WHO Requirements for Plasma for Fractionation for Contract and Domestic Fractionation Programmes

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Definitions

• “Plasma for transfusion”
  = “Clinical plasma” (directly used in hospitals)
  = “Therapeutic plasma”

• “Plasma for fractionation”
  = “Plasma for further manufacture” into purified therapeutic fractionated industrial protein products (immunoglobulins; Coagulation factors; albumin, etc.)

• “Recovered plasma” = plasma separated from whole blood donation

• “Source” plasma = apheresis plasma
Why WHO requirements for plasma for fractionation?

• Quality, safety, and consistency of fractionated plasma products

• Limit wastage of recovered plasma and improve the supply of fractionated plasma products (Essential medicines)

• Contribute to improved national blood collection systems and regulation systems
Initial statements – Initial Q&A
Can the same donors donating plasma for transfusion also donate plasma for fractionation?

The answer is: Yes!
Are the overall GMP requirements for plasma for transfusion and plasma for fractionation the same?

The answer is:

Yes!

(plasma for transfusion is on the WHO Model List of Essential Medicines)
Are the specifications for plasma for fractionation more stringent than for plasma for transfusion?

The answer is: No! (not necessarily)

Example: Plasma not frozen within 24 hrs can be used for producing IVIG and albumin.
Have GMP requirements of plasma for fractionation historically pushed for more stringent GMP requirements for plasma for transfusion?

The answer is: Yes!
Why, historically, more stringent GMP requirements for plasma for fractionation have been needed and implemented?

Before introduction of regulations, blood establishments were tempted to put more emphasis on the quality of labile blood components than that of plasma for fractionation.
Why, historically, more stringent GMP requirements for plasma for fractionation have been needed and implemented?

At least 3 reasons
Scale of production of industrial plasma products amplifies safety issue and risks to patients

Fractionation

\[ \approx 10'000 \text{ – } 20'000 \text{ donations} \]

Factor VIII → patients
Factor IX → patients
Albumin → patients
IgG → patients
Others → patients

hundreds
Reason N° 1: Plasma product pathogen safety

In the absence of virus reduction treatments

- Factor VIII
- Factor IX
- Albumin
- IgG
- Others

Risk of transmission

≈10’000 – 20’000 donations

Fractionation

Pathogen-contaminated donation

Hundreds

Patients
Reason N° 2: Plasma product quality and tolerance

Sub-optimal production procedures (e.g. cold chain failure; blood cell level)

- Proteases; activated coagulation factors

Risk of low yield or batch out of specification

- Thrombogenicity
- Hypotensive effects
- Etc.

Risk of Side-effects

- Factor VIII
- Factor IX
- Albumin
- IgG
- Others

"≈10’000 – 20’000 donations"

"Risk of Side-effects"

"hundreds"

"patients"
Reason N° 3: Regulations & international standard

International use and market
International regulations of medicinal products
Concept of GMP all along the production chain of industrial plasma products

Quality and Safety nets

Donors

Purification
Viral reduction

IgG

Factor VIII

Factor IX

Albumin

Alpha 1-AT

Patients

GMP

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Key safety nets/barriers in the production of plasma for fractionation

- Epidemiological surveillance (known & emerging pathogens)
- Donor's screening (approved questionnaire; established deferral criteria)
- Donations testing (licensed and approved test IVD kits; validated procedures; rejection criteria)
- Plasma separation, freezing, storage & transportation; validated and approved procedures
- Good manufacturing practices
- Audits by fractionators
- Inspection by NRA
- Traceability
Pathogen safety nets prior to fractionation

Epidemiological Control of population

Donor’s screening

Donation testing strategies; handling of sample

Mini-pool NAT testing

Plasma pool testing

Traceability
WHO guidelines, recommendations, and initiatives on blood products quality

Annex 4
Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products

Annex 4
Recommendations for the production, control and regulation of human plasma for fractionation

Annex 4
WHO guidelines on good manufacturing practices for blood establishments

11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

11.1 Blood and liberal components

In accordance with the World Health Assembly resolution WARM.33, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, in the supply of safe blood components based on voluntary, non-commercial blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

- fresh frozen plasma
- platelets
- red blood cells
- whole blood

11.2 Plasma-derived medicines

All human plasma-derived medicines should comply with the WHO requirements.

11.2.1 Human immunoglobulins

- anti-D immune globulin
- injection: 100 micrograms in single-dose vial.
- anti-D immune globulin
- injection: 150 IU/ml, in vial.

