# Benefits of Plasma Quality Programs in Blood Establishments

**Dr. Françoise Rossi,**

*Director of Scientific and Regulatory Affairs*

**International Plasma Fractionation Association**

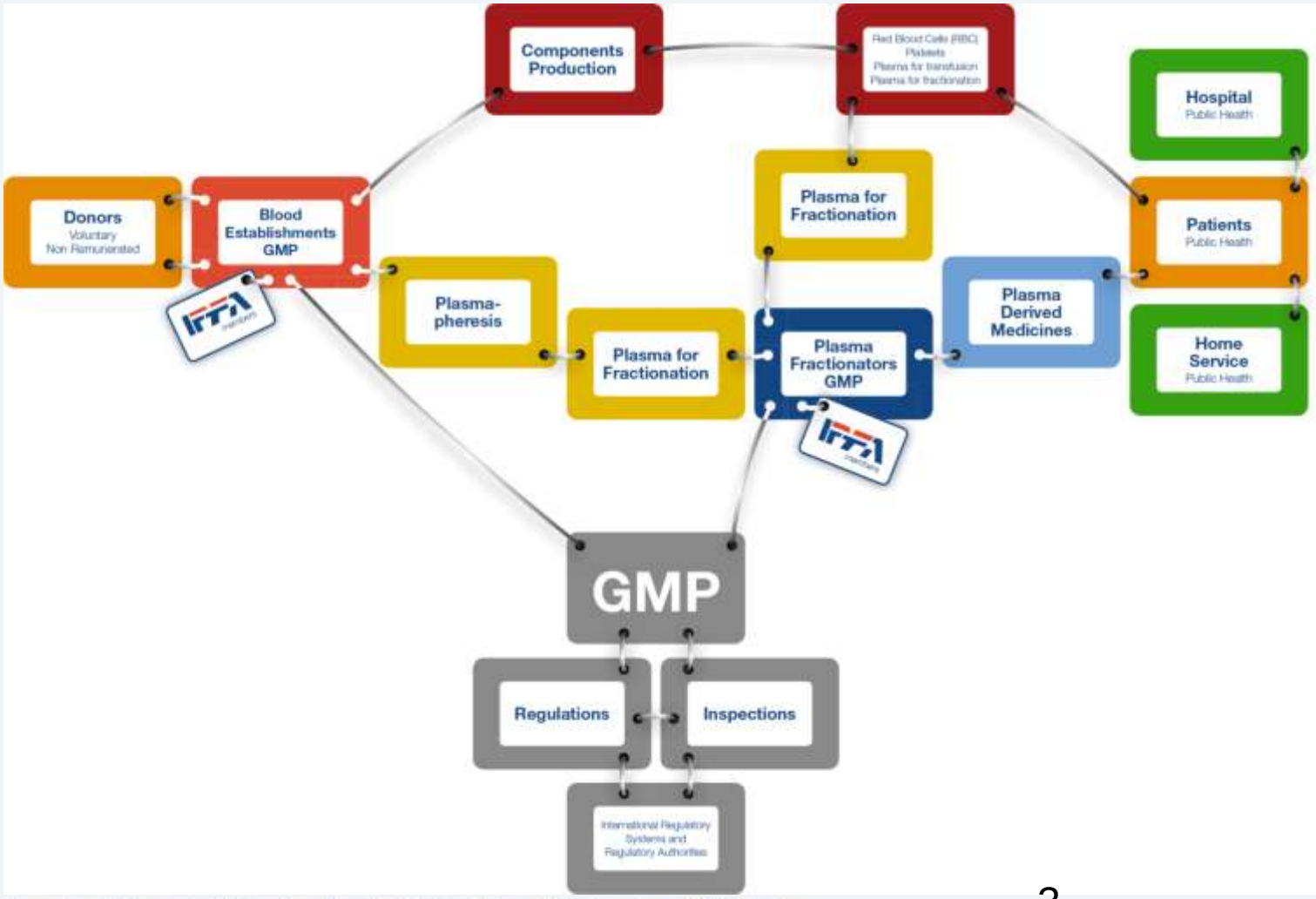
IPFA Asia Pacific Workshop on Plasma Quality *and* Supply
Taipei Medical University, Taiwan,
8-9TH March, 2016

