# Oversight of contract plasma fractionation

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**International Plasma Fractionation Association**

Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries:
Local Production & Pathways to Fractionation
GBS of ISBT 21-23 Sept 2021

# Disclosures

*I have the following disclosure:*

- *Employee of LFB, in addition to IPFA*

# IPFA Mission

IPFA supports and promotes the activities of not-for-profit organizations around the globe engaged in the collection and fractionation of plasma to enable robust, safe supply and patient access to plasma derived medicines.

Through education and collaboration with stakeholders, we advocate for public health values and donor health protection.

# Topics covered in the presentation

What is Contract Manufacturing/Toll fractionation?

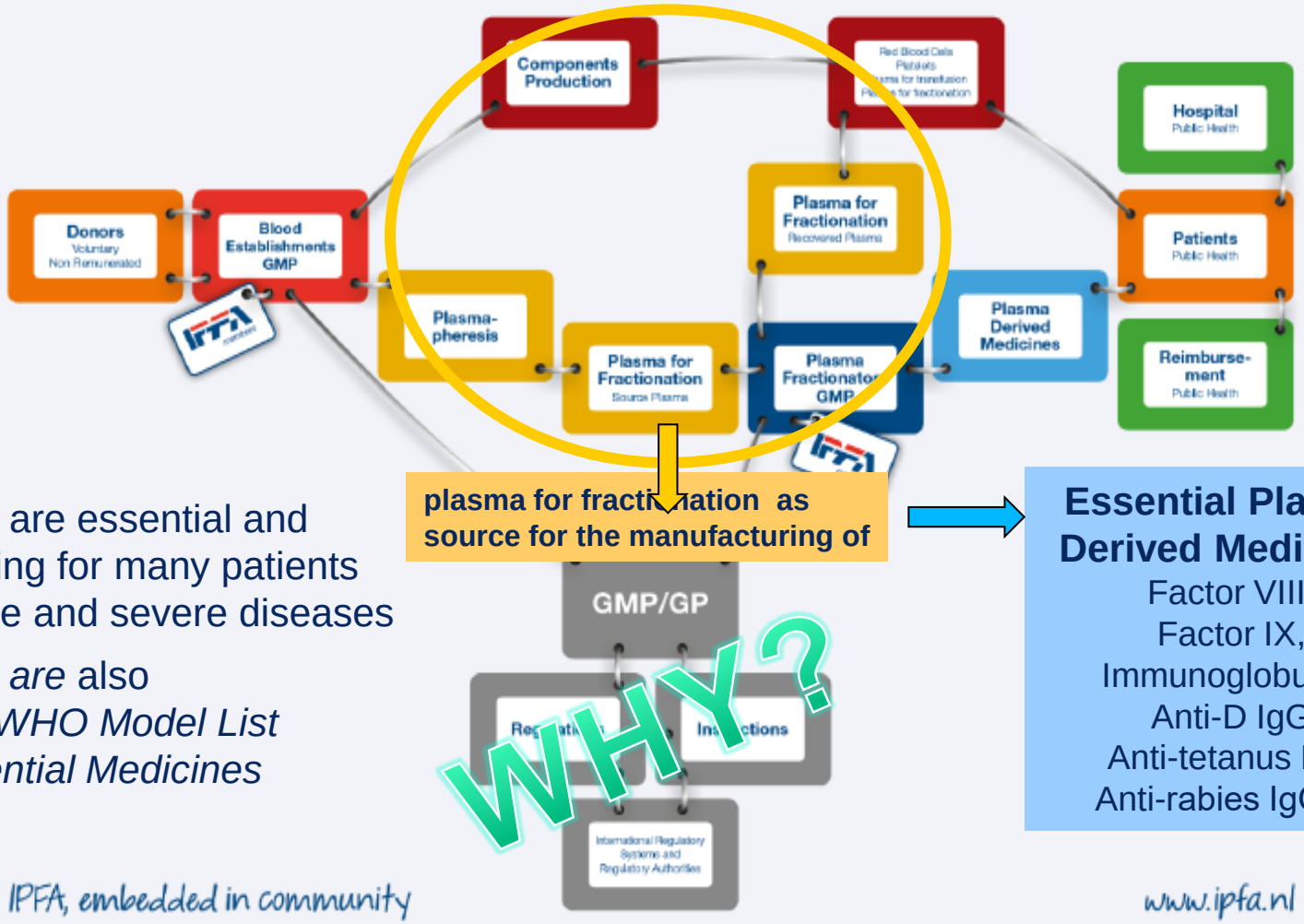
Why do Contract Manufacturing/Toll fractionation?

How to do it?

What are the issues and main challenges for implementation?

What is the way forward?

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

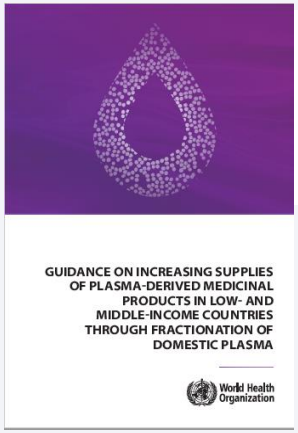



- PdMPs are essential and life saving for many patients with rare and severe diseases
- *PdMPs are* also *on the WHO Model List of Essential Medicines*

