Plasma fractionation: “Setting the scene”

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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

A myriad of proteins (Complex proteome)

Extraction of >3-15 therapeutic protein products

Unique raw material

Unique manufacturing technology
Plasma: a rich biological material

Abundant proteins + physiologically important trace proteins
The technological difficulties of the plasma fractionation process should be realized.
Clinical fields covered by plasma products

<table>
<thead>
<tr>
<th>Products</th>
<th>Clinical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvalent immunoglobulins</td>
<td>Substitutive therapy (IgG deficiency) Immunomodulation</td>
</tr>
<tr>
<td>Hyperimmune Immunoglobulins</td>
<td>Treatment and prophylaxis of infectious disease, Prevention of hemolytic disease of newborn</td>
</tr>
<tr>
<td>Coagulation factors (VIII, IX, vWF, VII)</td>
<td>Coagulation factor deficiency</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Congenital or acquired deficiency</td>
</tr>
<tr>
<td>Prothrombin complex</td>
<td>Coagulation defects due to liver disease</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Congenital deficiency</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin</td>
<td>Lung panacinar emphysema due to congenital deficiency</td>
</tr>
<tr>
<td>Albumin</td>
<td>Blood volume replacement / oncotic pressure</td>
</tr>
</tbody>
</table>

Diversity in the clinical indications covered by plasma products

- Immunological disorders
- Infectious diseases
- Hemolytic disease
- Coagulation & bleeding disorders
- Metabolic diseases
- Traumas, ...
Unique technological features

- 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 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 to accommodate all products “within the same roof”
Plasma fractionation: Key driving factors

- Access to qualified plasma
- Product portfolio
- Yield & quality
- Pathogen safety

Sourcing of Plasma for fractionation

Choice of plasma fractionation technology
Can a donor donating plasma for transfusion be eligible to donate plasma for fractionation?

The answer is? Yes or no?

Yes
Are storage or testing requirements for plasma for fractionation more stringent 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 virus reduction treatments integrated within the production processes

Conventional chromatography (rather than immuno-affinity)

Multiple products (>3) from one plasma pool

Precipitations + chromatography + ethanol fractionation
Plasma fractionation technologies

Current technology is typically based on combination of ...

<table>
<thead>
<tr>
<th>Technology</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitation</td>
<td>• (Still) used to isolate cryoprecipitate for Factor VIII production</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 production</td>
</tr>
<tr>
<td></td>
<td>• Decreasing use for IgG production</td>
</tr>
</tbody>
</table>

... and continues to evolve gradually to improve product yield and quality
Evolution of plasma fractionation scheme

Plasma

Thawing

Precipitation/adsorption

Cryoprecipitate

Chromatography

Cryopoor plasma

Chromatography

Cryo-poor plasma

Chromatography

Fraction (I+ II+III)

Chromatography

Fibrinogen

Ethanol fractionation

Alpha 1-AT

Albumin

+ viral reduction treatments integrated in this process

FVIII

vWF

Fibrinogen

FVII

FIX

PCC

PC

AT

Chromatography

Chromatography

Chromatography

Chromatography

Chromatography

Chromatography

Chromatography

Chromatography

IgG

Evolution of plasma fractionation scheme

E
Virus safety in plasma fractionation

Last 40 years:
from “no” to “multiple” virus safety steps
GMP from Z to A

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/manufacturing pool
- Virus reduction treatments

Robust set of safety measures under the supervision of the Competent Authorities

Emerging agents
General risk factors
Known pathogens (HIV, HBV, HCV)
Relevant known pathogens (HIV, HBV, HCV, HAV, B19)
Known and emerging pathogens (WNV, Dengue, Zika, etc.)
Donors and donations safety

Donors safety

Donation testing

Plasma for fractionation

Crucial importance of dedicated virus inactivation/removal treatments during fractionation to safeguard product safety

Risks of emerging viruses

Tested and known pathogens

Minimal infectious load in manufacturing plasma pool

Unknown/not tested viruses
Selection criteria of viral reduction methods

• Broad spectrum of inactivation/removal efficiency of viruses

• Optimal protein recovery and no protein denaturation (neoantigens)
Range of viral reduction methods

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

• Several types of virus reduction 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 so safe with regards to risks of HIV, HBV, HCV.

The answer is ? Yes or no?

Yes
What about emerging viruses?

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

The answer is? Yes or No

At least not when “orthogonal” complementary virus reduction treatments are implemented.
Technologies in place safeguard against recent “emerging” viruses

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>Enveloped (E)</th>
<th>Size (nm)</th>
</tr>
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<tbody>
<tr>
<td>Avian Flu</td>
<td>E</td>
<td>80-120</td>
</tr>
<tr>
<td>SARS</td>
<td>E</td>
<td>80-90</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>E</td>
<td>60-70</td>
</tr>
<tr>
<td>Dengue</td>
<td>E</td>
<td>40-45</td>
</tr>
<tr>
<td>West Nile</td>
<td>E</td>
<td>40-45</td>
</tr>
<tr>
<td>MERS-coronavirus</td>
<td>E</td>
<td>80-90</td>
</tr>
<tr>
<td>Ebola</td>
<td>E</td>
<td>120</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>NE</td>
<td>27-34</td>
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S/D Technologies in place safeguard against recent “emerging” viruses
Technologies in place can safeguard against recent “emerging” viruses

<table>
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<th>VIRUS</th>
<th>Size (nm)</th>
<th>Safety against emerging viruses should be built in the manufacturing process</th>
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<td>Avian Flu</td>
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S/D Technologies in place can safeguard against recent “emerging” viruses

nano-filtration
However, as 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)

http://www.leblogfinance.com

Slide inspired from Dr. Thomas Kreil presentations on viral safety

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

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

• **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 QA system
How to fractionate local plasma?

- Contract fractionation abroad
- Supply of plasma in exchange of products
- Domestic fractionation
Contract fractionation

Country of plasma collection

Country of plasma fractionation
Contract fractionation: organisational aspects

• Production of plasma for fractionation
  – Meet quality criteria (audits and inspections)
  – Meet minimum volume requirements (imposed by fractionator)

• Identification of a fractionator
  – Licensed
  – Product portfolio adapted to local needs
  – Spare 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
- Well 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 (in one site)
Minimum and maximum number of plasma donations (200 mL) needed for contract fractionation:

Minimum: 50,000 – 100,000 donations

Maximum: 1,250,000 donations
Excess products of contract fractionation must be destroyed by plasma fractionator.

The answer is **No**.

When the plasma quality meets the requirements of fractionator and the competent authorities.
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)
• “Gap analysis” between:
  – its collection criteria of plasma for fractionation
  – and current collection practices by the local audited blood establishment
• 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 on plasma fractionator auditing reports
  – Involve direct inspections of plasma supplier in coordination with the local RNA
Minimum yearly volume of plasma considered to be needed for domestic fractionation?

- 50,000 L
- > 1,000,000 L
- 300,000 L
Guarantee of plasma supply for at least 20 years
Established clinical needs for plasma products
Government commitment (e.g. NRA; product reimbursement)
Financial resources
Skilled management
Skilled manpower
Engineering skills
Domestic fractionation: possible phasing
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

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

Plasma

Other intermediates

IgG, FVIII, FIX

Albumin

Locally:

INTERNATIONALLY:
Domestic fractionation: possible phasing

FULL LOCAL FRACTIONATION

IgG, FVIII, FIX

Plasma

Assistance + product improvement

Albumin

FOREIGN FRACTIONATOR
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