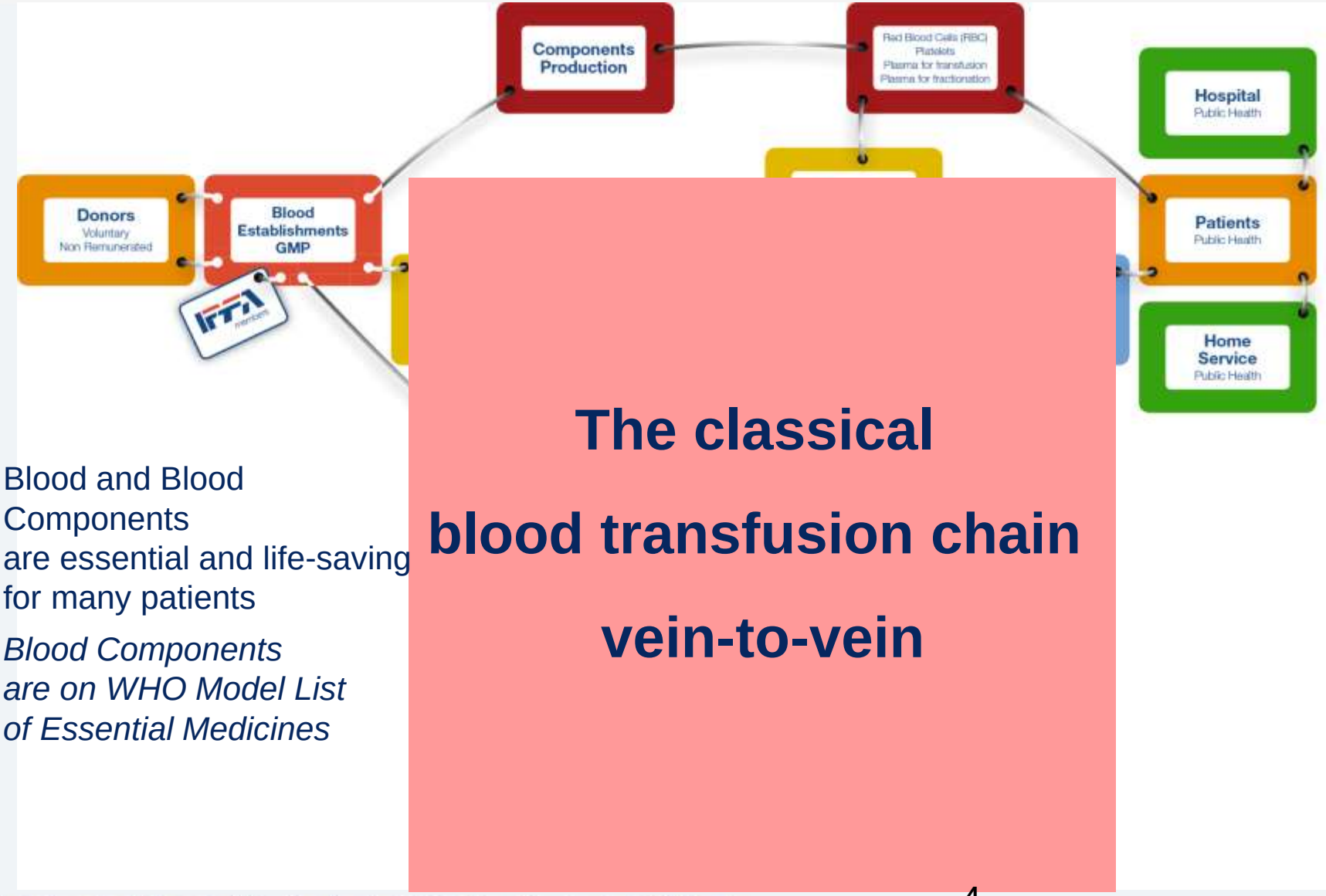
# IPFA Objectives and Focus

- **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

# Plasma Chain

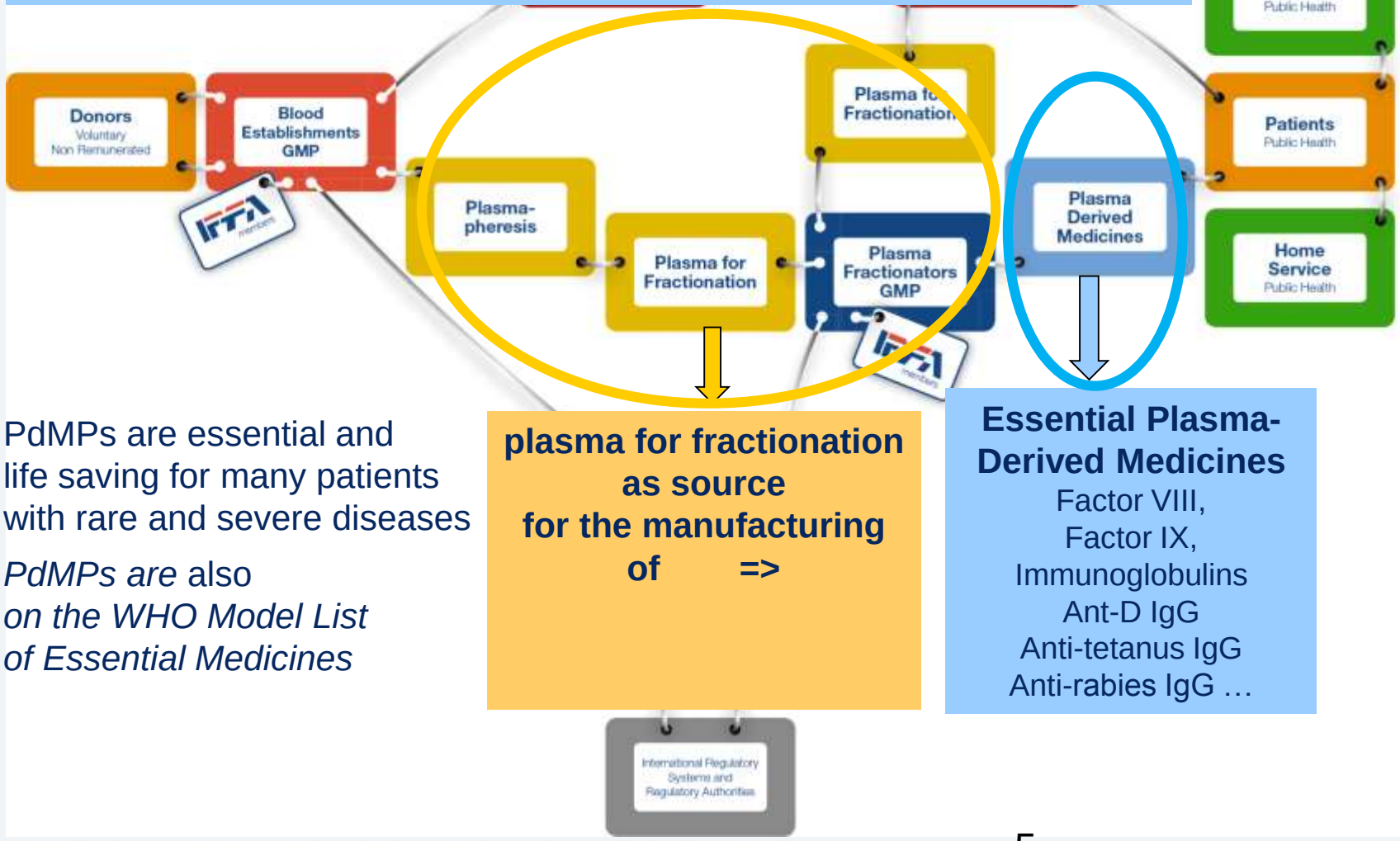





- Blood and Blood Components are essential and life-saving for many patients
- *Blood Components are on WHO Model List of Essential Medicines*