**Essential Plasma-Derived Medicines**

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

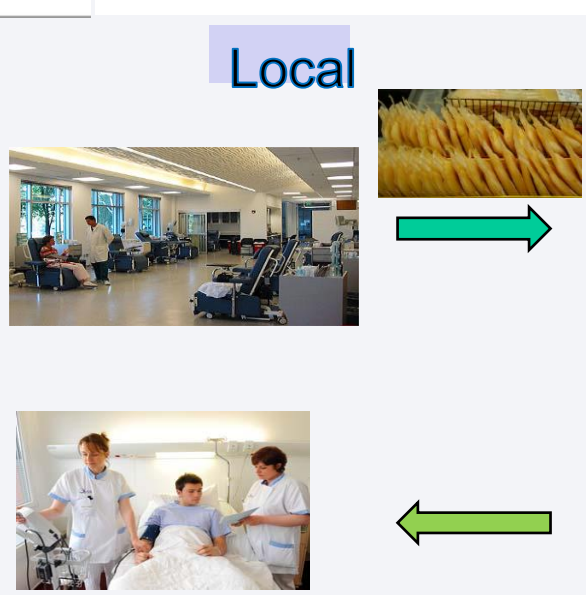
# What is Contract Fractionation






## GLOSSARY

| | |
|---|---|
| Contract plasma fractionation | An arrangement in which domestic plasma is provided to a fractionator licensed in a foreign country and PDMPs are provided in return, according to predetermined terms for use within the country. |

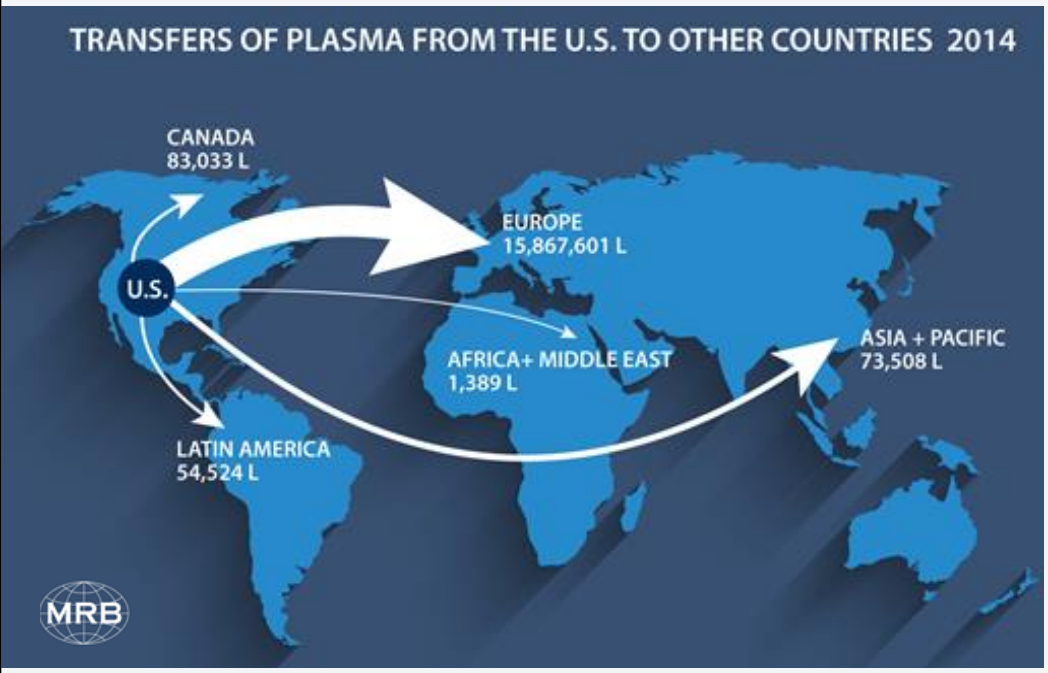





*From Thierry Burnouf, 4th Asia-Pacific IPFA workshop – Hanoi, Thailand – March 6-7, 2019*

# Worldwide use of Plasma for Fractionation

World of plasma for fractionation very diverse: 3 big areas to consider




## EU main supplier of Recovered plasma

- 4,4 Ml recovered plasma collected in Europe

Half of the world recovered plasma for fractionation
(from 10% of the world population)

## USA main supplier of Source plasma

- 26 ML of source plasma collected in USA

Two thirds of the world source plasma
(from 6% of the world population)

## Rest of the world

collected plasma not always compliant with WHO Quality standards/regulations for fractionation and any other local applicable regulations
=> large amounts of plasma are wasted

# Why valuing Plasma PfF?

*"Deficiencies in GMP compliance resulting in failure to utilize recovered plasma to make PDMPs constitute an unethical waste of valuable human resources"*


- Avoid wasting highly valuable quality PfF, sometimes thrown away, or not collected; let's fractionate it!

- Plasma represents around 30%-45% of the cost of PDMPs

# How to value Plasma PfF?

*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…. Custom Fractionation with a national fractionation(s) plant(s)

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

# 2. Contract Fractionation



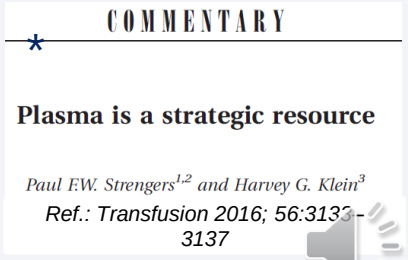
Annex 4
**WHO guidelines on good manufacturing practices for blood establishments**

**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 get into contract manufacturing?

- Availability of PDMPs is cyclical : when prices go up, manufacturers may be geographically selective
- Strategic independence from local plasma give some guaranty in PDMPs supply on long term*
- Proportion of the cost of plasma can be saved in comparison of PDMPs import
- Optimization of the diversity of products: more products got from a litre of plasma, highest the cost saving
- Increase of plasma (/blood) collection quality
- Improved by Plasmapheresis plasma
- Sustainability of BEs


COMMENTARY

*

Plasma is a strategic resource

Paul F.W. Strengers[1,2] and Harvey G. Klein[3]

Ref.: Transfusion 2016; 56:3133-3137

# 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

## WHEN get into contract manufacturing?

- No domestic fractionation plant
- The chance to build up a new profitable self-sufficiency fractionation plant is limited
- Large annual volume of plasma collected by the country not necessary
- Necessary supply of PDMPs defined by assessment of clinical needs in the country
- Government/ Regulatory authorities support
- Possible pathway toward domestic fractionation through a learning process