11.2.2 Complementary list

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WHO Technical Report Series No 961, 2011

Dr. Ana Padilla,
WHO, Geneva

Pr. W.G. Van Aken
ECBS

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WHO Technical Report Series No 924, 2004

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WHO guidelines on viral inactivation/removal procedures of industrial plasma products

Technical & scientific reference document for fractionators and regulatory authorities (evaluation and inspections) worldwide

Annex 4
Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products

First urgency due to past transmissions of HIV, HCV, and HBV by non-virally inactivated plasma products

- Review of viral inactivation and removal procedures
- Recommendations for proper industrial implementation
- Recommendations on virus validation methods
Production, control, and regulation of plasma for fractionation

Plasma is an active pharmaceutical ingredient used to manufacture fractionated plasma products.

Annex 4
Recommendations for the production, control and regulation of human plasma for fractionation

Intended to assist blood establishments and regulatory authorities in emerging countries considering a plasma fractionation programme (contract or domestic).
Annex 4
Recommendations for the production, control and regulation of human plasma for fractionation

1 Introduction
2 International Biological Reference Preparations
3 Glossary
4 General considerations
   4.1 Range of products made from human blood and plasma
   4.2 Composition of human plasma
   4.3 Pathogens present in blood and plasma
5 Measures to exclude infectious donations
   5.1 Appropriate selection of blood/plasma donors
   5.2 Screening of blood/plasma donations for infectious markers
   5.3 Epidemiological surveillance of donor population
   5.4 Strict adherence to Good Manufacturing Practices
   5.5 Post-donation events
6 Production of plasma for fractionation
   6.1 Methods used to obtain plasma for fractionation
   6.2 Characteristics of plasma for fractionation
   6.3 Premises and devices for collection of plasma for fractionation
   6.4 Blood/plasma collection process
   6.5 Separation of plasma
   6.6 Freezing of plasma
   6.7 Storage of plasma
   6.8 Compliance with plasma fractionator requirements
   6.9 Release of plasma for fractionation
   6.10 Packaging of plasma
   6.11 Transportation of plasma
   6.12 Recall system
7 Quality assurance system and Good Manufacturing Practices
   7.1 Organisation and personnel
   7.2 Documentation system
   7.3 Premises and equipment
   7.4 Materials
   7.5 Validation programme

Wide consultation worldwide

Contributions from over 50 organizations or experts

Approved by WHO Expert Committee of Biological Standardisation (ECBS)
Annex 4

Recommendations for the production, control and regulation of human plasma for fractionation

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7. Quality assurance system and Good Manufacturing Practices
   7.1. Organisation and personnel
   7.2. Documentation system
   7.3. Premises and equipment
   7.4. Materials
   7.5. Validation programme

How to exclude infectious donations:
• Selection of donors
• Screening of donations
• Epidemiological control
• GMP
• Handling of post-donation events

Recommendations on collection, Separation, freezing, storage and transportation methods of plasma

QA and GMP concepts applied to blood establishment
Production, control and regulation of plasma for fractionation

Role of NRA / license / inspections

Donor selection
Appendix 2

**Donor selection**

1. Preamble
2. Information to donors
3. Compliance with donor selection criteria
   3.1 Identification of donors
   3.2 Confidentiality
   3.3 Questionnaire and interview
   3.4 Physical examination, acceptance and deferral criteria

Appendix 3

**Donor immunization and plasmapheresis for the manufacture of specific immunoglobulins**

There is a need for hyperimmune plasma for the manufacture of specific immunoglobulins that are clinically valid for therapeutic and prophylactic uses.
Production, control and regulation of plasma for fractionation

Contract fractionation programmes
Principles of contract fractionation

Several models exist and should be defined in the contract.
Plasma Contract Fractionation Programs (parties involved)

GMP- common principles

NRA

GMP Licensing

Quality Assurance Program

PLASMA SUPPLIER

across countries

FRACTIONATOR

A. Padilla, WHO, Geneva
Table 1
Responsibilities and roles of blood establishment, plasma fractionator, and regulatory authorities