**The classical blood transfusion chain vein-to-vein**

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



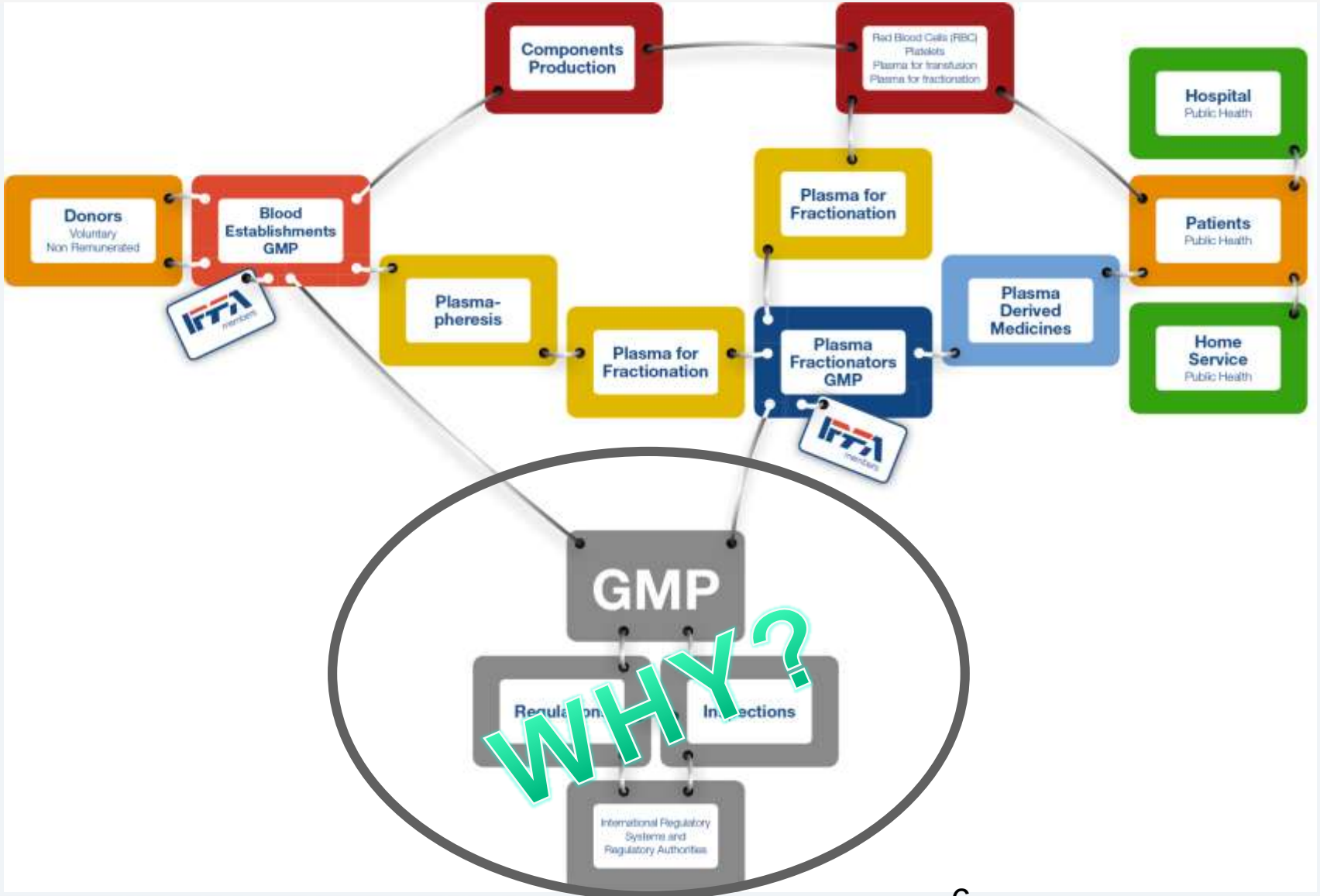

- PdMPs are essential and life saving for many patients with rare and severe diseases
- *PdMPs are* also *on the WHO Model List of Essential Medicines*

**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 …

# IPFA, embedded in community

international plasma fractionation association



# Quality of Plasma PfF?

- 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 manufacturing, 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**.

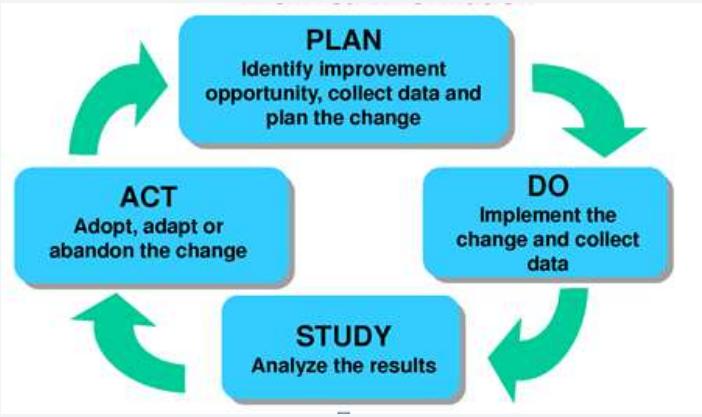
ISO 8402-1986 standard defines quality as
"*the totality of **features and characteristics of a product …***
*that bears its ability **to satisfy stated or implied needs**.*"