# Main Challenges for implementation

- Non engagement of Ministries of Health, Authorities
- Lack of financial resources or manpower/knowhow
- Volumes offered for fractionation
- Non willingness of fractionators to invest in the quality learning process of several BEs
- Failure to meet internationally recognized quality and safety standards for recovered plasma
- Variability of the spare production capacity of the fractionator

GUIDANCE ON INCREASING SUPPLIES OF PLASMA-DERIVED MEDICINAL PRODUCTS IN LOW- AND MIDDLE-INCOME COUNTRIES THROUGH FRACTIONATION OF DOMESTIC PLASMA

World Health Organization

*"Absence of adequately resourced regulatory oversight, precluding assurance that appropriate standards are met at all stages of plasma production"*

# How to do (1)

- Which plasma
  - Recovered from WBD?
  - Recovered/concurrent from combined apheresis (e.g., platelets)?
  - Plasmapheresis plasma?
  - Cryoprecipitate?
  - Combined options?
- Which fractionator
  - Licensed?
  - Portfolio adapted to local clinical needs?
  - Current plasma fraction protein recovery?
  - Volume of fractionator's spare capacity available?
  - Willingness to contribute toward improvement of plasma quality level?

# How to do (2)

Improving access to safe blood products through local production and technology transfer in blood establishments

World Health Organization

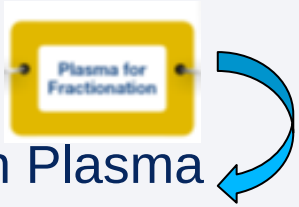
- Conditions required
  - Minimum volume fractionator's requirements
    - Volume of plasma for contract fractionation

| | |
|---|---|
| minimum +/- 40'000 L | maximum 250'000 L (in one site) |

  - Meet fractionator quality criteria …/…

# Meet fractionator quality criteria of PfF

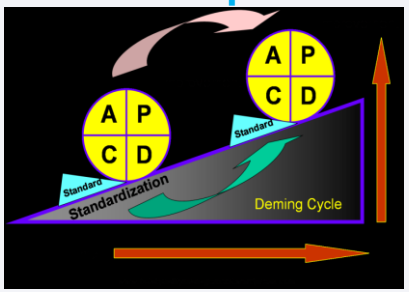
- PDMPs are registered by Competent Authorities (Marketing Authorisation - MA)
- PDMPs do satisfy GMPs
- PDMPs MA file includes documentation of Starting Material
- Starting material for PDMPs **is** the Plasma



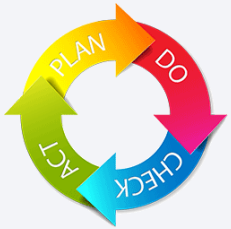

  - ✓ MA file: Scientific Data on Plasma includes quality of plasma

➢ Plasma PfF needs to be at high quality level

**Continual Improvement**

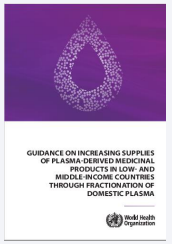



**Quality, a virtuous Process**



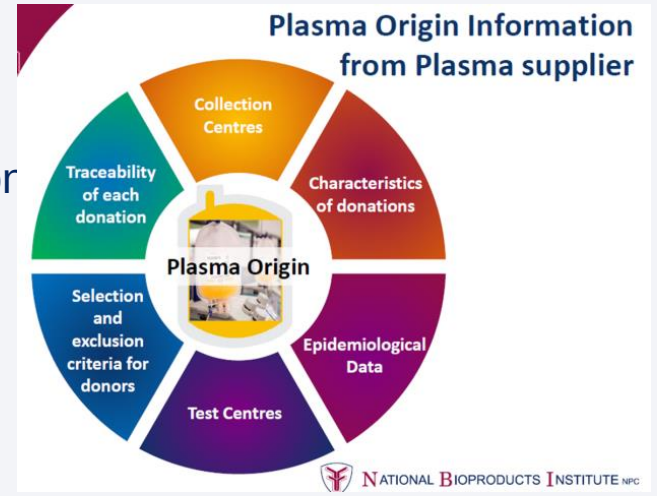
# Critical parameters for insuring quality of Plasma PfF

