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

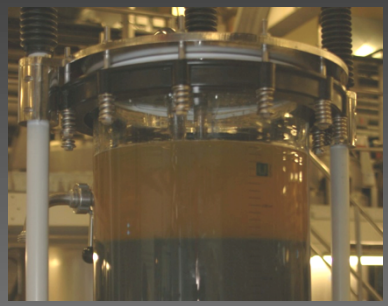
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IPFA workshop – Taipei, Taiwan – March 8th-9th , 2016









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?



Picture Source:

Global Database on Blood Safety

World Health Organization

The answer is:

Yes !

Are the overall GMP requirements for plasma for transfusion and plasma for fractionation the same?



Picture Source:

Global Database on Blood Safety

World Health Organization

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 ?



Picture Source:

Global Database on Blood Safety

World Health Organization

The answer is:

Example
Plasma not frozen within 24 hrs can be used
For producing IVIG and albumin

No !
(not necessarily)

Have GMP requirements of plasma for fractionation <u>historically</u> pushed for more stringent GMP requirements for plasma for transfusion ?



Picture Source:

Global Database on Blood Safety

World Health Organization

The answer is:

Yes !

Why, historically, more stringent GMP requirements for plasma for fractionation have been needed and implemented ?



Picture Source:

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

World Health Organization

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 ?



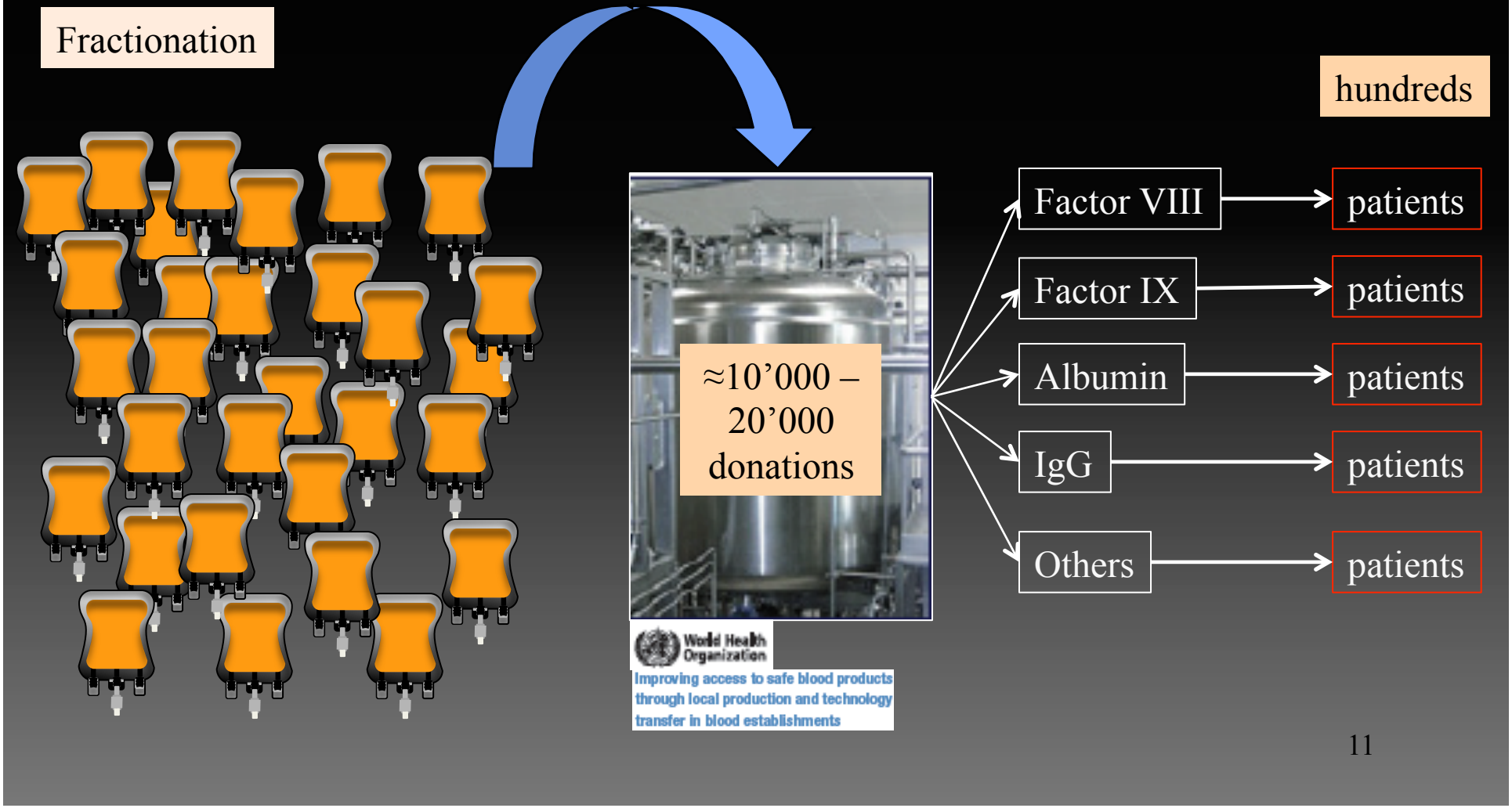
Picture Source:

