Plasma Fractionation Technologies Benefits and Limitations

Online Workshop organized by the Working Party for Global Blood Safety (GBS) of the ISBT

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Declaration of interest

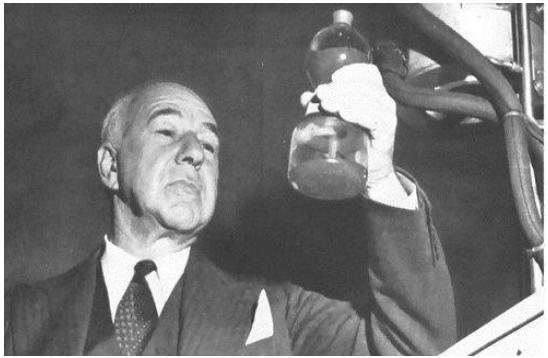
- Consulting services to
  - Biopharma Plasma
  - Plasma Protein Therapeutics Association
  - Prolacta BioScience
  - Prothya Biosolutions

Plasma Fractionation Technologies

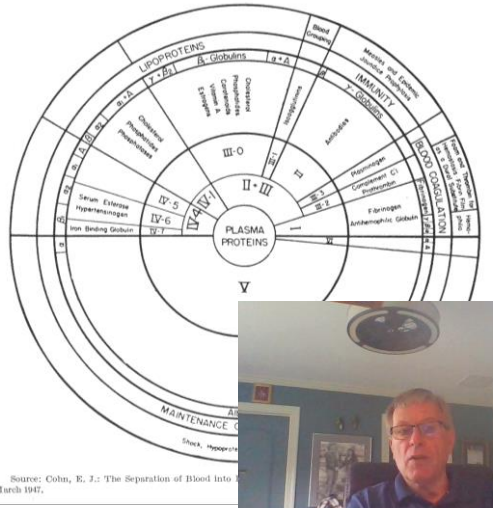
Benefits & Limitations

1. History of Cohn Fractionation
2. Modifications to Cohn
3. Recent LMIC Examples
4. Main Implementation Challenges
5. Solution: Step–by-Step
6. Key Points Learned