## = Acceptance Criteria by the Fractionator




**Quality management; Develop a culture of quality In BEs**

**Chap 5:** STANDARDS AND QUALITY MANAGEMENT IN BLOOD ESTABLISHMENTS

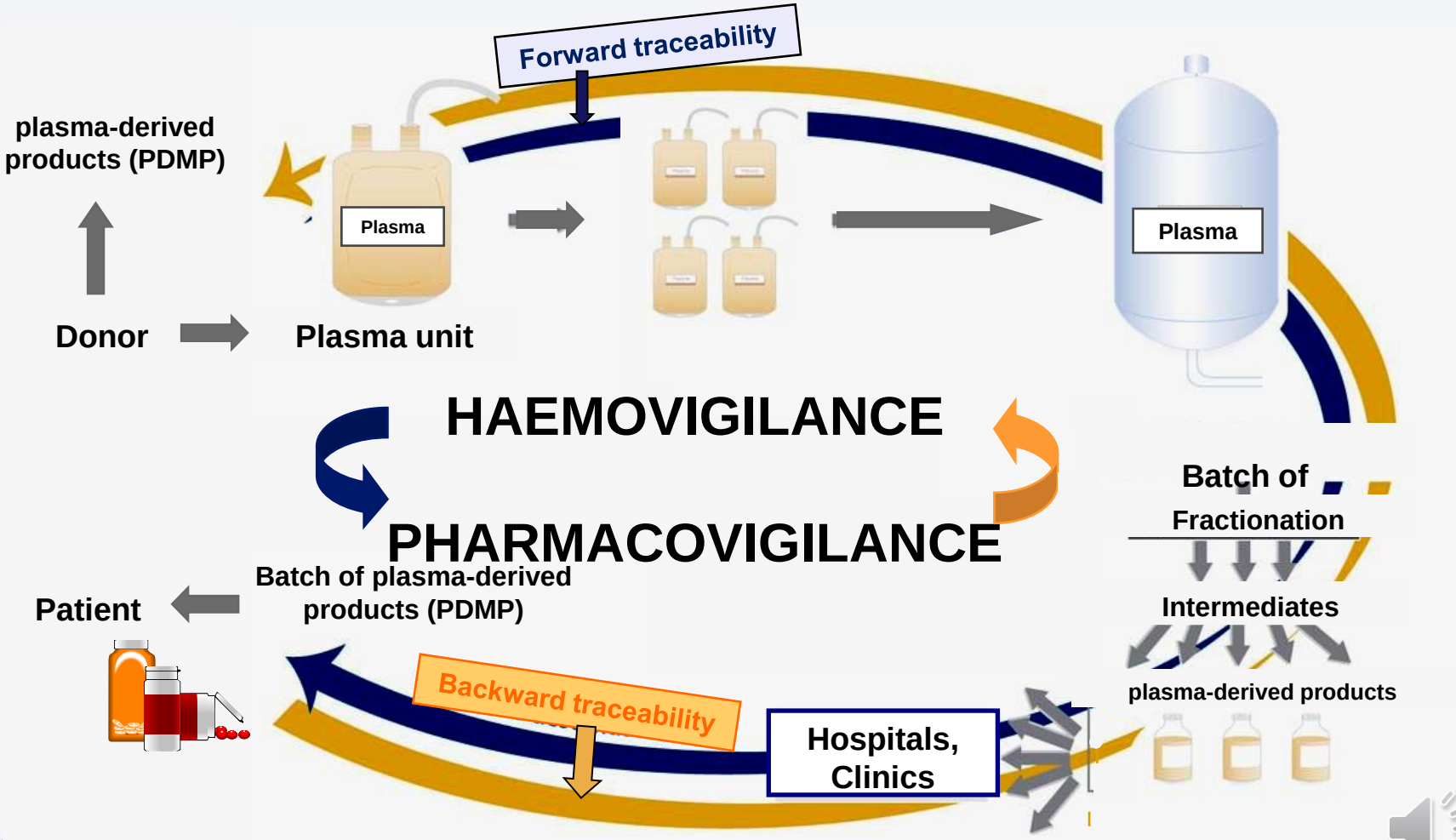



- 5.1 Standards for donor selection
- 5.2 Standards for quality-assured laboratory testing for evidence of transfusion-transmissible infection
- 5.3 Good manufacturing practices (GMP) and quality management
  - 5.3.1 Suitable organization and trained personnel
  - 5.3.2 Suitable facility and equipment
  - 5.3.3 System of documentation and traceability
  - 5.3.4 Validation of operating procedures and quality monitoring

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

# Traceability of plasma units and blood monitoring system (look-back management) HV/PV

**Additional Safety for recovered plasma, thanks to vigilance on recipients of labile products**



# Quality Contracts

**Mandatory Quality Agreements**

**A regulatory requirement**

CHAPTER 7: PRODUCTION OF PLASMA FOR FRACTIONATION 33

GUIDANCE ON INCREASING SUPPLIES OF PLASMA-DERIVED MEDICINAL PRODUCTS IN LOW- AND MIDDLE-INCOME COUNTRIES THROUGH FRACTIONATION OF DOMESTIC PLASMA

**Table 2. Areas of particular relevance for a quality agreement between a blood establishment and a fractionator**

Detailed « list of specifications », legally binding documents between the plasma supplier and the fractionator

Good communication between plasma suppliers and fractionators paramount, especially to anticipate and mitigate regulatory and quality constraints

**Regulatory Constraints**

If fractionation plant is located in EU,

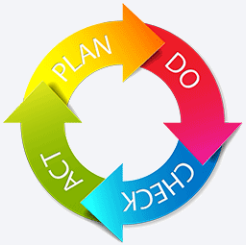
✓ EU GMPs Annex 14 applies

With special chapters for contract fractionation programs (parts thereof apply)

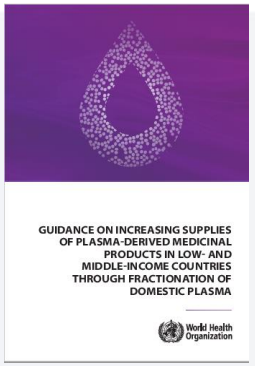
# Quality and Audit requirements of the Fractionator for the qualification of collection centers by fractionator
## => Benefits for the Blood Establishment

**Written Agreements and Audits,** a regulatory requirement for fractionator an opportunity to Develop a culture of quality,

- Opportunities for improvements/ Address open issues in persons
- Confirmation of compliance level by an external party
  - Identification of items for improvement
  - Implementation of CAPA (Corrective Actions and Preventive actions)
- Building expertise within the BEs
- Definition of Roles and Responsibilities (BE - Fractionator)
- Anticipate impacts of regulatory changes
- **Readiness for Regulatory Competent Authority Regular Inspections**

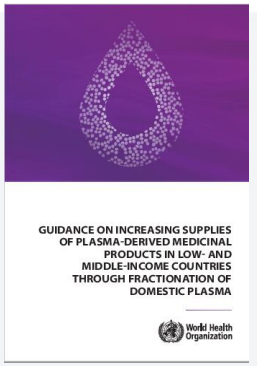


# Solution proposed




National/ Regional program for Contract Manufacturing with fractionators,
a win-win situation

