Plasma fractionation: Technical and organisational points to consider

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Technical points to consider
Plasma fractionation technologies

What makes plasma fractionation unique?
Plasma fractionation uniqueness

Unique raw material

Unique manufacturing technology
Plasma fractionation uniqueness

Unique raw material

Unique manufacturing technology
Plasma fractionation uniqueness


Unique raw material

Unique manufacturing technology
Plasma: Rich biological material
Plasma fractionation: Unique technology

VACCINE
Start material → Purification step → Finishing → Vaccine

RECOMBINANT
Cell cultures → Chromatography → Finishing → Rh-FVIII

ANTIVENOMS
Plasma pool → Precipitation enzymatic treatment → Finishing → IgG/IgG fragments

HUMAN PLASMA PRODUCTS
Plasma pool → Finishing → FVIII, PCC, Alb, IgG

Interconnected production lines
<table>
<thead>
<tr>
<th>Products</th>
<th>Clinical Indications</th>
</tr>
</thead>
</table>
| Polyvalent immunoglobulins                   | • Substitutive therapy in primary deficiency  
• Immunomodulation                              |
| Hyperimmune Immunoglobulins                 | • Treatment and prophylaxis of infectious disease, or prevention of hemolytic disease of the new born |
| Coagulation factors (VIII, IX, vWF, VII)     | • Coagulation factor deficiency                                        |
| Fibrinogen                                   | • Congenital or acquired deficiency                                    |
| Prothrombin complex                          | • Complex liver disease                                               |
| Antithrombin                                 | • Congenital deficiency                                               |
| Alpha 1-antitrypsin                          | • Lung panacinar emphysema due to congenital deficiency                |
| Albumin                                      | • Blood volume replacement / oncontic pressure                        |
## Clinical fields covered by plasma products

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- Immunological disorders
- Infectious diseases
- Hemolytic disease
- Coagulation & bleeding disorders
- Metabolic diseases
- Traumas
Unique technological requirements

• Variability of the plasma raw material
  – Each plasma unit and each pool are different
  – Risk of emerging (known and unknown) infectious agents

• Substantial process know-how
  – Purification steps + Viral inactivation
  – Process and quality control assays validations for a range of products
Unique technological requirements

- Advanced downstream process and highly regulated biotech industry:
  - Several products made from the same plasma batch (interconnected processes)
  - 1 to 3 virus reduction steps for each product
  - Risks of crossed and downstream-contaminations should be avoided by careful facility design, SOP, training, etc.
  - Complex engineering process to accommodate all products
Plasma fractionation: Key driving forces

- **Sourcing**
  - Access to qualified plasma

- **Choice of technology**
  - Product portfolio
  - Yield & quality
  - Pathogen safety
Can a donor donating plasma for transfusion also donate plasma for fractionation?

The answer is? Yes or no?

yes
Is storage or testing requirements for plasma more stringent for fractionation than for plasma for transfusion?

Examples:

- Plasma not frozen within 24 hrs can be used for producing IVIG and albumin
- Anti-HBc + plasma may be fractionated (if HBsAg -, and presence of anti-HBs)
- No need for NAT for WNV or Zika virus (USA) for plasma for fractionation

The answer is? Yes or No

Not necessarily!
Technological features of plasma fractionation

Integrated production chains

1-3 Viral reduction treatments integrated with the production processes

Conventional chromatography (rather than immuno-affinity)

Multiple products (>3) from one plasma pool

Precipitations + chromatography + ethanol fractionation
Technological features of plasma fractionation

Current technology is typically based on combination of:

<table>
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<tr>
<th>Technology</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Cryoprecipitation</td>
<td>• Still used to isolate cryoprecipitate for Factor VIII isolation</td>
</tr>
<tr>
<td>Chromatography</td>
<td>• Mostly ion-exchange and affinity</td>
</tr>
<tr>
<td></td>
<td>• Used for most proteins</td>
</tr>
<tr>
<td>Ethanol fractionation</td>
<td>• Still used for albumin</td>
</tr>
<tr>
<td></td>
<td>• Decreasing use for IgG</td>
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</table>
Evolution of plasma fractionation scheme