Edwin J. Cohn, PhD, 1892–1953

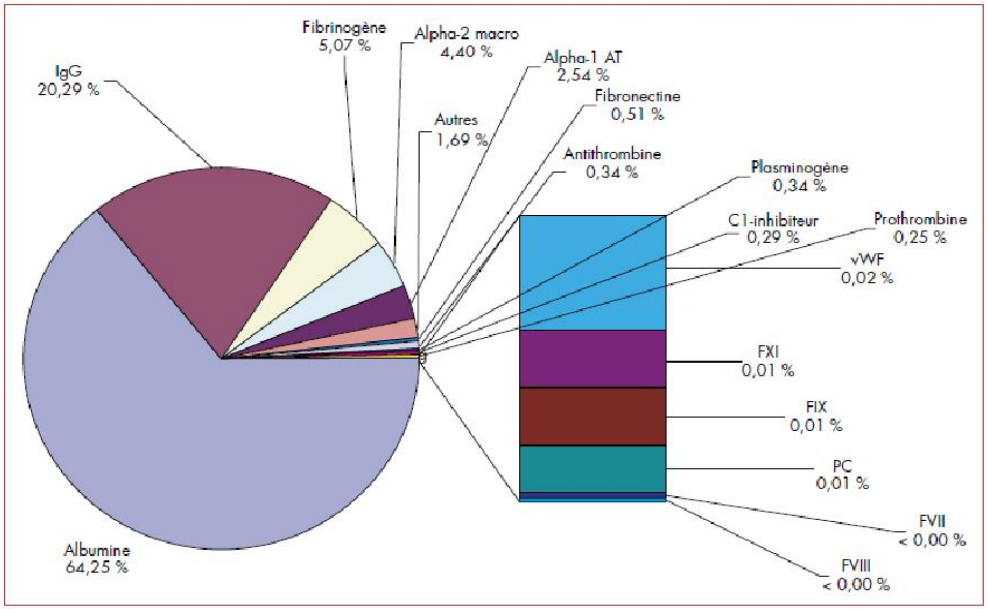


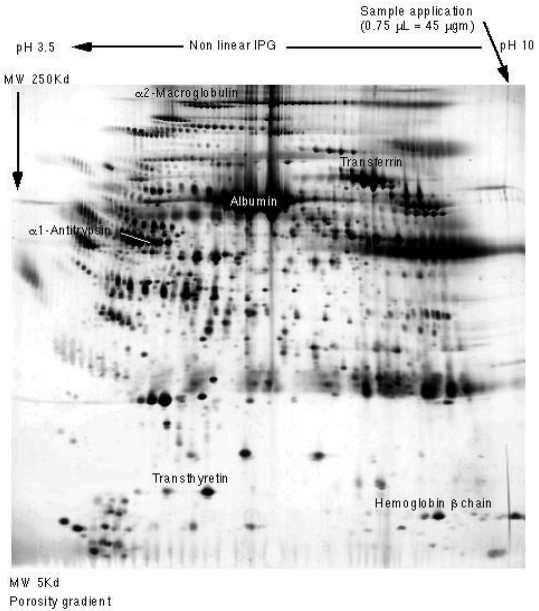
- **Developed techniques to isolate human serum albumin from plasma**
- **All Albumin prepared in his laboratory at Harvard Medical school was flown to Pearl Harbor**
- **Cohn worked with 15 chemists to define the characteristics of proteins**



Source: Cohn, E. J.: The Separation of Blood into
March 1947.

Plasma: Unique and Complex Biological Material





Unique combination of protein purification technologies to isolate abundant pro (albumin, immunoglobulins) and trace Proteins (factor VIII, Factor IX)

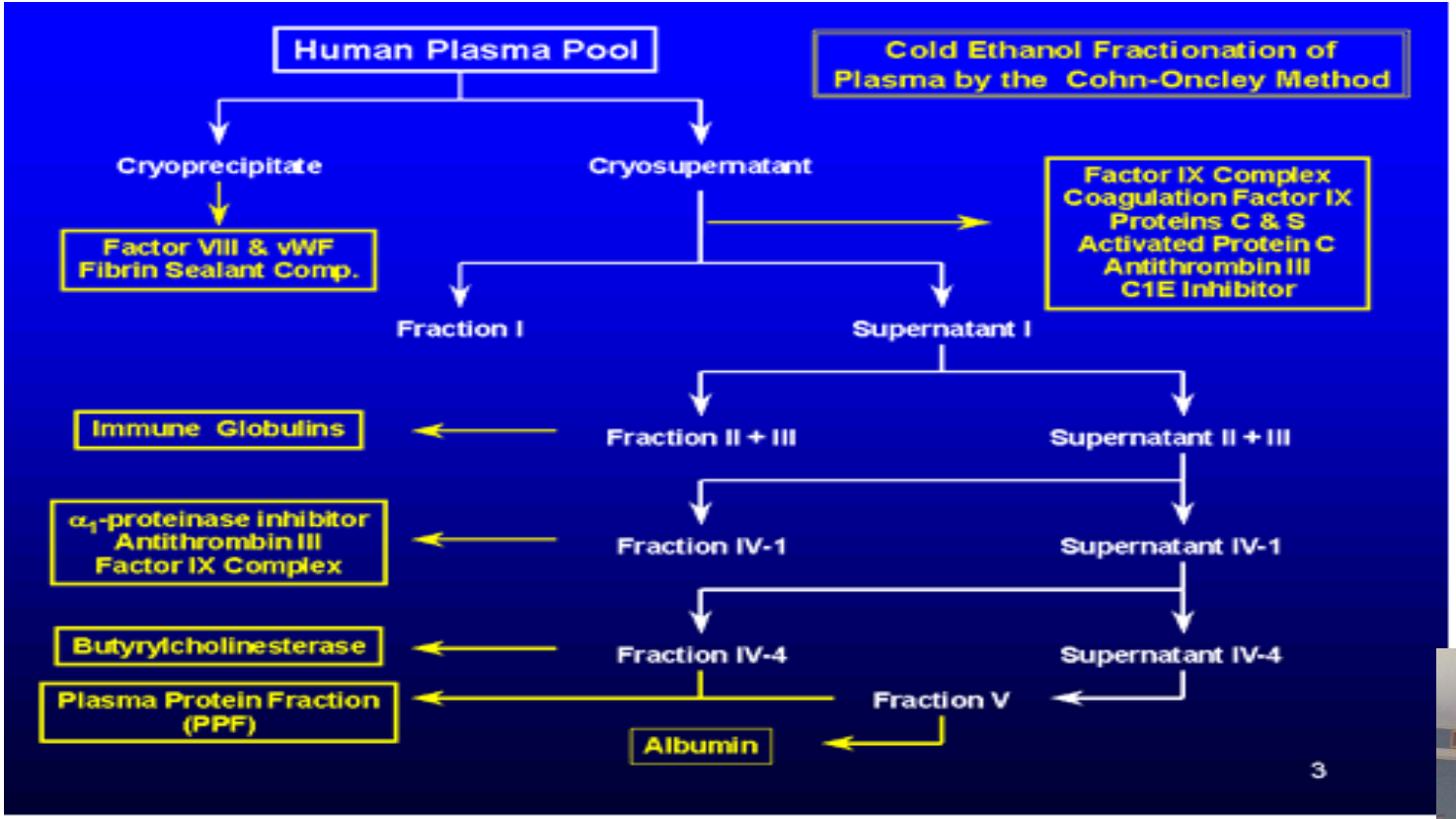
Source: Thierry Burnouf, IPFA Workshop Capetown, December 2015