- **For the collector/country client**
  - ✓ Improvement of quality level of blood & blood components and plasma collection by implementing same qualification procedure and systems programs in experienced BEs / countries;
  - ✓ Grouping of collection centers; technical platforms for testing; plasma freezing,…
  - ✓ Progress towards multiple products apheresis and plasmapheresis collection with the aim of best cost-effectiveness
  - ✓ Increase of authorities' involvement
  - ✓ Improvement in virus epidemiology surveillance data monitoring & Sensitization of the population to blood safety issue
  - ✓ Ethical best use and avoidance of destruction of collected recovered plasma
  - ✓ Stable supply of wide range of PDMPs for the patients in the country /region
  - ✓ PDMPs Cost stability through long-term contracts avoiding flexibility of Ig prices
  - ✓ Strategic independence in PDMPs
  - ✓ If excess production of e.g., coagulation factors, optimisation of the donor's gift as humanitarian use towards neighbour countries




# Solution proposed

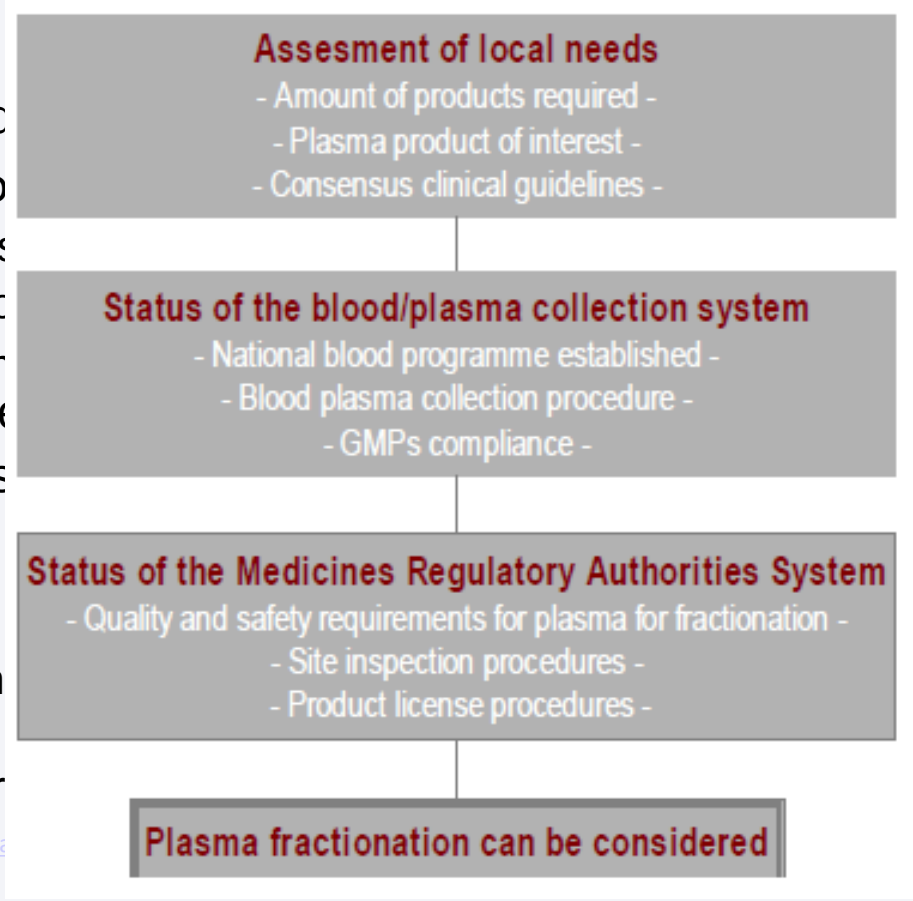
National/ Regional program for Contract Manufacturing with fractionators,
a win-win situation

- **For the fractionator**
  - ✓ Use of spare capacity of the plants (cost-effectiveness)
  - ✓ Market entry in the country/region
  - ✓ Supply of additional amounts of PDMPs manufactured from main production
  - ✓ Closer relationship with competent authorities


# Next steps (1)

Information sheet: plasma contract fractionation program. Geneva WHO
https://www.who.int/bloodproducts/publications/en/Infosheet_plasma_contract_fractionation.pdf

- Assess clinical needs
- Assess volumes wasted (anc
- Assessment by Plasma supp
  - ✓ local plasma quality as soon as
  - ✓ licensing of final products for lo
- Bring same quality managem of the country, in a coordinate
- Centralize blood donation tes
  donation testing and processing.9789240020825-eng
- Implement measures toward plasma products
- When blood components (wh have reach sufficient quality,
- Provide Donor information pr
  content/uploads/2019/04/IP-18-128-IPFA-donor-informa




# Next steps (2)
# Country bilateral and regional cooperation

- *"By combining plasma from countries whose national regulatory authorities have high maturity levels for blood regulation …, the combined plasma may be offered to the fractionator…"*
- *"Bringing the same Quality management program in all BE … in contiguous coordinated countries to increase the volume of plasma and the burden on reaching right Quality level."*

  increasing the chances of acceptance by the fractionator.

- Chapter 6. Country bilateral and regional cooperation

  *"Pooling of plasma from multiple countries within a region may be considered as a means to increase the cost-effectiveness of the fractionation, in agreement with the authorities of the countries and the fractionator"*

# Conclusion

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

Thank you for your attention

# Back-up Slides

# IPFA Mission and Vision

### Mission and Vision

The International Plasma and Fractionation Association (IPFA) is the international umbrella association promoting the interests and activities of its member organisations involved in the collection of human blood and plasma, and the manufacture and supply of essential medicines derived from human plasma.

### Essential medicines

The World Health Organization (WHO) has underlined the importance of Plasma Derived Medicinal Products (PDMPs) for global health care by including a number of PDMPs on the WHO Model List of Essential Medicines. These are identified as essential medicinal products and governments "should make sure that all people can access the medicines they need, when and where they need them. This is vital to countries' progress towards universal health coverage".