<table>
<thead>
<tr>
<th>Task</th>
<th>Blood establishment</th>
<th>Plasma fractionator</th>
<th>Regulatory authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology surveillance of donor population</td>
<td>Collects and analyses the data based on results of screening tests</td>
<td>Reviews the data</td>
<td>Reviews the data</td>
</tr>
<tr>
<td>Donor selection and interview</td>
<td>Develops and implements the criteria in selection and interview of donors</td>
<td>Verifies that criteria set by national regulatory authority are met; may provide additional selection criteria</td>
<td>Sets the criteria and inspects the blood establishment</td>
</tr>
<tr>
<td>Serological testing of donation</td>
<td>Performs validated tests (or the tests may be sub-contracted)</td>
<td>Agrees on the test kits used and audits the virology laboratory</td>
<td>Approves test kits and inspects the blood establishment</td>
</tr>
<tr>
<td>Post-donation follow-up and haemovigilance</td>
<td>Informs plasma fractionator (and when appropriate the regulatory authority) when relevant information is obtained</td>
<td>Takes appropriate measures if plasma pool or product quality is compromised</td>
<td>Evaluates haemovigilance/post-donation reports with regards to product quality and safety</td>
</tr>
</tbody>
</table>

Appendix 4
Contract plasma fractionation programme

Preparation of plasma
- Collects blood plasma, prepares, freezes, and stores the plasma, according to good manufacturing practice (GMP)
- Sets the specifications and audits
- Approves and inspects the blood establishment

Nucleic acid testing (NAT) (mini-pool)
- Prepares the NAT samples following fractionator’s specifications
- Provides the standard operating procedure for NAT samples and performs (or sub-contracts) the validated testing
- Approves the procedure and inspects the plasma fractionator

Fractionation methods including viral reduction
- Applies the fractionation methods following GMPs and processes described in marketing authorization
- Evaluates the data presented in the dossier prepared by the fractionator and inspects fractionation facility

Preparation of plasma product regulatory files
- Prepares the files
- Reviews and evaluates

GMP
- Implets GMP
- Audits the blood establishment
- Improves blood establishment and enforces GMP

Granting of marketing authorization
Plasma product pharmacovigilance
- Does pharmacovigilance studies and informs regulatory authorities and blood establishment when relevant side-effects are found
- Evaluates pharmacovigilance reports with regards to product quality and safety
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 way 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.
<table>
<thead>
<tr>
<th>Expected benefits from WHO Guidelines</th>
</tr>
</thead>
</table>

- Build-up technical expertise of National Regulatory Authorities (NRA) and plasma suppliers (BE)

- Establish common GMP standards, as a basis for mutual recognition of quality standards and inspections results between NRA’s

- Compliance with GMP, a key tool for implementation of successful plasma contract fractionation programs

- Tools for risk assessment
Importance of scientifically-based “risk assessment” of the safety of plasma products

Blood establishments

- Epidemiological surveillance (known & emerging pathogens)
- Donor’s screening (approved questionnaire; established deferral criteria)
- Donations testing (licensed and approved test IVD kits; validated procedures; rejection criteria)
- Plasma separation, freezing, storage and transportation (validated procedures)
- Good manufacturing practices

Fractionator

- Virus reduction barriers
  - IgG
  - Factor VIII
  - Factor IX
  - Albumin
  - Alpha 1-AT

Safety wheel in Blood establishment

The manufacturing plasma pool is not virus-free (known or emerging viruses, NYIV)

NYIV = Not-Yet Identified Virus
Other intended benefits of WHO Guidelines

Avoid wasting plasma
This report examines the volume of plasma separated from whole blood that is currently wasted worldwide and identifies challenges and opportunities and the key steps needed to improve the situation. Evidence reveals that a substantial and increasing volume of recovered plasma potentially available in LMIC is currently wasted. This volume has been estimated, based on the global number of whole blood donations and volume of recovered plasma currently used for direct transfusion or for fractionation, to be close to 9.3 million litres each year. This corresponds to more than 40% of the world resources in recovered plasma, and represents a market value of about US$ 650 to US$ 1020 million (based on a price range of US$ 70 to US$ 110 per litre). This plasma
“Deficient systems and documentation render the plasma unsuitable for production into fractionated medicinal products and lead to its destruction, which is not only unethical but also a waste of valuable human resources.”
Low-Medium income countries (case 1)

Blood separation

Blood

Red blood cells
Platelets
Plasma

Cryo

Clinical Plasma

Excess plasma

Destruction
Storage

Many possible reasons

Many countries in Asia, Eastern Europe, South & Central America, and Africa
Why is plasma destroyed (not fractionated) ?

