. Laboratory tests are carried out for each donation to detect the following viral markers:

1. antibodies against human immunodeficiency virus 1 (anti-HIV-1),
2. antibodies against human immunodeficiency virus 2 (anti-HIV-2),

the introduction of micro-organisms. No antibacterial or antifungal agent is added to the plasma. The containers comply with the requirements for glass containers (*3.2.1*) or for plastic containers for blood and blood components (*3.2.3*). The containers are closed so as to prevent contamination.

If 2 or more units are pooled prior to freezing, the operations are carried out using sterile connecting devices or under aseptic conditions and using containers that have not previously been used.

When obtained by plasmapheresis, plasma intended for the recovery of proteins that are labile in plasma is frozen by cooling rapidly at −30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended for the recovery of proteins that are labile in plasma is separated from cellular elements and is frozen by cooling rapidly at −30 °C or below as soon as possible and at the latest within 24 h of collection.

When obtained from whole blood, plasma intended solely for the recovery of proteins that are not labile in plasma is separated from cellular elements and frozen at −20 °C or below as soon as possible and at the latest within 72 h of collection.

It is not intended that the determination of total protein and factor VIII shown below be carried out on each unit of plasma. They are rather given as guidelines for good manufacturing practice, the test for factor VIII being relevant for plasma intended for use in the preparation of concentrates of labile proteins.

The total protein content of a unit of plasma depends on the serum protein content of the donor and the degree of dilution inherent in the donation procedure. When plasma is obtained from a suitable donor and using the intended proportion of anticoagulant solution, a total protein content complying with the limit of 50 g/l is obtained. If a volume of blood or plasma smaller than intended is collected into the anticoagulant solution, the resulting plasma is not necessarily unsuitable for pooling for fractionation. The aim of good manufacturing practice must be to achieve the prescribed limit for all normal donations.

Preservation of factor VIII in the donation depends on the collection procedure and the subsequent handling of the blood and plasma. With good practice, 0.7 IU/ml can usually be achieved, but units of plasma with a lower activity may still be suitable for use in the production of coagulation factor concentrates. The aim of good manufacturing practice is to conserve labile proteins as much as possible.

Total protein. Carry out the test using a pool of not fewer than 10 units. Dilute the pool with a 9 g/l solution of *sodium chloride R* to obtain a solution containing about 15 mg of protein in 2 ml. To 2.0 ml of this solution in a

General Quality Points For Blood Products

HUMAN PLASMA FOR FRACTIONATION — **EU**

Plasma Humanum Ad Separationem

Eur. Pharmacopeia Monograph 07/2008:0853

Definition		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 anti-coagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure; it is intended for the manufacture of plasma-derived products.
Production		
	Donors	Only carefully selected healthy donors - after medical examination - laboratory blood tests - study of medical history free from detectable agent of infection transmissible by plasma-derived medicinal products recommandation of the CoE N° R (95)15
	Records	records of - donors and donations are kept, while maintening required degree of confidentiality regarding donor's identity, - origin of each donation - results of corresponding acceptance procedure - laboratory test
	Laboratory	Anti-HIV-1 Anti-HIV-2 HBsAg anti-HCV test methods of suitable sensitiviy and specificity If repeat-reactive result of any is found : the donation is not accepted
	Individual plasma units	practical techniques for preparation plasma from plasmapheresis : Freezing at -20°C within 24h plasma from Whole blood: Freezing at -20°C within 72h total protein content: 50g/l
	Storage and Transport	Stored in conditions designed to maintain temperature ≤ -20°C with exceptions no more than 72h at not above -15°C ; never at < -5°C
	Plasma pool	for fractionators tested for HBs and HIV antibodies ; Hep C RNA
Character		Before freezing, clear to slightly turbid liquid without any visible signs of haemolysis; yellow to green
Labelling		The label enables each individual unit to be traced to a specific donor

Bridging the interests of: Donors - Collection Centers -

The Rules Governing Medicinal Products in the European Union — **EU**

Volume 4

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

1. Scope — This Annex applies 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.
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.

2. Principles — 2.1 In principle active substances used as starting material for medicinal products must comply with the principles and guidelines of Good Manufacturing Practice. 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 [Ref] are to be observed [Directive 2004/33/EC Annex I Part III No. 4.4.1].

3. Quality Management — All steps from donor selection to delivery of the finished product.
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.
Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures.
The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer.
An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents.