### Voluntary Non-Remunerated Blood Donation

IPFA and its member organisations strive to ensure greater global and national access to these lifesaving PDMPs for patients and healthcare providers based on a preference for and commitment to the "gift model" of blood and plasma donation without remuneration (Voluntary Non-Remunerated Blood Donation, VNRBD).

### Not for Profit

IPFA supports the "not-for-profit business model" where no financial gain flows from the donation to external or individual shareholders.

# 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**

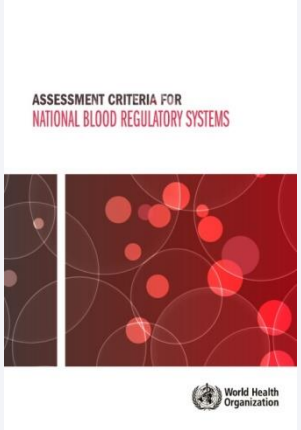
**FDA** e-CFR data is current as of November 24, 2015
Title 21 → Chapter I → Subchapter F → Part 606
Title 21: Food and Drugs

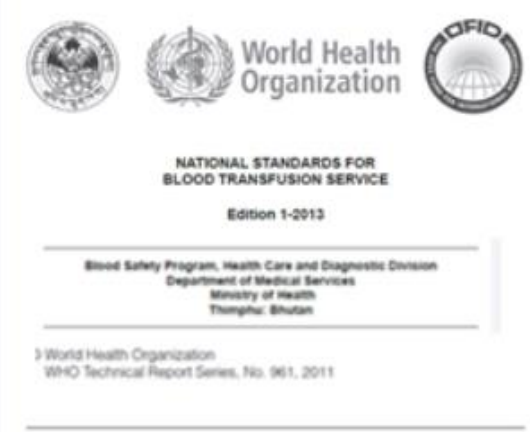
PART 606— **Current Good Manufacturing Practice for Blood and Blood Components**

## © 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






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<br>*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<br>*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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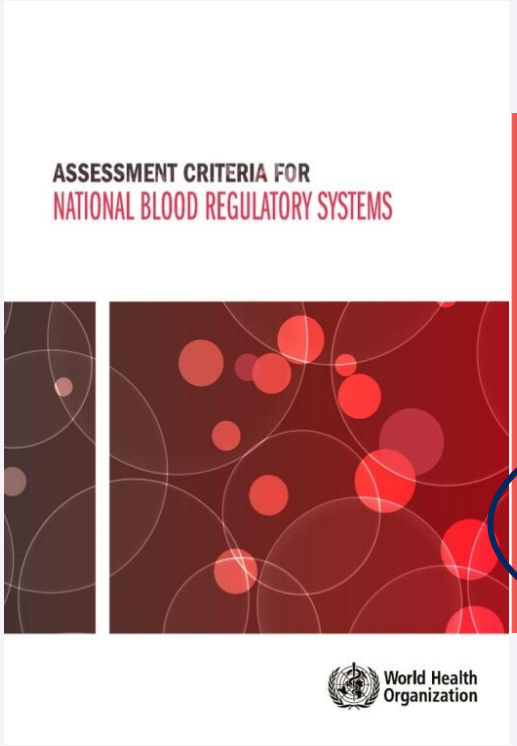
Title 21 → Chapter I → Subchapter F → Part 606
Title 21: Food and Drugs

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

# © World Health Organization 2012

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

| TABLE OF CONTENTS | | PAGE NO. |
|---|---|---|
| | Glossary | 6-9 |
| | Acronyms | 9-10 |
| Chapter 1 | Introduction | 12-13 |
| Chapter 2 | Code of ethics for blood donation and transfusion | 14-15 |
| Chapter 3 | The blood donor | 16-23 |
| Chapter 4 | Testing of donated blood | 24-25 |
| Chapter 5 | Blood and blood components | 26-27 |
| Chapter 6 | Clinical use of blood and blood component | 28-29 |
| Chapter 7 | Quality System | 30-39 |
| Chapter 8 | Waste management in blood transfusion service | 40-42 |
| Annexure | Process flow | Annex 1 |
| | Donor questionnaire and consent form | Annex 2 |
| | Donor deferral | Annex 3 |
| | Blood request form | Annex 4 |
| | Informed consent form for transfusion of blood & blood components | Annex 5 |
| | Blood transfusion report | Annex 6 |
| | Transfusion reaction form | Annex 7A |
| | Transfusion reaction investigation form | Annex 7B |
| | Organogram of Blood Transfusion Service | Annex 8 |
| | National Blood Transfusion Committee | Annex 9 |
| | National Blood Transfusion Service | Annex 10 |
| | National Blood Center | Annex 11 |
| | Regional Blood Center | Annex 12 |
| | Blood storage center | Annex 13 |
| | Standard tests at centers | Annex 14 |
| | Basic equipment at centers | Annex 15 |
| | Basic reagents at centers | Annex 16 |
| | Equipment record | Annex 17 |
| | Standard Operating Procedures | Annex 18 |
| | Equipment specifications | Annex 19 |
| | Reagents specifications | Annex 20 |



5 | National Standards for Blood Transfusion Service/2013

**FDA**

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

Title 21 → Chapter I → Subchapter F → Part 606



Browse Previous | Browse Next

Title 21: Food and Drugs

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

**Contents**

# 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<br>- after medical examination<br>- laboratory blood tests<br>- study of medical history<br>free from detectable agent of infection transmissible by plasma-derived medicinal products<br>recommandation of the CoE N° R (95)15 |
| | Records | records of<br>- donors and donations are kept, while maintening required degree of confidentiality regarding donor's identity,<br>- origin of each donation<br>- results of corresponding acceptance procedure<br>- laboratory test |
| | Laboratory | Anti-HIV-1<br>Anti-HIV-2<br>HBsAg<br>anti-HCV<br>test methods of suitable sensitiviy and specificity<br><br>If repeat-reactive result of any is found : the donation is not accepted |
| | Individual plasma units | practical techniques for preparation<br>plasma from plasmapheresis : Freezing at -20°C within 24h<br>plasma from Whole blood: Freezing at -20°C within 72h<br>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<br>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 |