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

World Health Organization

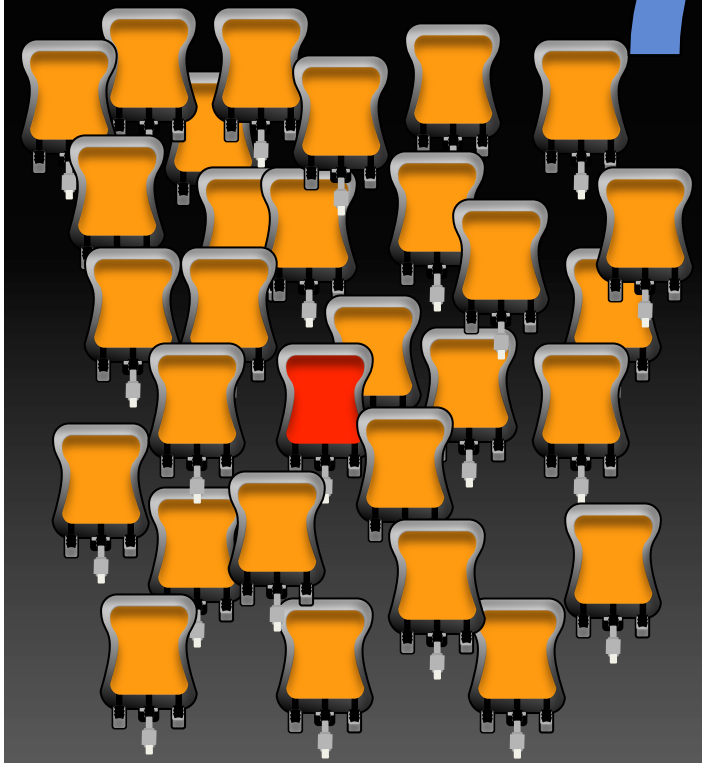
At least 3 reasons

Scale of production of industrial plasma products amplifies safety issue and risks to patients



Reason N° 1: Plasma product pathogen safety

Fractionation



Pathogen-contaminated donation



≈10'000 – 20'000 donations

World Health Organization

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

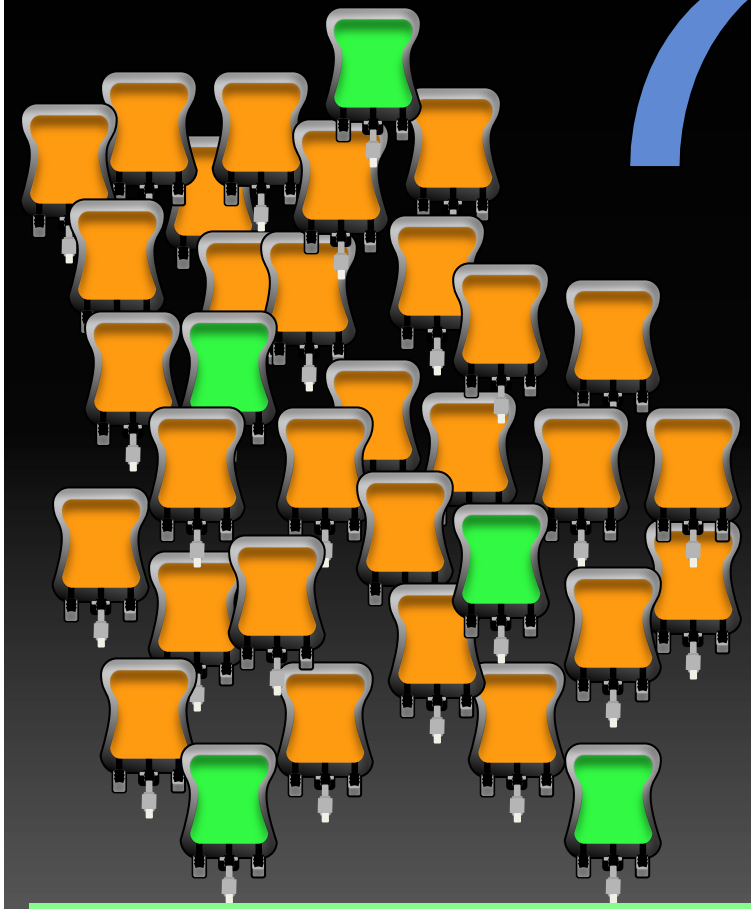
In the absence of virus reduction treatments