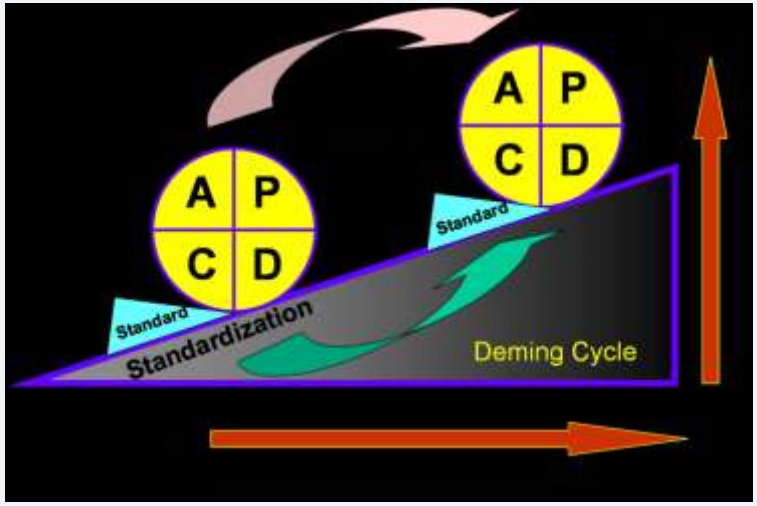
# Quality, a virtuous Process

***Define, Measure, Analyse, Improve and Control***

to support Continual Improvement

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



# Quality Reference Documents




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

Annex 4

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

Annex 4 WHO guidelines on good manufacturing practices ...

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**

Manufacture of Products derived from Human Blood or Human Plasma

**Human Plasma for Fractionation**

Plasma Humanum Ad Separationem

**Eur. Pharmacopeia Monograph 01/2014:0853**

Human Plasma for Fractionation Plasma humanum ...

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

Title 21 → Chapter I → Subchapter F → Part 606

Title 21: Food and Drugs

21 CFR Part 606 - CURRENT GOOD MANUFACTURING

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

# Quality




## Quality management; Develop a culture of quality

Strict and consistent commitment to certain standards that achieve uniformity of a product to satisfy specific customer (patients) 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

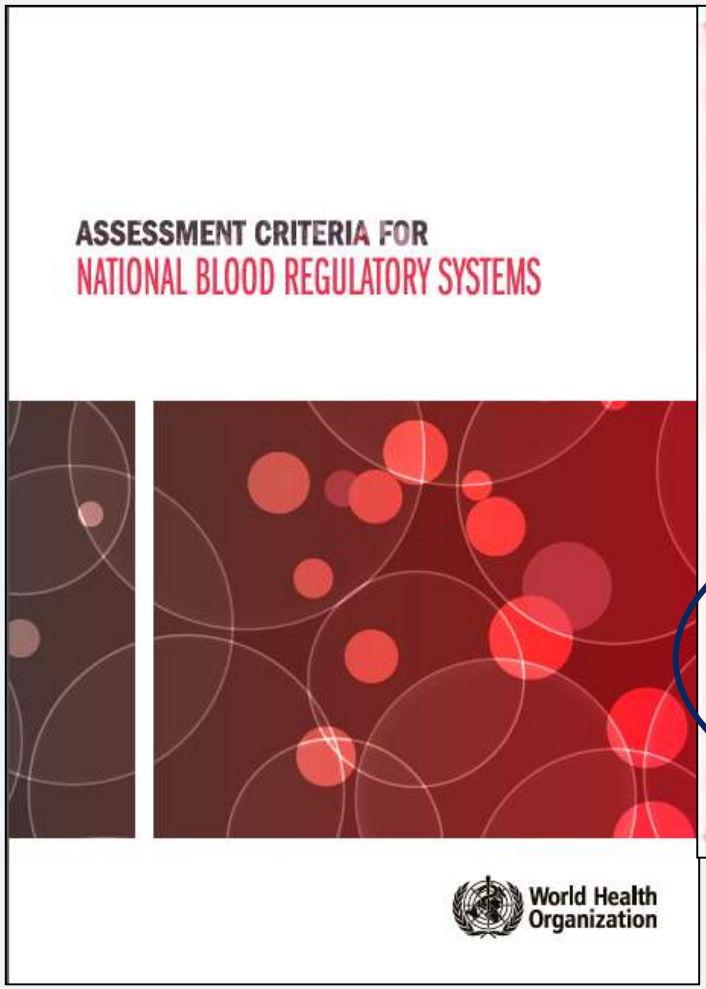
# Political background

## Developing a national blood programme

*Requires a serious,* ***sustainable commitment of resources*** *(capital and operating budgets)*
*Senior management have the* ***responsibility*** *of securing sufficient resources for the work to be done.*
*This entails developing a* ***strategy****,* ***estimating budget*** *requirements, understanding the requirements of funding agencies and developing proposals accordingly*
*It is likely that a mix of fund providers, e.g. government plus external agencies, will be necessary, and that there will be a mix of cost recovery plus external subsidy*
***Development, execution and transparent reporting of costing*** *are necessary to* ***demonstrate to funders that spending is appropriately managed*** *and will* ***help strengthen the case for funding support***

Governance and funding of a national blood donor programme: Dr Yasmin Ayob

# © World Health Organization 2012




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.

# In the region

http://www.pmda.go.jp/files/000152975.pdf#page=1

## GMPs for Blood products

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

**PFSB/ELD (Yakushoku-shinsa) Notification No. 0330006 / PFSB/CND (Yakushoku-kanma) Notification No. 0330005 / PFSB (Yakushoku) Notification No.0330008 March 30, 2005**

**The "GMP" for drugs**, quasi-drugs, and medical devices in accordance with the Pharmaceutical Affairs Law (Law No.145 of 1960) as **amended by the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services** Control Law (Law No.96 of 2002) has been notified to prefectural governors under PFSB (Yakushoku) Notification No.0330008 by the Director-General of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 30, 2005, "Establishment and Revision/Abolishment of Ministerial Ordinance and Ministerial Notification **on the Good Manufacturing Practice and Quality Management System (GMP/QMS)** of Drugs, Medical Devices, etc., Pursuant to the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Control Law."