4. Traceability and Post Collection Measures — 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.
Responsibilities for traceability of the product should be defined.
- from the donor and the donation to the blood establishment
Data needed for full traceability must be stored for at least 30 years.
The blood establishments should notify the fractionating manufacturer of any event which may affect the quality or safety of the product including events
notification procedures also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing licence/certificate/approval.
management of post-collection information should be described in standard operating procedures [SOP]

5. Premises and equipment — for fractionators

6. Manufacturing — starting material should comply with the requirements of all relevant monographs of the European Pharmacopoeia
All processing steps [e.g. qualification and/or operation, sampling, labelling, freezing] should be defined in written procedures.
Freezing should therefore be performed as soon as possible after collection
The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded.
Qualified equipment and validated procedures should be used.
Certification/release of plasma for fractionation as — Plasma for fractionation should only be released, i.e. from a quarantine status, through systems and procedures that ensure the quality needed for the manufacture of the finished product
Responsible Person

7. Quality Control — for fractionators

8. Release of intermediate and finished products — for fractionators

9. Retention of plasma pool samples — for fractionators

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 intermediates or finished products]

Good Practice Guidelines for Blood Establishment Required to Comply with Directive 2005/62/EC

Per Commission Directive (EU) 2016/1214

1. General principles
1.1. General requirements
1.2. Quality system
1.3. Good practice
1.4. Quality risk management
2. Personnel and organisation
3. Premises
3.1. General
3.2. Blood donor area
3.3. Blood collection area
3.4. Blood testing and processing areas
3.5. Storage area
3.6. Ancillary areas
3.7. Waste disposal area
4. Equipment and materials
4.1. General requirements
4.2. Data processing systems
4.3. Qualification and validation
4.4. Process validation
4.4.1. General
4.4.2. Concurrent validation
4.4.3. Prospective validation
4.5. Validation of test methods
4.6. Change control
4.7. Control of equipment and materials
4.7.1. General principles
4.7.2. Calibration and monitoring of equipment
5. Documentation
5.1. General principles
5.2. Required good practice documentation (by type)
5.3. Generation and control of documentation
5.4. Good documentation practices
5.5. Retention of documents
5.6. Specifications
5.7. Preparation Instructions
5.8. Labelling
5.9. Procedures and records
5.10. Sampling
5.11. Other
6. Blood collection, testing and processing
6.1. Donor eligibility
6.2. Collection of blood and blood components
6.3. Laboratory testing
6.4. Testing for infectious markers
6.5. Blood group serological testing of donors and donations
6.6. Processing and validation
6.7. Labelling
6.8. Release of blood and blood components
7. Storage and distribution
8. Outsourced activities management
8.1. General principles
8.2. The contract giver
8.3. The contract acceptor
8.4. The contract
9. Non-conformance and recall
9.1. Deviations
9.2. Complaints
9.3. Recall
9.4. Deviation management and corrective and preventive actions
10. Self-inspection, audits and improvements
11. Quality monitoring and control
11.1. Quality monitoring
11.2. Quality control

General Quality Points For Blood Products

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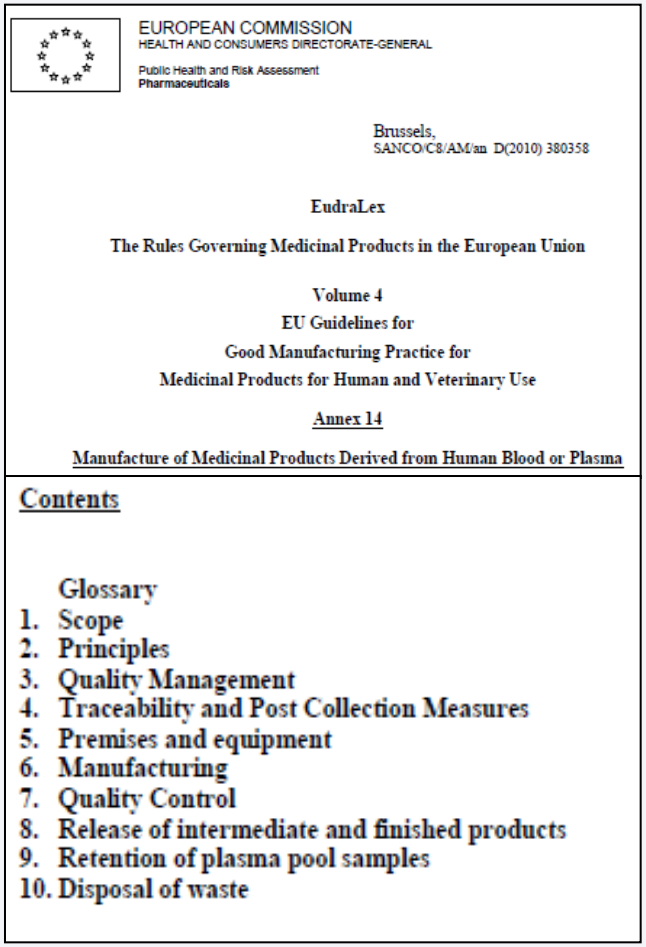

EUROPEAN COMMISSION
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Public Health and Risk Assessment
Pharmaceuticals

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EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

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

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9. Retention of plasma pool samples
10. Disposal of waste

Additional points for PfF for Contract Manufacturing

- Freezing, storage and transportation equipment
  - Freezing process must be as quick as possible
  - Large capacity cold rooms as the volume of each shipment of plasma to fractionator can barely be smaller than 9000 litres (may be centralized plasma storage facility)
  - Validation and monitoring
- Sampling
  - One dedicated sample attached to the bag to be sent to the fractionator for possible additional tests, in particular for the first year of the contract
- Bag size to be of similar size and preferentially not smaller than 200 ml
- National, regional or global, quality system with unique barcode system