hundreds

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

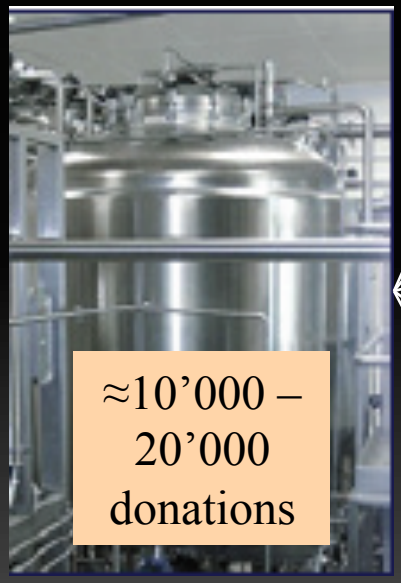
Risk of transmission

Reason N° 2:
Plasma product quality and tolerance



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

Proteases; activated coagulation factors



≈10'000 – 20'000 donations

hundreds

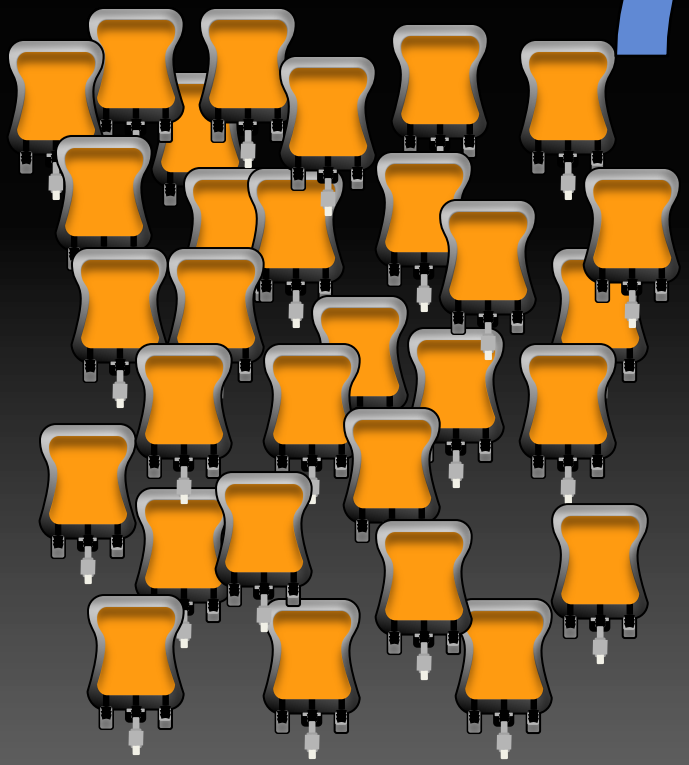
- Factor VIII → patients
- Factor IX → patients
- Albumin → patients
- IgG → patients
- Others → patients

Risk of low yield
or batch out of specification

Risk of Side-effects

- Thrombogenicity
- Hypotensive effects
- Etc.