# In the region

## GMPs for Blood products

Australian Government
Department of Health
Therapeutic Goods Administration

Revised code of GMP for human blood and tissues - TGA

**Manufacturers of blood, blood components,** tissues and cellular therapy products, including biologicals, **must meet the requirements of the Manufacturing Principles** (unless exempt).

The Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2013 references the **Australian Code of Good Manufacturing Practice for human blood and blood components**, human tissues and human cellular therapy products 2013 (2013 Code of GMP). These requirements commence from 31 May 2013.

# In the region

## GMPs for Blood products

MINISTRY OF FOOD AND DRUG SAFETY Korean

MFDS - Ministry Of Food And Drug Safety - DRUG > Main Task

### Pharmaceutical safety control

- Development of policies and establishment of comprehensive plans on the pharmaceutical safety control
- E stablishment and revision of the laws and notifications on drugs
- Provision of information on the proper use of pharmaceuticals
- Post-marketing safety control
- Re-evaluation of the safety and efficacy of human placenta based pharmaceuticals
- Introduction of Plasma Master File (PMF) system for plasma derivatives reinforcement of a management standard for imported blood plasma
- E stablishment of guidelines on an excellent management standard for human tissues (GTP) and management of tissue bank

# In the region

**GMPs for Blood products**

Challenges of Centralization of Blood Services in Indonesia

**Indonesian Red Cross 2014/LSIF/PD/018**

**Policy Dialogue and Workshop on Attaining a Safe and Sustainable Blood Supply Chain, Manila, Philippines, 30 Sept – 1 Oct 2014**

APEC CHINA 2014

- **Future Direction**
  - The IRC BC will be strengthened as the National Blood Center
  - Standardized quality of blood and blood products
    - Implementation of GMP on Blood Establishment
    - Regionalizing blood testing and processing in Java, Bali and some part of Sumatera island → >70% of Total Donation
    - Strengthening guidance, inspection and audit involving Provincial Blood Centers, Local Health Authority and Regional NADFC

APEC Asia-Pacific Economic Cooperation

# In the region

**Biregional WHO Workshop on Blood Donor Management**
**Ha Noi, Viet Nam,** 14–16 June 2010

***Bi Regional*** WHO Workshop on Blood Donor Management Ha Noi Viet Nam 14–16 June 2010

**2.1.3 & 2.1.4 Country reports:**

**South-East Asia Region**: Bangladesh; DPR Korea; Indonesia; Myanmar; Nepal; Sri Lanka

**Western Pacific Region**: Cambodia; China; Fiji; Lao PDR; Malaysia; Mongolia; Papua; New Guinea; The Philippines; Republic of Korea; Singapore; Viet Nam

**3. Recommendations**

3.1 For Member States

3.2 For WHO

# In the region

## 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

Africa Society for Blood Transfusion Standards Guidance Document

# In other regions

**African Accreditations by Africa Society for Blood Transfusion AfSBT**

Step-Wise Accreditation Programme strives to improve the quality and safety of Blood Products

**Compliance with the standards is set at three levels – Requiring progressively improved quality and safety**

- **Step 1**: Certification: minimum (basic) quality and operational requirements
- **Step 2**: Certification: intermediate quality and operational requirements
- **Step 3**: Accreditation at international standard

**Four main documents**

- AfSBT Step-Wise Accreditation Standards
- AfSBT Standards Guidance Document
- Chart of Evidence of Compliance for the Standards
- Tool: Assessment of Preparedness for Accreditation




From Rob Wilkinson: Accreditation Manager

# 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*

PIC Scheme — Pharmaceutical Inspection Cooperation Scheme

**Accessions Dates**

| | |
|---|---|
| Singapore: | Jan 2000 |
| Malaysia: | Jan 2002 |
| Indonesia: | Jan 2012 |
| Taiwan: | Jan 2013 |
| New Zeeland: | Jan 2013 |
| Taipei TFDA: | Jan 2013 |
| Hong-Kong SAR/PPB: | Jan 2016 |

**Applicants**

Japan PMDA, MHLW and Prefectures
Korea MFDS
Philippines PFDA
CFDA

**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".

# Some PIC/S recommendation & Guideline Documents

- ✓ 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 of Medicinal Products in Healthcare Establishments.
- ✓ Validation (master plan, IQ/OQ, process, cleaning).
- ✓ Validation of Aseptic Processes.
- ✓ Inspection of Isolator Technology.
- ✓ Quality Systems for Inspectorates.
- ✓ Sterility Testing.
- ✓ Validation of Computerised Systems.

http://slideplayer.com/slide/5865015/#

# 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

Annex 4 WHO guidelines on good manufacturing practices ...

**EU**

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 Products derived from Human Blood or Human Plasma

**FDA**

21 CFR Part 606 - CURRENT GOOD MANUFACTURING

# 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

## EU

**HUMAN PLASMA FOR FRACTIONATION**
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>plasma-<br>uired<br>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 poo | 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 |

Human Plasma for Fractionation Plasma humanum ...

## FDA

[redacted]

# General Quality Points For Blood Products

- Donor screening
- Validation of SOP's
- Documentation
- Training of personnel
- Virological screenings
- Traceability
- Maintenance of all equipment
- …



# Why valuing Plasma PfF?

- Plasma represents around 30% of the cost of PdMPs
- Plenty of plasma is thrown away, let's fractionate it!
- The bill for importing PdMPs is costly and increasing;
  IVIG usage, 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

# How to value the Plasma PfF?

Appendix 5

**Technical points to consider in establishing plasma specifications criteria and obligations between blood establishment and plasma fractionator**

The purpose of the contract is to have a "legally binding" document between the plasma supplier and the fractionator.

The following is an example of the quality control and documentation required by a plasma fractionator to acquire plasma for fractionation from a blood establishment. It is not meant to represent the only possible w to define plasma specifications criteria and obligations between a blood establishment and a plasma fractionator. Depending upon the prevalence of blood-borne diseases in a country, additional safety requirements on donor selection and testing should be considered.