- Plasma
  - Thawing
    - Cryoprecipitate
      - Precipitation/adsorption
        - Chromatography
          - Cryo-poor plasma
            - Chromatography
              - Fraction (I+) II+III
                - Chromatography
                  - aFII
                    - Chromatography
                      - FVII
                      - FIX
                      - PCC
                      - PC
                      - AT
                    - Chromatography
                      - Fibrinogen
                        - Ethanol fractionation
                          - Alpha 1-AT
                            - Albumin
                          - IgG
                          - Chromatography
                            - Fibrinogen
                              - Evolution of plasma fractionation scheme
                                - FVIII
                                - vWF
        - Chromatography
          - Fibrinogen
            - + viral reduction treatments integrated in this process
Viral reduction technologies in plasma fractionation

Last 40 years:
from “no” to “multiple” viral inactivation treatments
Fractionation technology selection criteria

Donors

Purification
Viral reduction

IgG
Factor VIII
Factor IX
Albumin
Alpha 1-AT

Patients

Quality and Safety nets

GMP
Plasma products overall viral safety nets

Epidemiological surveillance

Donor’s screening

Donation testing

Mini-pool NAT testing

Viral reduction treatments

A robust set of safety measures under Regulatory Authorities supervision

Emerging agents

General risk factors

Tested known pathogens (HIV, HBV, HCV)

Tested known pathogens (HIV, HBV, HCV, HAV, B19)

Known and emerging pathogens (WNV, Dengue, Zika, etc.)
Donors and donations safety

Donors safety

Donation testing

Minimal infectious load in manufacturing plasma pool

Crucial importance of dedicated virus inactivation/removal treatments during fractionation

Risks of emerging pathogens

Tested and known pathogens
• Broad spectrum of inactivation/removal efficiency

• Optimal protein recovery

• Absence of protein denaturation
Range of viral reduction methods

• Since 1970’s-1980’s: plasma fractionation at the forefront of development of viral reduction treatments:
  ✓ Before: in response to existing virus threats
  ✓ Now: to safeguard against future viruses

• Several viral reduction (inactivation and removal) methods used in plasma fractionation
Viral reduction treatments in plasma fractionation

1960's: Pasteurisation
1980's: Low pH
1983: Dry-heat
1987: Solvent-detergent
1991: Nanofiltration
2000: Caprylic acid

HBV: Albumin (then some other products):
Enveloped viruses: IgG
HIV: Coagulation factors
HIV, HCV, HBV: All products
HAV, B19: All products
IgG
Fractionated plasma products have never been safer for HIV, HBV, HCV? The answer is yes or no?

The answer is yes.
What about emerging viruses?

- Ebola virus
- MERS- Coronavirus virus
- Chikungunya virus
- Hepatitis E virus
- Avian flu virus
- SARS coronavirus virus
- Dengue virus
- West Nile virus
- NYIV (Not Yet Identified Virus)
Plasma products transmit emerging viruses?

The answer is? Yes or No

NO
### Technologies in place safeguard against recent “emerging” viruses

<table>
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<tr>
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S/D Technologies in place safeguard against recent “emerging” viruses.
### Technologies in place can safeguard against recent “emerging” viruses

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Safety against emerging viruses should be built in the manufacturing process.

**nano-filtration**
However, with any biological products, one should not lower the guard.

Importance of using proven robust technologies to avoid mistakes from the past to happen again.

“Those who do not remember the past are condemned to repeat it” (George Santayana)

Slide inspired from Dr. Thomas Kreil presentations on viral safety.

Source: https://en.wikipedia.org/wiki/George_Santayana#/media/File:George_Santayana.jpg
Organisational points to consider
Supply of plasma products at national level: options

• **Import of products**
  
  – Plasma-derived (wide range of products)
  – [Recombinant FVIII & FIX]

• **Use of local plasma: fractionation**
  
  – Contract fractionation (or similar arrangements)
  – Domestic fractionation
Why fractionation of local plasma?