Reason N° 3: Regulations & international standard





IgG

Factor VIII

Factor IX

Albumin

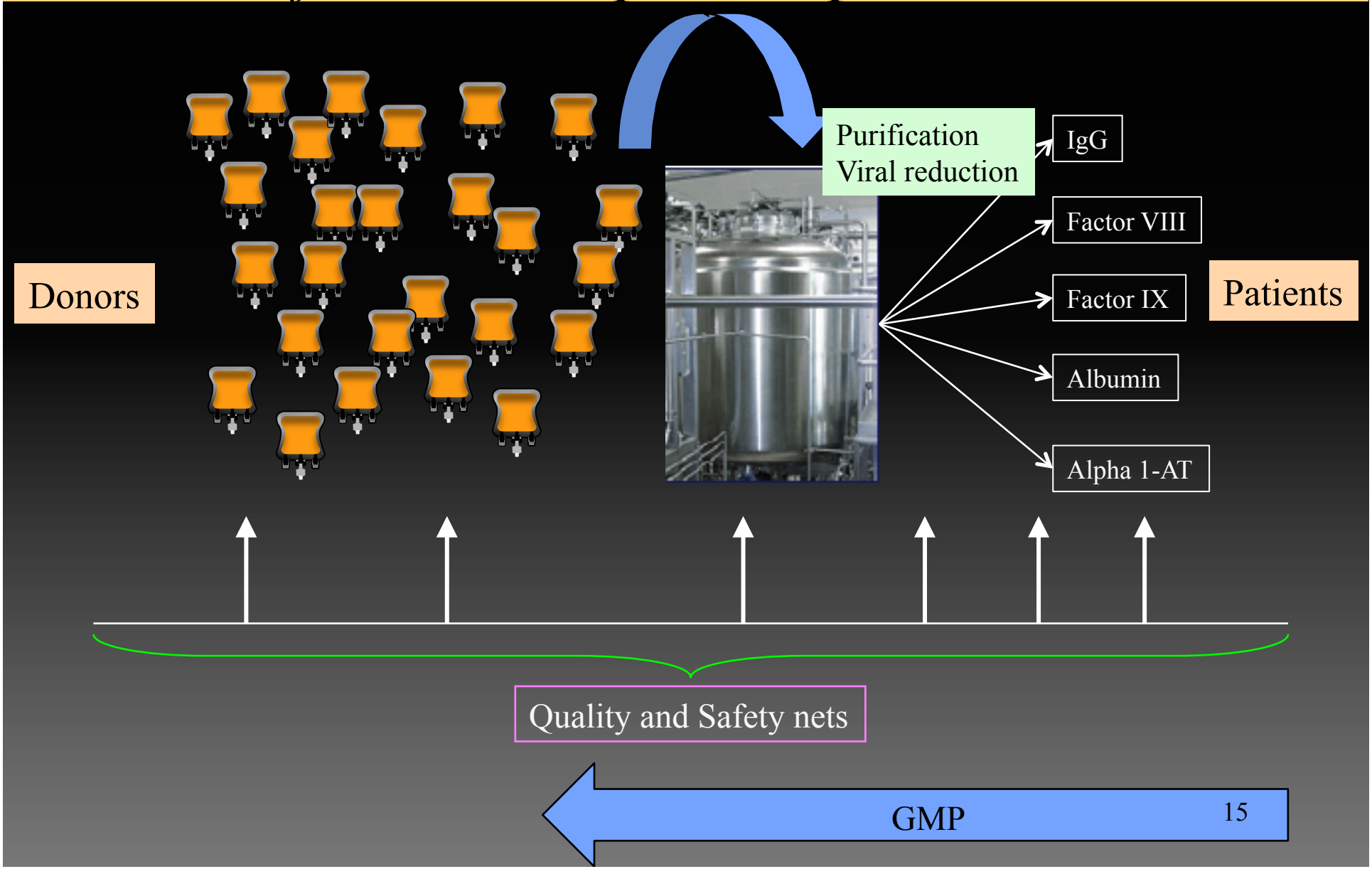
Alpha 1-AT



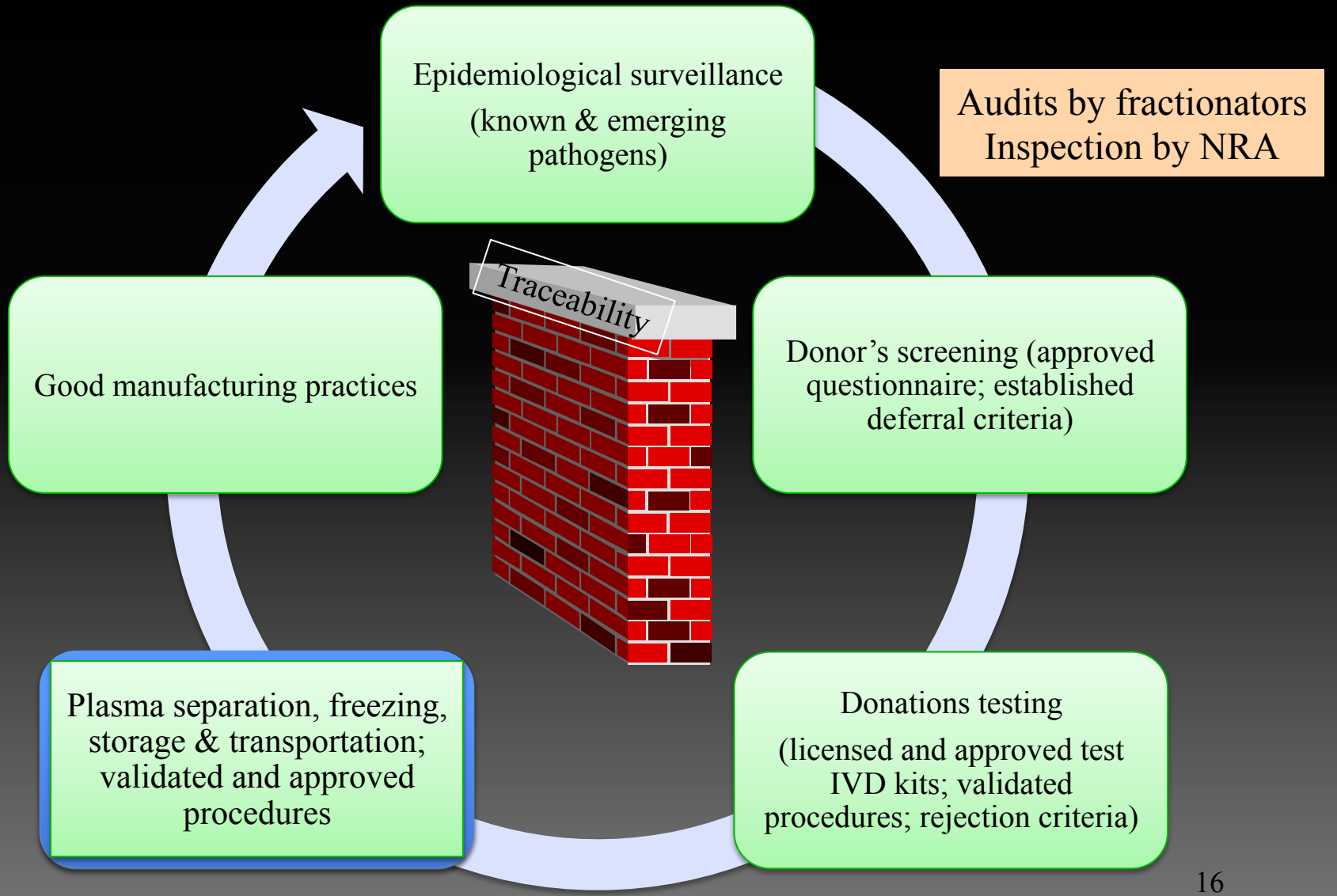
"Products without Borders"