## General specifications

### Donors

Reference should be made to local regulations pertaining to the selection, eligibility, and exclusion criteria for donors of blood or plasma used for the manufacture of blood components and plasma derivatives. Newly introduced criteria may be spelled out (such as travel restrictions rel to vCJD).

### Blood establishments

Reference should be made to the official legislation of blood es in the country of origin and to relevant legislation relatin fractionation.

### Donation process and plasma unit specifications

The contract should cover the following aspects of the donation process plasma unit specifications.

- *Collection process of the blood/plasma units:*
  - containers, collection sets and anticoagulants with relevant registration;
  - duration of the whole blood collection (e.g. less than 15 minutes (*1*) for recovered plasma);
  - guarantee that blood will be mixed with the anticoagulant as soon as the collection starts, by regular manual shaking or using a validated automated method (*1*);

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**Appendix 5**

Annex 4

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

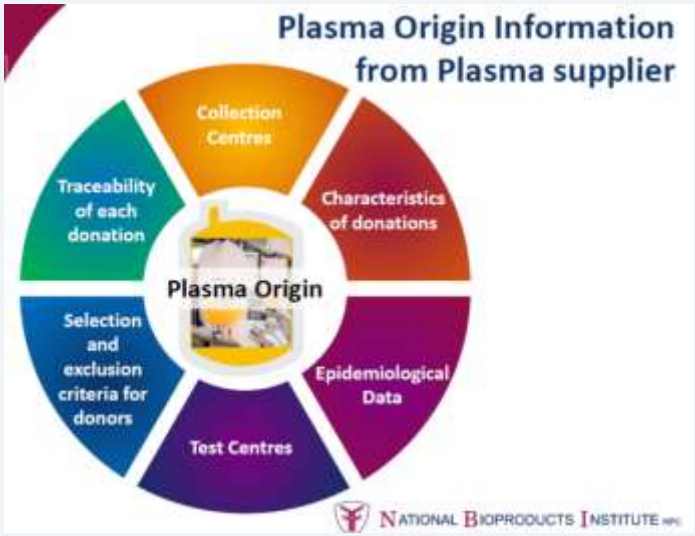
Annex 4 Supplementary guidelines on good manufacturing **Appendix 5 : Page 259**

The purpose of the contract is to have a **"legally binding" document between the plasma supplier and the fractionator**.

... **example** of the **quality control and documentation required by a plasma fractionator** to acquire plasma for fractionation **from a Blood Establishment**

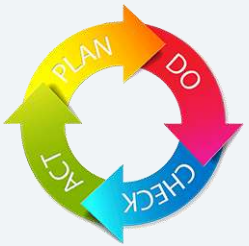
# Critical parameters for insuring quality of Plasma PfF

**= 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) (see haemovigilance and pharmacovigilance)

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

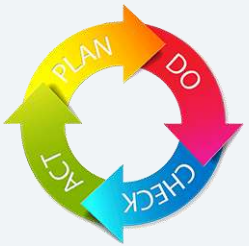



**Written Agreements and Audits, an opportunity to**

Develop a culture of quality,



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




**Written Agreements and Audits, 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**

# How to value Plasma PfF?

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

# 1. Vending of Plasma to Fractionators

**The foreseen impact of vending one's plasma to a fractionator 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

## Why perform contract manufacturing?

- Avoid wasting quality PfF that is highly valuable
- The bill for importing plasma products is often costly and increasing (IgIV, etc…)
- Availability of the 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
- Optimize the diversity of products. The more products got from a litre of plasma, the highest is the cost saving

# 2. Contract Fractionation

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

**Appendix 4**
**Contract plasma fractionation programme**

## When perform a contract manufacturing?

Annex 4 Supplementary guidelines on good manufacturing
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- **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 40 000 litres**)
- Nevertheless, this volume must not be to small because the fractionator has to spend a significant amount of resources in auditing the centres
- It will **allow the country to get the knowledge** of plasma fractionation process before possibly building its own plant for fractionating domestic plasma

# 3. Technology Transfer to Custom Fractionation

## When to plan technology transfer?

- Custom fractionation is an opportunity
  for developing countries fully dependent on importations, provided there is a political will for changes to the local transfusion system
- Where self-sufficiency is at stake
  IgIV are driving the medical standard of care of a lot of pathologies
  from immunodeficiencies to auto-immune diseases
- Few countries have secured a domestic fractionation plant
  for self-sufficiency
- Favourable for countries with more than 30 M inhabitants

# 3. … to Custom Fractionation

**The minimal Capacity and manufacturing Batch Size are a key regarding production costs**

- Plants with a capacity of 150 000 **or** 300 000 litres have similar costs
- Fractionation is a mainly fixed-cost industry, so the actual output must be close to the full capacity in order to be profitable
- Manufacturing batch size regarding production costs ≥ 3 000 litres

=> A plant is profitable starting at an annual volume of 300 000 litres (around 1 500 000 donations)

# Developing a national blood programme

- IPFA supporting strong collaboration between suppliers of plasma (blood transfusion organizations) and fractionators

Vietnam to have first plasma fractionation plant - Saigon Times

## Vietnam to hav… …lasma fractionation plant

Quoc Hung

Friday, Nov 20,2015 …

By Quoc Hung - The Saigon Times Daily




Nguyen Dang Thong (L) of An Phat Pharmaceutical and Medical Equipment Joint Stock Company gets an investment certificate from the Saigon Hi-Tech Park (SHTP) authority's head Le Hoai Quoc on November 19 - PHOTO: QUOC HUNG

**HCMC - An Phat Pharmaceutical and Medical Equipment Joint Stock Company on November 19 got an investment certificate to build what will become the country's first plasma fractionation factory at Saigon Hi-Tech Park (SHTP).**

# Benefits of developing a national blood programme

## The consequence observed in countries which have started plasma fractionation is a general improvement of transfusion safety

I**mproved efficiency in the transfusion system network**:
regrouping of collection centers, creation of centralized “state of the art” technical platforms for the qualification, creation of hubs for plasma freezing,…

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

**Development of the look-back information system**

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

# Conclusion
# Improving Quality of Blood Establishments

**High positive impact on public health**

Improving Quality of Blood Establishments

=> Improves Quality and Safety of Blood and Plasma
=> Allows less dependency on importations
=> Enhances Self-Sufficiency
=> Increases Availability of Blood and PdMPs for the Patients

- Drastic upgraded transfusion safety and viral epidemiology management by custom fractionation
- With a high positive impact on Public Health

# Thanks

For your attention

To the Colleagues of Plasma Regulatory and Quality Teams from IPFA Organisation Members

# Back-up Slides

# General Quality Points For Blood Products

Annex 4 WHO guidelines on good manufacturing practices...