Average Yield of Plasma Proteins Per Liter

Range of Plasma Derived Medicinal Products

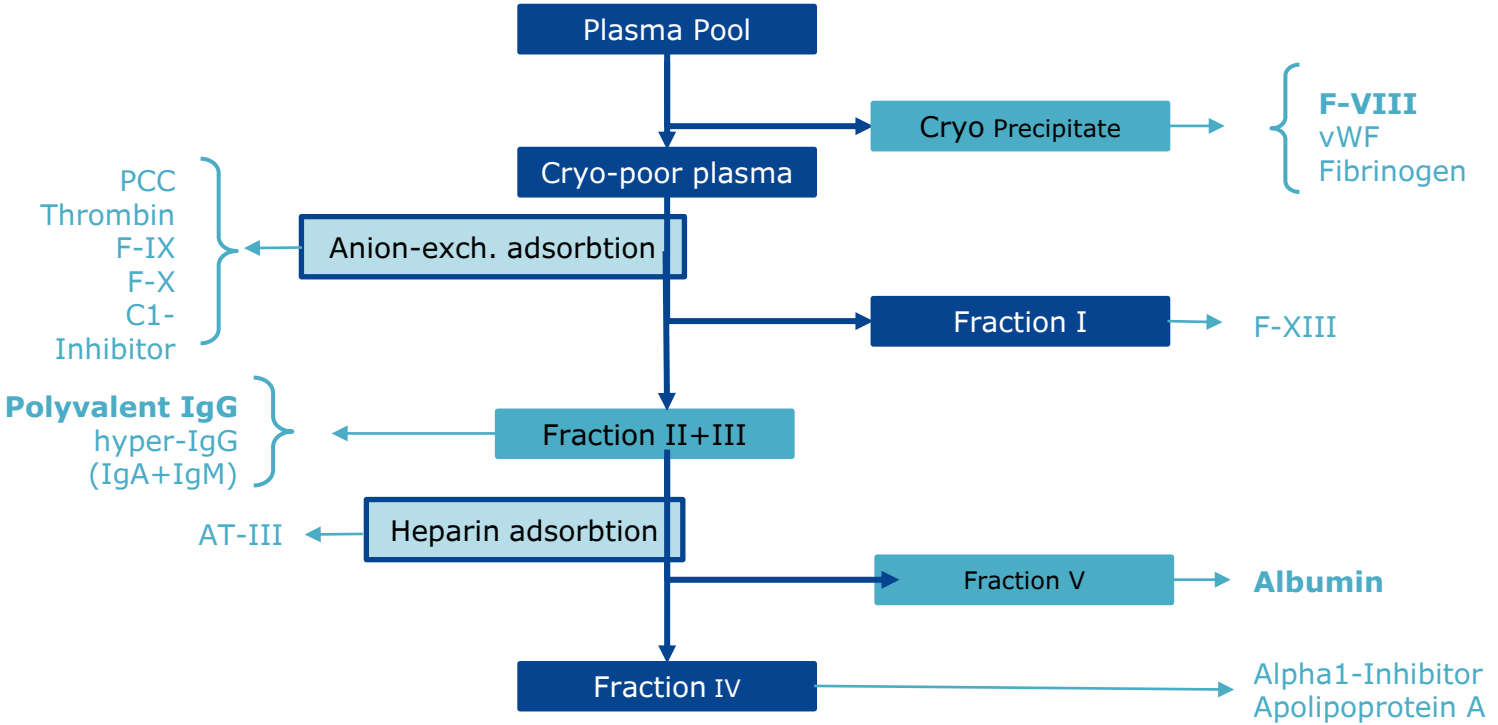
Albumin	Anti coagulant	Coagulation factors	Immuno globulins	Protease inhibitors	Others
	Antithrombin	Factor II	**Polyvalent***	Alpha – 1 antitrypsin	Coeruloplasmin
	Protein C	Factor VII	anti-CMV	C1-esterase inhibitor	IgA, IgM
		Factor VIII*	anti-D		Apolipoprotein A1
		Factor IX*	anti hepatitis B		Haptoglobin
		Factor X	**anti-rabies***		Plasminogen
		Factor XI	**anti-tetanus***		
		Factor XIII	anti—varicella zoster		
		Fibrinogen			
		Fibrin sealant			
		Prothrombin complex			
		Von Willebrand factor			
*** WHO Essential Medicines**					