International use and market
International regulations of medicinal products

Concept of GMP all along the production chain of industrial plasma products



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



Pathogen safety nets prior to fractionation

BE

Fractionator







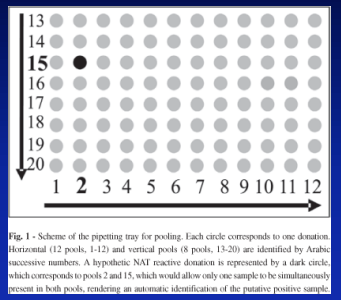


Fig. 1 - Scheme of the pipetting tray for pooling. Each circle corresponds to one donation. Horizontal (12 pools, 1-12) and vertical pools (8 pools, 13-20) are identified by Arabic successive numbers. A hypothetic NAT reactive donation is represented by a dark circle, which corresponds to pools 2 and 15, which would allow only one sample to be simultaneously present in both pools, rendering an automatic identification of the putative positive sample.



Epidemiological Control of population

Donor's screening

Donation testing strategies; handling of sample

Mini-pool NAT testing

Plasma pool testing

Traceability

Traceability

WHO guidelines, recommendations, and initiatives on blood products quality

© World Health Organization
WHO Technical Report, Series No. 924, 2004

Annex 4

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

© World Health Organization
WHO Technical Report Series No 941, 2007

Annex 4

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

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WHO Technical Report Series, No. 961, 2011

Annex 4

WHO guidelines on good manufacturing practices for blood establishments

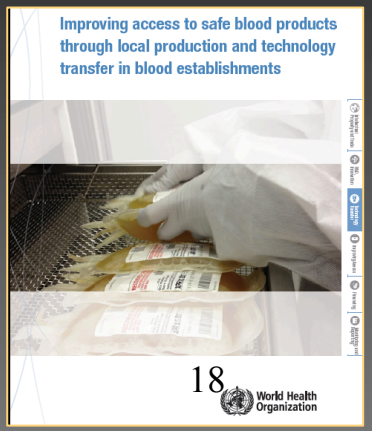


Dr. Ana Padilla, WHO, Geneva

Pr. W.G. Van Aken ECBS

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, in 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.	
11.2.1 Human immunoglobulins	
anti-D immunoglobulin	**Injection:** 250 micrograms in single-dose vial.
Anti-rabies immunoglobulin	**Injection:** 150 IU/ mL in vial.
Anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	

19th WHO Model List of Essential Medicines (April 2015) page - 26



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

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

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WHO Technical Report, Series No. 924, 2004

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

Annex 4

Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood 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

© World Health Organization
WHO Technical Report Series No 941, 2007

Second urgency

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





Technical & scientific document

Intended to assist blood establishments and regulatory authorities in emerging countries considering a plasma fractionation programme (contract or domestic)

© World Health Organization
WHO Technical Report Series No 941, 2007

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

Production, control and regulation of plasma for fractionation

Wide consultation worldwide

The Drafts prepared were circulated for Consultation to Representatives of National Regulatory Authorities, National Blood Programs and to the respective WHO Regional Advisors in all the WHO Regional Offices. Plasma fractionators were consulted through their respective plasma fractionation associations or through the regulatory agencies in their countries. Both the Plasma Protein Therapeutic Association and the International Plasma Fractionation Association presented consolidated comments of their Members.

Contributions from over 50 organizations or experts

Approved by WHO Expert Committee of Biological Standardisation (ECBS)

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Annex 4

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- 7.4 Materials
- 7.5 Validation programme

Production, control and regulation of plasma for fractionation

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

7.6 Quality monitoring data
7.7 Virology safety testing
7.8 Electronic information system
7.9 Storage and transport
7.10 Change control system
7.11 Quality assurance auditing
7.12 Defect reporting system
7.13 Quality agreement between blood establishment and fractionator
7.14 Blood/plasma establishment audit and inspection

8 Regulatory control of plasma for fractionation
8.1 Role of national regulatory authority
8.2 Establishment licence and inspections
8.3 Impact of Good Manufacturing Practices
8.4 Inspections

Authors

References

Appendix 1
Plasma products and clinical applications

Appendix 2
Donor selection

Appendix 3
Donor immunization and plasmapheresis for specific immunoglobulins

Appendix 4
Contract plasma fractionation programme

Appendix 5
Technical points to consider in establishing plasma specifications
criteria and obligations between blood establishment and plasma fractionator

Role of NRA / license / inspections

Donor selection

Production, control and regulation of plasma for fractionation

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

More concrete examples of Points to consider in donor selection procedures

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.