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

Annex 4

## WHO guidelines on good manufacturing practices for blood establishments


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10. Contract manufacturing, analysis and services
11. Authors and acknowledgements
12. References

# General Quality Points For Blood Products



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**

Manufacture of Products derived from Human Blood or Human Plasma

**Manufacture of medicinal products derived from human blood or plasma**

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10. **Disposal of waste**

# General Quality Points For Blood Products

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**HUMAN PLASMA FOR FRACTIONATION**

Plasma humanum ad separationem

Human Plasma for Fractionation Plasma humanum ...



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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 immunized donors. Recommendations for such immunization are formulated by the World Health Organization (*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),
3. hepatitis B surface antigen (HBsAg),
4. antibodies against hepatitis C virus (anti-HCV).

Pending complete harmonization of the laboratory tests to be carried out, the competent authority may require that a test for alanine aminotransferase (ALT) also be carried out.

The test methods used are of suitable sensitivity and specificity and comply with the regulations in force. If a repeat-reactive result is found in any of these tests, the donation is not accepted.

*INDIVIDUAL PLASMA UNITS*

The plasma is prepared by a method that removes cells and cell debris as completely as possible. Whether prepared from whole blood or by plasmapheresis, the plasma is separated from the cells by a method designed to prevent 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.*

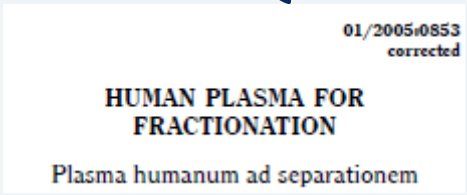
*The total protein content of a unit of plasma depends on the serum protein content of the donor and the degree of dilution inherent in the donation procedure. When plasma is obtained from a suitable donor and using the intended proportion of anticoagulant solution, a total protein content complying 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 round-bottomed centrifuge tube add 2 ml of a 75 g/l solution of *sodium molybdate R* and 2 ml of a mixture of 1 volume of *nitrogen-free sulphuric acid R* and 30 volumes of *water R*. Shake, centrifuge for 5 min, decant the supernatant liquid and allow the inverted tube to drain on filter paper. Determine the nitrogen in the residue by the method of sulphuric acid digestion (*2.5.9*) and calculate the protein content by multiplying the quantity of nitrogen by 6.25. The total protein content is not less than 50 g/l.

**Factor VIII.** Carry out the test using a pool of not fewer than 10 units. Thaw the samples to be examined, if necessary, at 37 °C. Carry out the assay of factor VIII (*2.7.4*), using a reference plasma calibrated against the International Standard for blood coagulation factor VIII in plasma. The activity is not less than 0.7 IU/ml.

# General Quality Points For Blood Products

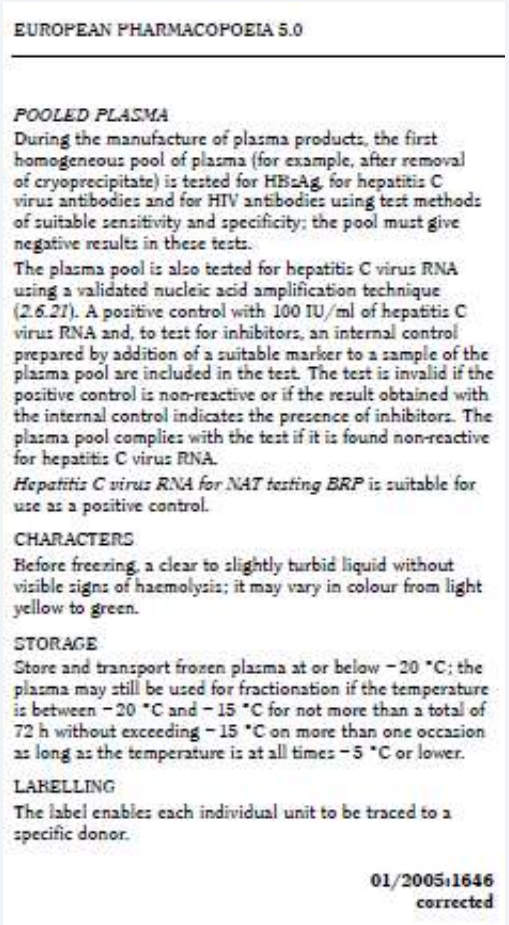


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**HUMAN PLASMA FOR FRACTIONATION**

Plasma humanum ad separationem

Manufacture of Products derived from Human Blood or Human Plasma



EUROPEAN PHARMACOPOEIA 5.0

*POOLED PLASMA*

During the manufacture of plasma products, the first homogeneous pool of plasma (for example, after removal of cryoprecipitate) is tested for HBsAg, for hepatitis C virus antibodies and for HIV antibodies using test methods of suitable sensitivity and specificity; the pool must give negative results in these tests.

The plasma pool is also tested for hepatitis C virus RNA using a validated nucleic acid amplification technique (*2.6.21*). A positive control with 100 IU/ml of hepatitis C virus RNA and, to test for inhibitors, an internal control prepared by addition of a suitable marker to a sample of the plasma pool are included in the test. The test is invalid if the positive control is non-reactive or if the result obtained with the internal control indicates the presence of inhibitors. The plasma pool complies with the test if it is found non-reactive for hepatitis C virus RNA.