- Some guarantee in plasma product supply
- Diversity in range of plasma products available
- Sustainability of blood establishments: more products from blood donations (recovered plasma)

**Added benefits:**

*enhancement of Quality Assurance system*
How to fractionate local plasma?

- Contract fractionation abroad
- Supply of plasma / exchange of products
- Domestic fractionation
Contract fractionation
Contract fractionation: organisational aspects

- Production of plasma for fractionation
  - Meet quality criteria
  - Meet minimum volume requirements

- Identification of a fractionator
  - Licensed
  - Product portfolio adapted to local needs
  - Free fractionation capacity
Contract fractionation: local requirements

- Harmonized blood/plasma collection practices at national levels, or at least in major blood establishments
- Guarantee/continuity of plasma supply on long term
- Identified local plasma product needs for 3 – 4 products (albumin, IgG, FVIII, FIX/PCC)
- Government/regulatory authorities support
What is the minimum and maximum volume of plasma for contract fractionation?

Minimum: +/- 10’000 – 20’000 L

Maximum: 250’000 L
Minimum and maximum number of plasma donations (200 mL) needed for contract fractionation

Minimum: 50,000 – 100,000 donations

Maximum: 1,250,000 donations
Selection plasma fractionator: criteria to consider

- Willingness/interest in (contract) fractionation services
- Licensing status, GMP inspection records, products quality and safety records are evident
- Portfolio of licensed products, dosages, and clinical indications matches local needs
- Minimum/maximum volume capacity
- Contract terms (cost, obligations, legal aspects)
Plasma fractionator’s audits role

• “Gap analysis” between:
  – its collection criteria of plasma for fractionation
  – and current collection practices by the audited blood establishment
Plasma supplier’s NRA roles

- Assessment of local plasma quality as soon as the project appears technically realistic
- Licensing of final products for local marketing
Plasma fractionator’s NRA roles

• Approval of fractionation of foreign plasma

• Such approval may rely:
  – Rely on plasma fractionator auditing reports
  – involve direct inspections of plasma supplier in coordination with the local RNA
Parties involved

GMP- common principles

NRA

Quality Assurance Program

PLASMA SUPPLIER

across countries

FRACTIONATOR

GMP Licensing

GMP Licensing

A. Padilla, WHO
Minimum volume of plasma considered to be needed for domestic fractionation?

Minimum

300'000 L
Domestic fractionation: points to consider

- Guarantee/continuity of plasma supply for at least 20 years
- Established needs for plasma products
- Government commitment (e.g. NRA; product reimbursement)
- Financial resources
- Skilled management
- Skilled manpower
- Engineering skills
Domestic fractionation: possible phasing

Final products

Plasma

CONTRACT FRACTIONATOR

LOCAL

ABROAD
Domestic fractionation: possible phasing

**CONTRACT FRACTIONATOR**
Downstream processing
(purification, viral inactivation, dispensing, QC)

**Plasma**

**LOCAL**
Bulk fractionation

**Intermediates**

**Final products**

**LOCAL**

**ABROAD**
Domestic fractionation: possible phasing

Plasma

Other intermediates

IgG, FVIII, FIX

CONTRACT FRACTIONATOR
Downstream processing
(purification, viral inactivation, dispensing, QC)

Albumin

LOCAL

ABROAD
Domestic fractionation: possible phasing

- IgG, FVIII, FIX
- Assistance + product improvement
- FULL LOCAL FRACTIONATION
- FOREIGN FRACTIONATOR
- Plasma
- Albumin
Further reading

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

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

© World Health Organization

Annex 4
WHO guidelines on good manufacturing practices for blood establishments

© World Health Organization
Conclusions

Human plasma fractionation: well-established, unique biotech industry

Human plasma products: high quality and safety margins built on over 50 years of production history and clinical use

Clinical needs for human plasma products: expected to continue to grow in the foreseeable future, justifying efforts to avoid wasting plasma

Local plasma fractionation programs: require technical, regulatory (government) & financial commitments to meet international quality and safety benchmarks