Anti—D (Rh); anti-HBs; anti-tetanus IgG on WHO Model List of Essential Medicines

- Production of hyperimmune plasma
- Immunization with RBC

Production, control and regulation of plasma for fractionation

7.6 Quality monitoring data
7.7 Virology safety testing
7.8 Electronic information system
7.9 Storage and transport
7.10 Change control system
7.11 Quality assurance auditing
7.12 Defect reporting system
7.13 Quality agreement between blood establishment and fractionator
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References

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criteria and obligations between blood establishment and plasma fractionator

Contract fractionation programmes

Principles of contract fractionation











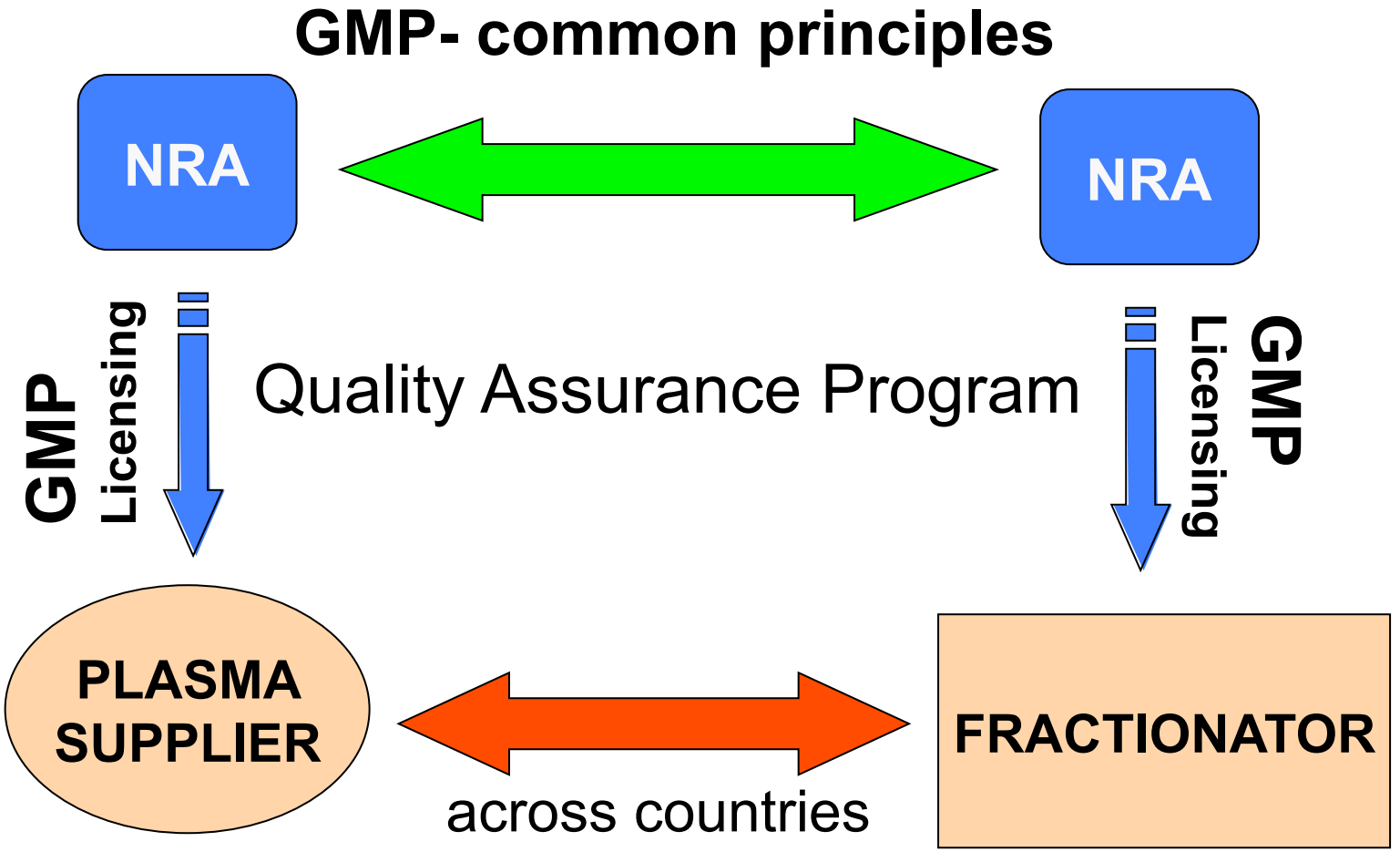






Several models exist and should be defined in the contract

Plasma Contract Fractionation Programs (parties involved)



A. Padilla, WHO, Geneva

Table 1
Responsibilities and roles of blood establishment, plasma fractionator, and regulatory authorities

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

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 dossiers prepared by the fractionator, and inspects fractionation facility
Preparation of plasma product regulatory files		Prepares the files	Reviews and evaluates
GMP[a]	Implements GMP	Audits the blood establishment	Inspects blood establishment and enforces GMP
Granting of marketing authorization			Grants the 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.