*Hepatitis C virus RNA for NAT testing BRP* is suitable for use as a positive control.

CHARACTERS

Before freezing, a clear to slightly turbid liquid without visible signs of haemolysis; it may vary in colour from light yellow to green.

STORAGE

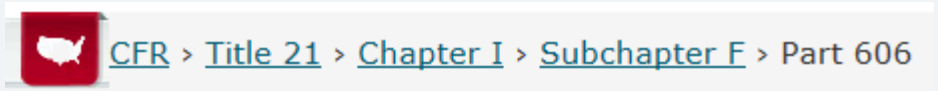
Store and transport frozen plasma at or below −20 °C; the plasma may still be used for fractionation if the temperature is between −20 °C and −15 °C for not more than a total of 72 h without exceeding −15 °C on more than one occasion as long as the temperature is at all times −5 °C or lower.

LABELLING

The label enables each individual unit to be traced to a specific donor.

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# General Quality Points For Blood Products




**21 CFR Part 606 - CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS**

✓ There are 2 Updates appearing in the Federal Register for *21 CFR Part 606*. View below or at eCFR (GPOAccess)

CFR Updates Authorities (U.S. Code) Rulemaking

SUBPART A — General Provisions (§§ 606.3 - 606.3)

SUBPART B — Organization and Personnel (§§ 606.20 - 606.20)

SUBPART C — Plant and Facilities (§§ 606.40 - 606.40)

SUBPART D — Equipment (§§ 606.60 - 606.65)

SUBPART E — [Reserved]

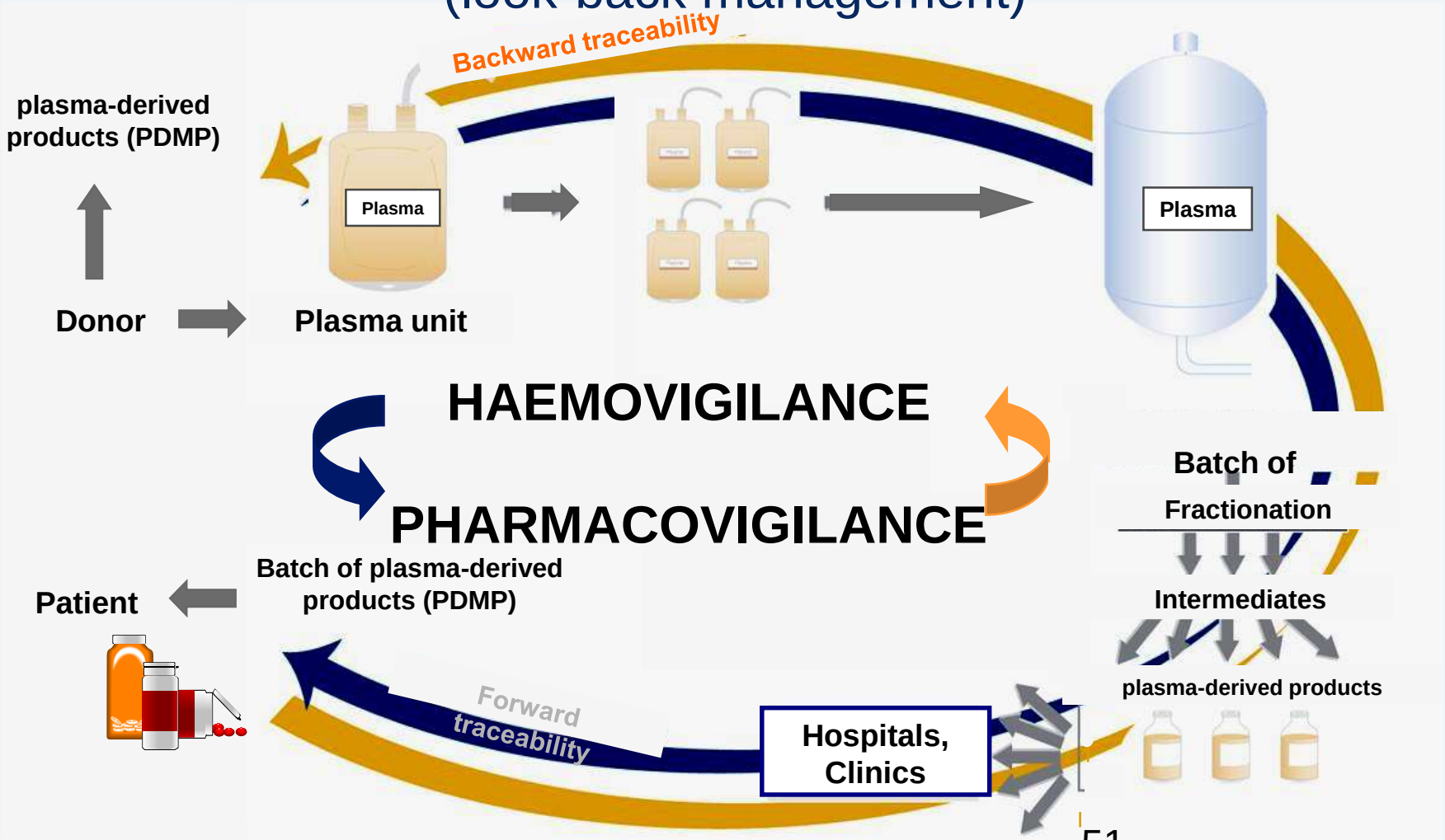
SUBPART F — Production and Process Controls (§§ 606.100 - 606.110)

SUBPART G — Additional Labeling Standards for Blood and Blood Components (§§ 606.120 - 606.122)

SUBPART H — Laboratory Controls (§§ 606.140 - 606.151)

SUBPART I — Records and Reports (§§ 606.160 - 606.171)

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



# 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