
بسم الله الرحمن الرحيم

Plasma Products Testing Safety and Quality Issues

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Introduction

The safety and quality of the Plasma products depends on:

- Careful selection of donor screening program
- Identifying areas of potential risk
- Implementing a proper testing procedures
- Implementing effective measures to minimize contamination during processing

Sources of plasma products:
(starting raw material)

1-Human Plasma

a-Recovered plasma

obtained from whole blood donation within 24 hour

b-Source plasma

obtained by plasmapheresis within one hour

2 - Recombinant products

Plasma-derived versus recombinant products:

1- Recombinant products can not be considered to be totally free of risk of transmitting infectious agents

2- The recombinant products are more expensive than their plasma-derived counterparts

3- The biotechnological production systems may generate protein variants different slightly from the native human ones and this may lead to a lower than normal in vivo recovery and half-life after in vivo administration

Risks in Blood Products Transfusion

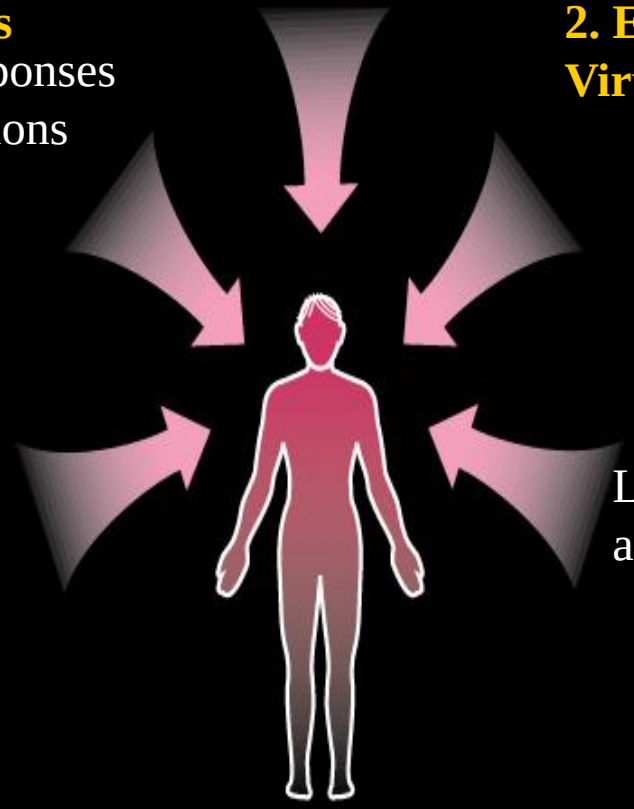
1. Bacteria

Introduced during collection

5. Leukocytes

Adverse immune responses and transfusion reactions

2. Emerging/Unknown Viruses



4. Known Pathogens

For which no assay is available

3. Window Period

Limits of detection of current assays (e.g., false negatives)

Window periods

	Mean days of window period	Range days of window period
Anti-HIV	22	6-38
+ HIV p24-Ag	-6	
+ HIV PCR	-11	
HBsAg	59	37-87
+ HBV PCR	-25	
Anti-HCV	82	54-192
+ HCV PCR	-59	

[1] Schreiber GB; N Engl J Med 1996;334:1685-1690

Viral Safety of Plasma Products

1- Donor selection

2- Single-donation testing

3- Mini-pool NAT

4- Manufacturing pool testing

5- Viral reduction step[s]

Viral reduction steps are essential to maintain the viral load of starting plasma pool within acceptable limits.

Donor Selection

Is Important

To Be Sure That The Donor Is Fit To Donate The Required Amount Of Blood

Blood Donation Will Not Harm The Donor

The Donated Blood Should Be Safe And Free From Transfusion Transmitted Infections TTI

Donor Selection

I. Interview

II. Questionnaires → **Donor safety**

→ **Patient safety**

III. Physical examination

Single Donation Testing

Different countries screen for different organisms. Each country has to set its own policies for screening of donors.

i. Serological screening

ii. Microbiological screening

- HIV I & II (Ag-Ab), HBV, HCV, Syphilis

  HTLV-I & II

  HBcAb

- Special donors for CMV

  Malaria screen (in some countries)

Confirmatory tests

Any reactive donation should repeat testing in duplicate. If any of the repeated tests is reactive, a sample should be send to a reference laboratory and the donation will be destroyed by autoclaving or used for batch validation or quality control purposes.