Contract document between plasma supplier and plasma fractionator

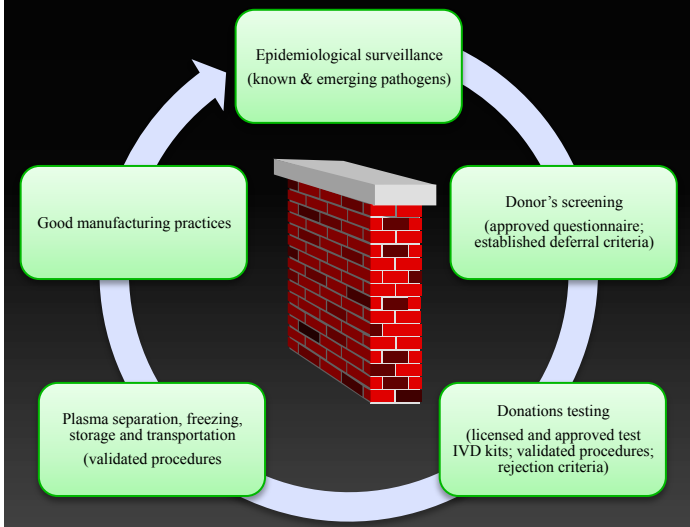
Expected benefits from WHO Guidelines

- 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

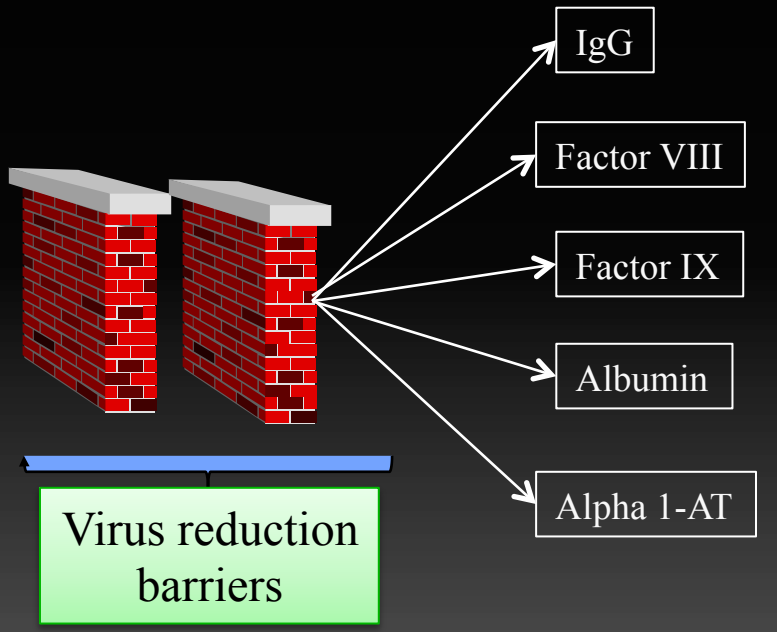
Blood establishments

Fractionator



Safety wheel in Blood establishment



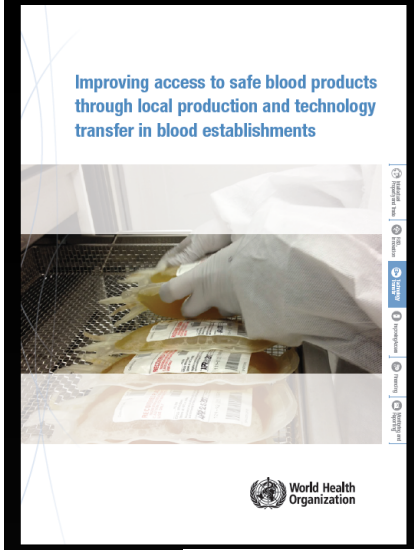


The manufacturing plasma pool is **not** virus-free (known or emerging viruses, NYIV)

NYIV = Not-Yet Identified Virus

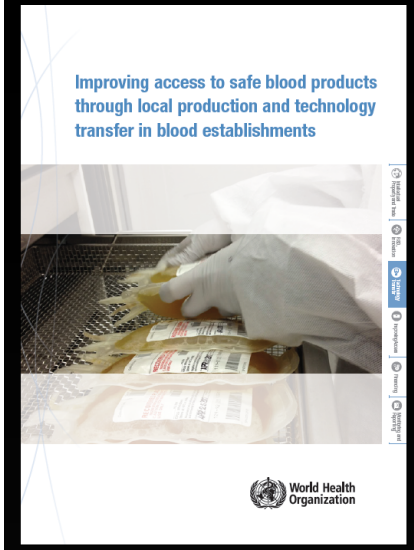
Other intended benefits of WHO Guidelines

Avoid wasting plasma



Volume of recovered plasma wasted

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).[2] 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

Blood

Blood separation

Red blood cells

Platelets

Plasma

Clinical Plasma

Cryo

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)

Extracted from **WHA63/2010/REC/1**
WHA63.12 Availability, safety and quality of blood products 19

WHA63.12 Availability, safety and quality of blood products[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:[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;