• **GMP issues**
  – No freezing equipment
  – No storage facility
  – Quality criteria for fractionation are not met:
    • Traceability
    • testing criteria
    • Time between blood collection and plasma freezing

• **Organizational issues**
  – Scattered blood collection centers: volume is too low in individual collection centers
  – Collection methods are not harmonized at national level (or among major blood establishments)
WHA63.12  Availability, safety and quality of blood products\textsuperscript{1,2}

The Sixty-third World Health Assembly,

Aware that a major factor limiting the global availability of plasma-derived medicinal products is an inadequate supply of plasma meeting internationally recognized standards for fractionation;

1. URGES Member States:\textsuperscript{1}

   (1) to take all the necessary steps to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency, unless special circumstances preclude it;

   (2) to take all the necessary steps to update their national regulations on donor assessment and deferral, the collection, testing, processing, storage, transportation and use of blood products, and operation of regulatory authorities in order to ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards;

   (3) to establish quality systems, for the processing of whole blood and blood components, good manufacturing practices for the production of plasma-derived medicinal products and appropriate regulatory control, including the use of diagnostic devices to prevent transfusion-transmissible diseases with highest sensitivity and specificity;
Transfers of technology

WHA63.12  Availability, safety and quality of blood products

The Sixty-third World Health Assembly.

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

http://www.who.int/phi/publications/blood_prods_technology_transfer.pdf
Options to improve access to plasma products

Cost consideration

Need for regulations

9 million L plasma wasted/year
Annex 4

WHO guidelines on good manufacturing practices for blood establishments

GMP for blood establishments

GMP production of plasma for fractionation has beneficial impacts on the quality and safety of all blood components
### WHO Model List of Essential Medicines

#### 11. BLOOD PRODUCTS OF HUMAN ORIGIN AND PLASMA SUBSTITUTES

**11.1 Blood and blood components**

In accordance with the World Health Assembly resolution WHA63.12, WHO recognizes that achieving self-sufficiency, unless special circumstances preclude it, is the supply of safe blood components based on voluntary, non-remunerated blood donation, and the security of that supply are important national goals to prevent blood shortages and meet the transfusion requirements of the patient population. All preparations should comply with the WHO requirements.

- fresh-frozen plasma
- platelets
- red blood cells
- whole blood

**11.2 Plasma-derived medicines**

All human plasma-derived medicines should comply with the WHO requirements.

<table>
<thead>
<tr>
<th>Human immunoglobulins</th>
<th>Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-D immunoglobulin</td>
<td>250 micrograms in single-dose vial.</td>
</tr>
<tr>
<td>Anti-rabies immunoglobulin</td>
<td>150 IU/mL in vial.</td>
</tr>
<tr>
<td>Anti-tetanus immunoglobulin</td>
<td>500 IU in vial.</td>
</tr>
</tbody>
</table>

**Complementary List**

- normal immunoglobulin
  - Intramuscular administration: 16% protein solution.*
  - Intravenous administration: 5%; 10% protein solution.**
  - Subcutaneous administration: 15%; 16% protein solution.*
  
* Indicated for primary immune deficiency.

**11.2.2 Blood coagulation factors**

<table>
<thead>
<tr>
<th>Complementary List</th>
<th>Powder for injection: 500 IU/vial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td></td>
</tr>
<tr>
<td>Factor IX</td>
<td>500 IU/vial, 1000 IU/vial.</td>
</tr>
</tbody>
</table>

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**Message to Government and National Health Authorities**

- Highlight the importance of sufficient supply of therapeutic blood products at national level.
- Importance of professional and sustainable national blood system and National Regulatory Authority.
• Plasma is a crucial source of essential therapeutic products to treat bleeding and immunological disorders, and other pathologies.

• Retrospectively, in the 1980-1990’s, pooled plasma products (which were not virally inactivated, and were produced following processes non compliant with GMP) were:
  • At higher risks of viral contamination than single-donor blood components
  • And side-effects (pyrogens, thrombogenicity, hypotensive effects, etc.)
Conclusions (2)

• Technological progresses (viral inactivation; improved fractionation technologies; process control) and needed regulations/enforcement (GMP) have much improved the quality and safety of plasma and plasma products making these products among the best known, safe, and scrutinized biological products

• Improving collection of quality plasma usable for fractionation, as described in WHO guidelines, can:
  • Improve supply of life-saving essential plasma products
  • Enhance the safety and quality of all blood components (essential medicines)
  • Reduce wastage of plasma
  • Contribute to sustainability of blood systems
Thank you for your attention

Welcome to Taiwan and to TMU