NAT Tests in Plasma Fractionation:

- Specific blood sample withdrawn and identified at time of collection.
- Mini-pool (>50-100) is made prior to the fractionation pool.
- HCV…HIV…HBV…B19 …HAV…?…? : + donations are discarded

Viral Inactivation Procedures

The aim of viral inactivation is to remove or selectively inactivate the infectious agents, whilst preserving the biological activity and safety of the product.

I. Heat treatment

Liquid state

Albumin → heated in final containers for 10 hrs at 60°C

the enveloped and unenveloped viruses are destroyed

Dried state for 72 hrs at 80°C

II. Chemical agent

Beta propanolactone

III. Solvent-detergent inactivation

Tri (n-Butyl) phosphate (INBP) + Triton x 100

Methylene blue

IV. Photochemical Inactivation

Several photosensitizers

Sodium chlorite

UV irradiation + psoraline

Effect depends on dose, nature and concentration of product

The effect also varies from virus to virus

Separation Techniques

- Chon’s fractionation (cold ethanol)
- Ion exchange
- Hydrophobic chromatography
- Immunoaffinity chromatography
- Adding neutralizing antibodies
- Ultra filtration

PROCESS IMPLEMENTATION

- Ensure and assess that viral inactivation/removal procedures are correctly carried out at the manufacturing stage
- Cross-contaminations are avoided

Process design

Equipment

Lay-out

Qualification

Process control

SOPs, etc…

Technology / Products

- **Solvent-detergent**
  - IVIgG
  - Coagulation factors, anti-proteases, fibrin sealant
- **Pasteurization**
  - Albumin, ATIII, Alpha 1 AT
  - FVIII, IVIgG
- **Dry heat**
  - Coagulation factors

Guidelines on Viral Inactivation and Removal Procedures Intended to Assure the Viral Safety of Human Blood Plasma Products