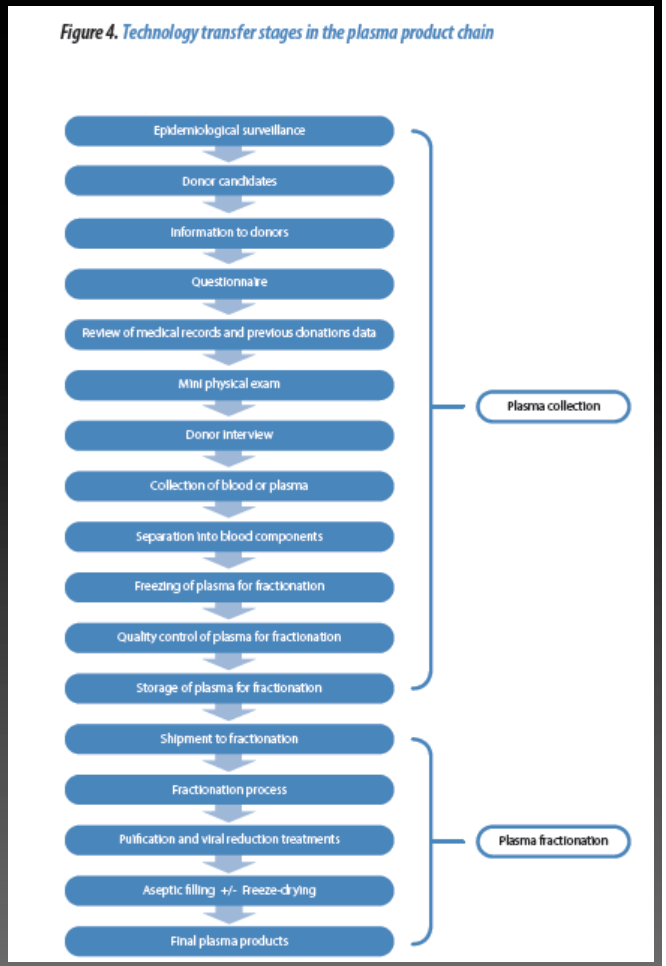
Transfers of technology

Extracted from **WHA63/2010/REC/1**
WHA63.12 Availability, safety and quality of blood products 19

WHA63.12 Availability, safety and quality of blood products[1,2]

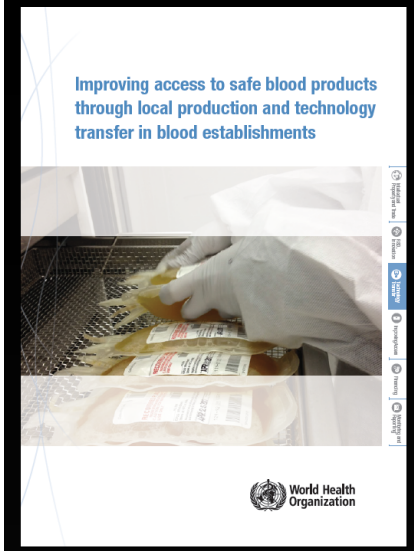
The Sixty-third World Health Assembly,





x

http://www.who.int/phi/publications/blood prods_technology_transfer.pdf



Contents

List of abbreviations . . . iv
Glossary . . . 1
Executive summary . . . 5
1. Introduction . . . 8
Improving access to safe blood products: a framework to improve public health . . . 8
Lack of access to safe and effective plasma-derived medicinal products: economic and public health impact . . . 13
World Health Assembly resolution on availability, safety and quality of blood products . . . 15
2. Project objectives and activities . . . 18
Activities . . . 18
Methodology . . . 18
3. Volumes of recovered plasma wasted in the world . . . 20
4. Options to secure production of safe blood components and improve access to plasma derivatives . . . 23
Plasma fractionation technology . . . 26
Options for fractionation of recovered plasma . . . 28
Contract fractionation . . . 28
Local fractionation . . . 30
5. Economics of plasma fractionation . . . 31
Product mix is a critical aspect of contract fractionation . . . 32
Contract fractionation should be protected from fluctuating 'spot' prices . . . 33
What contract fractionation volume is viable or cost effective? . . . 34
6. Points to consider in technology transfer for local production in LMIC . . . 36
7. Need for regulation of blood and blood products . . . 41
8. Discussion summary . . . 49
What we have learned . . . 51
Ways forward . . . 52
9. Conclusions . . . 54
References . . . 56
Annex: Case studies . . . 58
A. Production of recovered plasma for fractionation . . . 58
B. Plasma contract fractionation programmes . . . 62
C. Local plasma fractionation activities . . . 68
D. Regulatory framework: needs for development . . . 74

9 million L plasma wasted/year

Options to improve access to plasma products

Cost consideration

Need for regulations

GMP for blood establishments

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Annex 4

WHO guidelines on good manufacturing practices 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

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Anti-tetanus immunoglobulin	**Injection:** 500 IU in vial.
Complementary List	

Recent addition

normal immunoglobulin	***Intramuscular administration:** 16% protein solution.** ***Intravenous administration:** 5%; 10% protein solution.*** ***Subcutaneous administration:** 15%; 16% protein solution.** * *Indicated for primary immune deficiency.* ***Indicated for primary immune deficiency and Kawasaki disease.*
11.2.2 Blood coagulation factors	
Complementary List	
☐*coagulation factor VIII*	***Powder for injection:** 500 IU/vial.*
☐*coagulation factor IX*	***Powder for injection:** 500 IU/vial, 1000 IU/vial.*

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

Conclusions (1)

- 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