Cohn-Oncley Fractionation and Products



Oncley, et al. J. Am. Chem. Soc. 71: 41-550, 1949

Main Plasma Fractions and Products



Legend

- Base Fractionation
- Globally traded intermediates
- Optional steps
- Downstream purficiation

Adapted from: Oncley, et al. J. Am. Chem. Soc. 71: 41-550, 1949; "Cold ethanol fractionation"

Important to Consider

- ✓ Only high quality, well controlled raw material sources and well established production processes will result in high quality, safe products
- ✓ Uncompromised quality control and quality assurance is mandatory
- ✓ Deviations or process modifications can lead to serious product adverse events, e.g Fractionation I-II-III will increase IgG yield, but requires more efficient separation of “contaminating” proteins
- ✓ Risk of thromboembolic active substances not being separated as e.g immunoglobulins and FXIa are comparable in size and iso-electric point.
- ✓ NM- filtration requires specific know-how and virus reduction experiments to decide the pore size e.g 20 or 35 nm.
- ✓ Strategies for virus inactivation depend on the plasma protein product and its formulation e.g. liquid or freeze-dried.
- ✓ Continuous training and education of personnel is essential.

IT IS ALL IN THE DETAILS!

Purification Schemes of Selected IVIG Products

Plasma → Cohn Fraction (I+) II + III
Kistler-Nitschmann Precipitate A

Flebogamma	Gamunex	Intratect	Kiovig	Octagam	Privigen
PEG precipitation	addition of caprylate	Separation of Fraction I + III	Separation of Fraction I + III	Separation of Fraction I + III	caprylic acid fractionation
Anion-exchange chromatography	Depth filtration	Fraction II	Depth filtration	Fraction II	Depth filtration
Ultra / diafiltration	addition of caprylate	Ultra/ diafiltration	Fraction II	Ultra/ diafiltration	pH4 incubation
pH4 treatment	Depth filtration	Caprylic acid / Ca-acetate treatment	CM - Sepharose	S/D treatment	Depth filtration
Pasteurization	pH adjustment	S/D treatment	S/D Treatment	Oil / solid phase extraction	Anion-exchange chromatography
S/D treatment	Anion exchange chromatography	Cation-exchange chromatography	pH adjustment	pH4 treatment	20 nm nanofiltration
PEG precipitation	pH adjustment	20 nm nanofiltration	Anion-exchange chromatography		
TFF / resuspension	pH4 treatment		Depth filtration		
Ultra /diafiltration / formulation			35 nm nanofiltration		
35 and 20nm nanofiltration			pH4 treatment		

Virus elimination steps, caprylic acid contributes to purification, too

Ultra-Diafiltration, Product specific formulation
Sterile filtration & aseptic filling

«The process *is* the product»

Sequence and conditions of each step are pivotal for **purity AND safety*** of a product.