WHO Website…

http://www.who.int/biologicals

Testing final products for viral markers

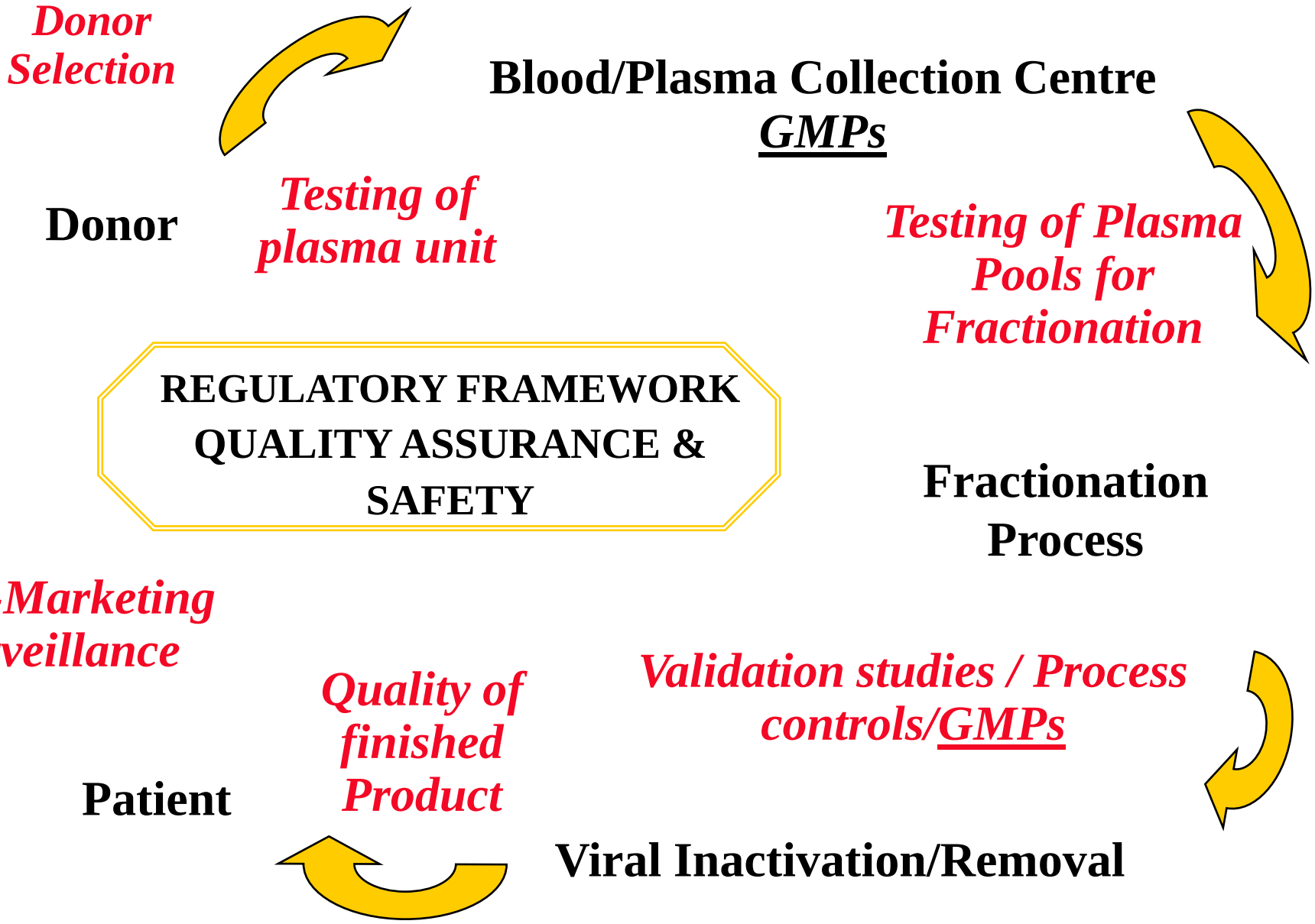
-Final product testing for viral markers, as part of the routine batch release, is not recommended as the outcome is generally of limited value in determining viral safety.

-The results of these tests, both serological and NAT tests, can often be misleading and difficult to interpret.

- Negative testing of final products does not indicate viral safety.

Post-Marketing Surveillance

- National Policies and Guidelines for testing plasma products.
- Follow up their clinical efficacy and viral safety on patients.


Donor Selection
Blood/Plasma Collection Centre
GMPs
Donor
Testing of plasma unit
Testing of Plasma Pools for Fractionation
REGULATORY FRAMEWORK
QUALITY ASSURANCE &
SAFETY
Fractionation Process
Post-Marketing surveillance
Quality of finished Product
Validation studies / Process controls/GMPs
Patient
Viral Inactivation/Removal

PLASMA MASTER FILE (PMF):

- **For plasma-derived products, information on collection and control of the starting material, human blood or plasma, has to be documented as part of the dossier for marketing authorization**

- **The Plasma Master File applies to all blood and plasma-derived medicinal products of one fractionator**

- **Main tool in plasma contract fractionation (regulatory authority and manufacturers)**

PMF

Donor/donation information

- **Epidemiological information of donor population**
- **Donor selection/exclusion for pathogens**
- **Screening tests for markers of infection**
  - **tests performed + action in respect of positive result**
  - **test kits used + validation for donations and pools**

PMF

Information on starting material

- Plasma specifications
- Conditions for storage and transport
- Tests on samples of the plasma pool: validation of assays in plasma pools/mini pool strategies/manufacturing pools
- Post-pooling information:
  - Information related to infected plasma pools and communication to Medicines Regulatory Authorities

