Benefits of Plasma Quality Programs in Blood Establishments

Dr. Françoise Rossi,

*Director of Scientific and Regulatory Affairs*

International Plasma Fractionation Association
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
      o Safe, robust supply of plasma
      o Avoid wasting of Recovered plasma
      o Increase plasmapheresis plasma in developed countries
      o 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 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*
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.
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

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
Bridging the interests of Donors - Collection Centers - Fractionation Centers - Patients
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**.
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

GMPs for Blood products

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

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

In the region

**GMPs for Blood products**

- Development of policies and establishment of comprehensive plans on the pharmaceutical safety control
- Establishment 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
- Establishment of guidelines on an excellent management standard for human tissues (GTP) and management of tissue bank
Challenges of Centralization of Blood Services in Indonesia

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
In the region

Biregional 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
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.
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/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”.

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

Applicants
- Japan PMDA, MHLW and Prefectures
- Korea MFDS
- Philippines PFDA
- CFDA

PIC Scheme
Pharmaceutical Inspection Cooperation Scheme
Some PIC/S recommendation & Guideline Documents

- PIC/S GMP Guide (similar to EU GMP Guide).
- 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

Annex 4 WHO guidelines on good manufacturing practices...
General Quality Points For Blood Products

**WHO**

**National Standards for Blood Transfusion Service**

**TABLE OF CONTENTS**

- Glossary
- Acronyms
- Chapter 1: Introduction
- Chapter 2: Code of ethics for blood donation and transfusion
- Chapter 3: The blood donor
- Chapter 4: Testing of donated blood
- Chapter 5: Blood and blood components
- Chapter 6: Clinical use of blood and blood component
- Chapter 7: Quality System
- Chapter 8: Waste management in blood transfusion service

**Annexure**

- Process flow
- Donor questionnaire and consent form
- Donor deferral
- Blood request form
- Informed consent form for transfusion of blood & blood components
- Blood transfusion report
- Transfusion reaction form
- Transfusion reaction investigation form
- Organogram of Blood Transfusion Service
- National Blood Transfusion Committee
- National Blood Transfusion Service
- National Blood Center
- Regional Blood Center
- Blood storage center
- Basic tests at centers
- Basic reagents at centers
- Equipment record
- Standard Operating Procedures
- Equipment specifications
- Reagents specifications

**EU**

**Human Plasma for Fractionation Plasmaplanum humanum**

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

**Production**

Donors
- Only carefully selected healthy donors
- After medical examination
- Laboratory blood tests

Human Plasma for Fractionation Plasmaplanum humanum...

degrees of confidence regarding donors' identity are required:
- 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 sensitivity and specificity

Repeat reactive result of any is found: the donation is not accepted.

- 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

**Individual plasma units**

- Stored in conditions designed to maintain temperature ≤ -20°C with exceptions no more than 72h at not above -35°C; never at ≤ -5°C

**Storage and Transport**

- 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

**FDA**

**National Standards for Blood Transfusion Service 2013**
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
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

When perform a 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 40,000 litres](#))
- Nevertheless, this volume must not be too 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.
Benefits of developing a national blood programme

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

**Improved 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...
General Quality Points For Blood Products

Manufacture of Products derived from Human Blood or Human Plasma

Manufacture of medicinal products derived from human blood or plasma

Contents

- Glossary
- Scope
- Principles
- Quality Management
- Traceability and Post Collection Measures
- Premises and equipment
- Manufacturing
- Quality Control
- Release of intermediate and finished products
- Retention of plasma pool samples
- Disposal of waste
General Quality Points For Blood Products

**Human Plasma for Fractionation Plasma humanum**...
General Quality Points For Blood Products

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.
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)

<table>
<thead>
<tr>
<th>CFR</th>
<th>Updates</th>
<th>Authorities (U.S. Code)</th>
<th>Rulemaking</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBPART A — General Provisions (§§ 606.3 - 606.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART B — Organization and Personnel (§§ 606.20 - 606.20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART C — Plant and Facilities (§§ 606.40 - 606.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART D — Equipment (§§ 606.60 - 606.65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART E — [Reserved]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART F — Production and Process Controls (§§ 606.100 - 606.110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART G — Additional Labeling Standards for Blood and Blood Components (§§ 606.120 - 606.122)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART H — Laboratory Controls (§§ 606.140 - 606.151)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUBPART I — Records and Reports (§§ 606.160 - 606.171)</td>
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Traceability of plasma units and blood monitoring system (look-back management)


HAEMOVIGILANCE

PHARMACOVIGILANCE

IPFA, embedded in community

International plasma fractionation association

Bridging the interests of: Donors - Collection Centers - Fractionation Centers - Patients
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