**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.<br>The Annex applies also to the starting material [e.g. human plasma] for these products.<br>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.<br>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.<br>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.<br>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.<br>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.<br>Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures.<br>The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer.<br>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.<br>Responsibilities for traceability of the product should be defined.<br>- from the donor and the donation to the blood establishment<br>Data needed for full traceability must be stored for at least 30 years.<br>The blood establishments should notify the fractionating manufacturer of any event which may affect the quality or safety of the product including events<br>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.<br>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<br>All processing steps [e.g. qualification and/or operation, sampling, labelling, freezing] should be defined in written procedures.<br>Freezing should therefore be performed as soon as possible after collection.<br>The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded.<br>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<br>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 intended for 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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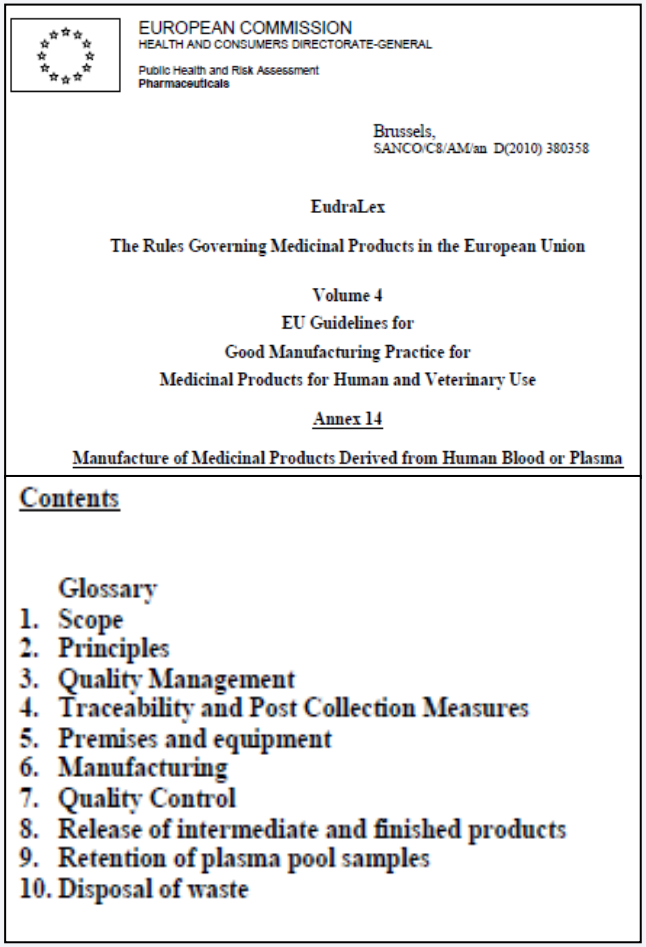

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Public Health and Risk Assessment
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Medicinal Products for Human and Veterinary Use

Annex 14

Manufacture of Medicinal Products Derived from Human Blood or Plasma

Contents

# 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.

# Present status of Contract manufacturing

## Examples of Current and Past experiences

- **Historically**, national NfP fractionators: Australia at first, Denmark, Finland, France, Italy, South Africa, Spain, the Netherlands, China up to recently for Albumin…
- **Toll manufacturing**: Morocco, Algeria; Tunisia; sub-Saharan Africa neighboring South Africa; Hungary to come, Thailand before local plant; Canada…
- **In advance of tech transfer**: Brazil, Vietnam, Malaysia, Poland, Egypt…

"*Five of the six commercial fractionators are engaged in this activity*"

Farrugia; Biologicals 46 (2017) 159-167

# 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

# At EMA level: Plasma Master File

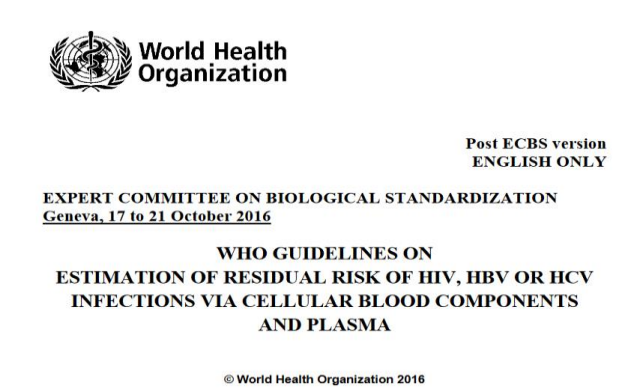
## PMF : Certification Principe

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

# Epidemiological Data



World Health Organization

Post ECBS version
ENGLISH ONLY

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2016

WHO GUIDELINES ON
ESTIMATION OF RESIDUAL RISK OF HIV, HBV OR HCV
INFECTIONS VIA CELLULAR BLOOD COMPONENTS
AND PLASMA



WHO and EMA guidelines on epidemiological data

Requirements to report rates for HCV/HBV/HIV markers and provide statistical analysis

Data to be reported at the level of centres (fixed address), not always relevant/possible for recovered plasma

Alert limits should be settled ; First time and Repeat Tested Donations

CAPAs to be initiated if alert limits are reached

Exchanges with plasma suppliers, root cause analysis

Slide Regulation

## Pros & cons – Recovered and Source

Regulatory constraints to register recovered collection sites:

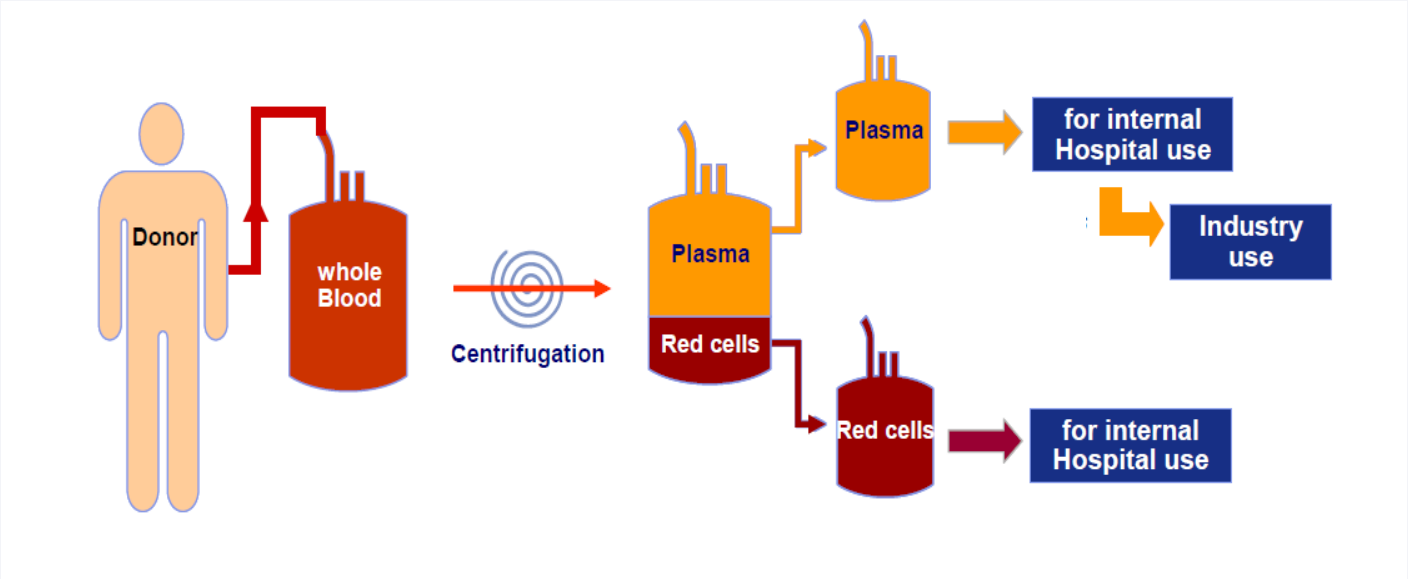
- regular inspections and availability of resources in inspectors
- epi data follow-up at level of centres
- resources in auditors for small centres

In practice, easier to qualify and register source plasma collection centres

But

- Recovered plasma: usually higher rates in key proteins especially in IgG
- Price of recovered plasma is usually lower
- Additional safety for recovered plasma which benefits from the haemovigilance system on recipients of labile products
- Recovered generally associated to VNRD / Not-for Profit Blood Establishments

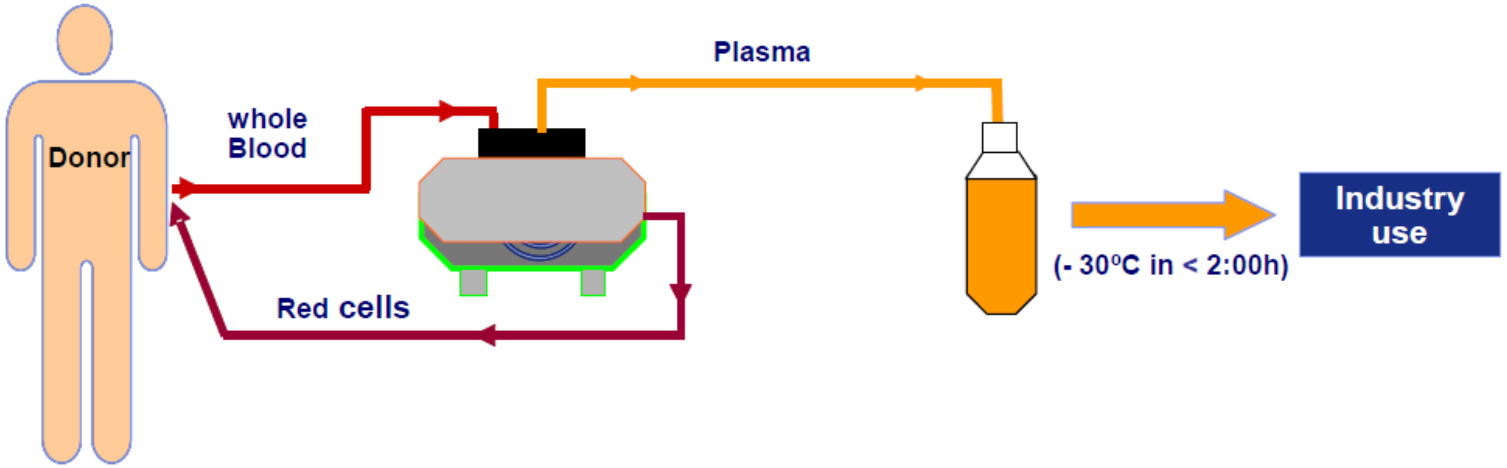
# PLASMA COLLECTION FROM WHOLE BLOOD (MAINLY RECOVERED PLASMA)




## Usual scheme:

- Collection in multiple small-medium collection centres (few kL per year) and multiple mobile units
- Separation and freezing in processing centres

# COLLECTION OF SOURCE PLASMA




Red cells are immediately re-injected into the donor

Usual scheme:

One collection/processing centre (can collect 30-70 kL per year)