PMF

Quality Assurance System

- Traceability of donations
- Post-donation information
- GMPs in blood plasma collection centres and testing sites
- Legal environment

Role of Medicines Regulatory Authorities (MRAs)

- Relevant Regulations and Guidelines
- Inspect and license all manufacturing premises: GMPs
- Batch Release Post-Marketing surveillance
- Product Licensing
- International Harmonization

Plasma Contract Fractionation

Role of Medicines Regulatory Authorities

Country giving Plasma & receiving final products MRA 1

- Product licensed in country 1
- Possible Inspection of MRA1 to fractionator
- Accept batch information certificates from MRA2
- Post-marketing surveillance

Country receiving Plasma for manufacturing MRA2

Should be informed by the manufacturer

- Epidemiological and testing data
- MRA2 could Inspect Blood/Plasma Collection Centres in country 1
- Can deliver a certificate about the batches re manufacturer and production in compliance with Norms in country 2

Plasma Contract Fractionation

Assessment of local needs

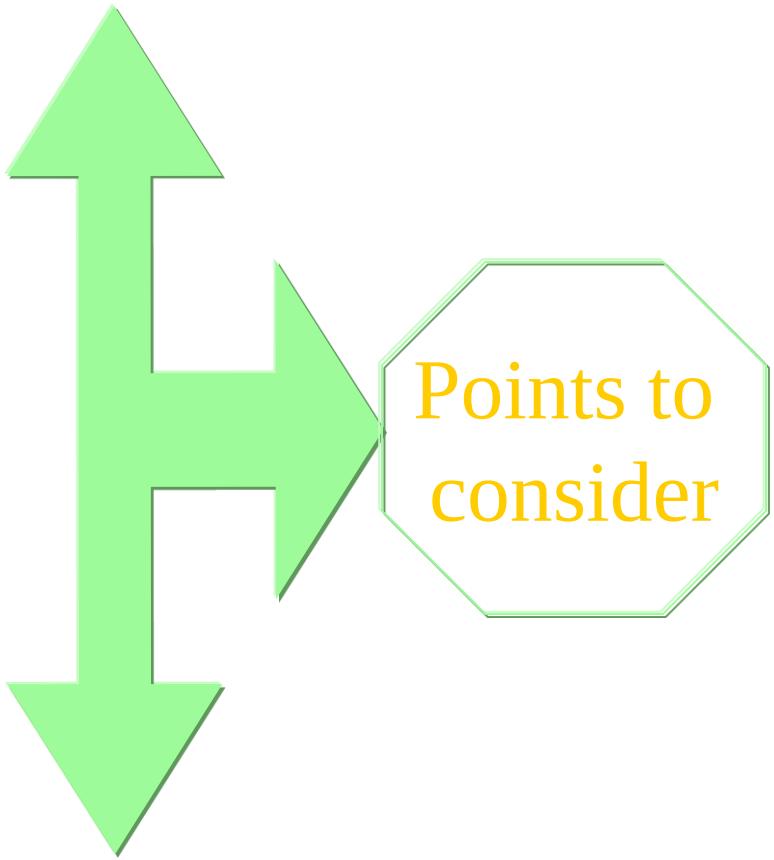
- Amount of products required -
- Plasma products of interest -
- Consensus guidelines -

Mature blood/plasma collection system

- National blood programme established -
- Sustainable supply of plasma -
- GMPs Compliance -

Medicines Regulatory Authority

-Requirements for plasma for fractionation-
- Site inspection procedures -
- Product license procedures -



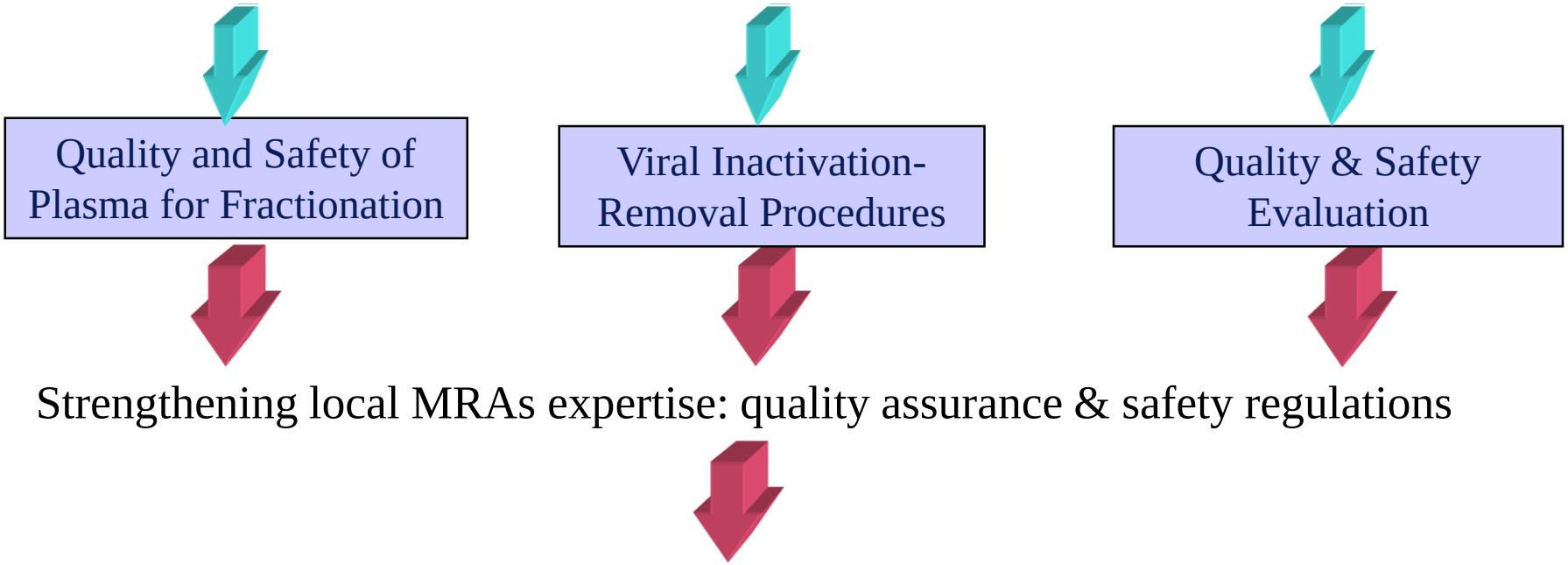
Plasma Contract Fractionation

- **Access to affordable plasma derived medicinal products**
- **Select appropriate fractionation & viral inactivation and removal technology**
- **Optimise available resources**

Quality Assurance of Plasma Derived Products

Regulatory Framework

Prevent transmission of blood borne viral diseases via plasma products



Strengthening local MRAs expertise: quality assurance & safety regulations

- Regional Training Workshops for blood collection/fractionation/regulatory sectors
  - Quality of plasma for fractionation/regulation environment
  - Good Manufacturing Practices
  - Viral inactivation/removal procedures/validation and implementation

Points to Consider

- Mandatory serology of all plasma units
- NAT mini-pool testing - HCV RNA
- Testing for virus markers in intermediates
- Virus inactivation / removal steps
- Validation studies/ Documentation
- Strict adherence to GMPs
- Post-Marketing Surveillance
- Certification/ MRA
- Master File

Conclusions

- Donor selection and refined testing methods, have reduced greatly the risk of a contaminated unit entering the manufacturing pool and contribute to safety margin

- Although there were several incidence of transmitted blood –borne infections through plasma products in the past, There is no documented case of transmission of HIV, HBV, HCV by virally inactivated plasma products in > 10 years.

- Safe products require control of starting material and production processes, through effective GMPs.

Conclusions

- Validation, Implementation, and Documentation of all steps are essential for safety and efficacy of plasma products.

- Finished product testing is not a substitute for effective quality systems and arrangements for regulation/ control.

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