«Keep it simple »

The more process steps, the lower the yield, the worse the economics.

e.g. for the undesired activation of F-XI or F-XII

Ada
Proc
Th

Modern Fractionation, Purification, Fill & Lyophilization Plant

Pool sizes vary from 300 – 6000 liter

Some Examples of Recent Improved Access to PDMP's in Resource Constrained Countries

Thailand


ศูนย์บริการโลหิตแห่งชาติ
สภากาชาดไทย
NATIONAL BLOOD CENTRE
THAI RED CROSS SOCIETY

Ukraine

- First step: sufficient supply of PDMP's to Ukraine
- Next step: Export

Biopharma is a company in Eastern Europe that has a state-of-the-art plant, built in 2019, to produce PDMP's

Planned capacity: 1 million liter per year

Ukraine

Total investments : $100 - $200 million (and counting)

Main Challenges for Implementation

It Is Not Easy

STATENS SERUM INSTITUT

INSTITUT MERIEUX

bpl
Bio Products Laboratory
a commitment for life

biovitrum.

Novo Nordisk And HemaSure Make Plasma Deal

12-02-1996

Finnish Red Cross Blood Service

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE®

An LFB Company
CAF-DCF
A HUMAN TO HUMAN APPROACH

Sanquin
Plasma Products

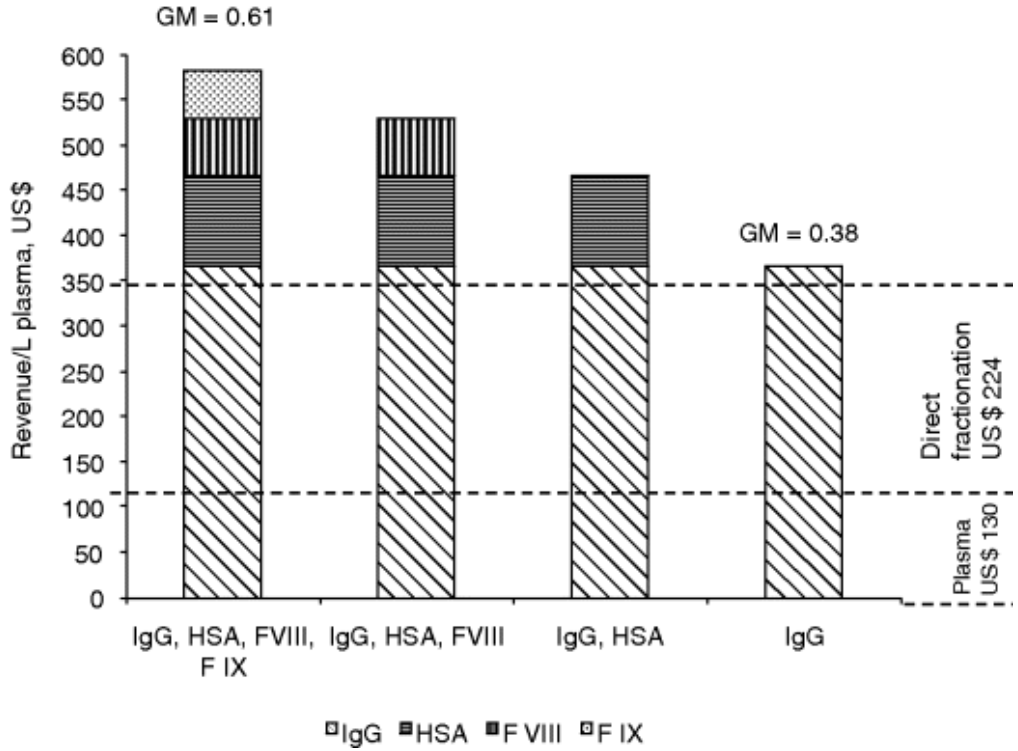
PHARMACIA

Pharmacia &Upjohn

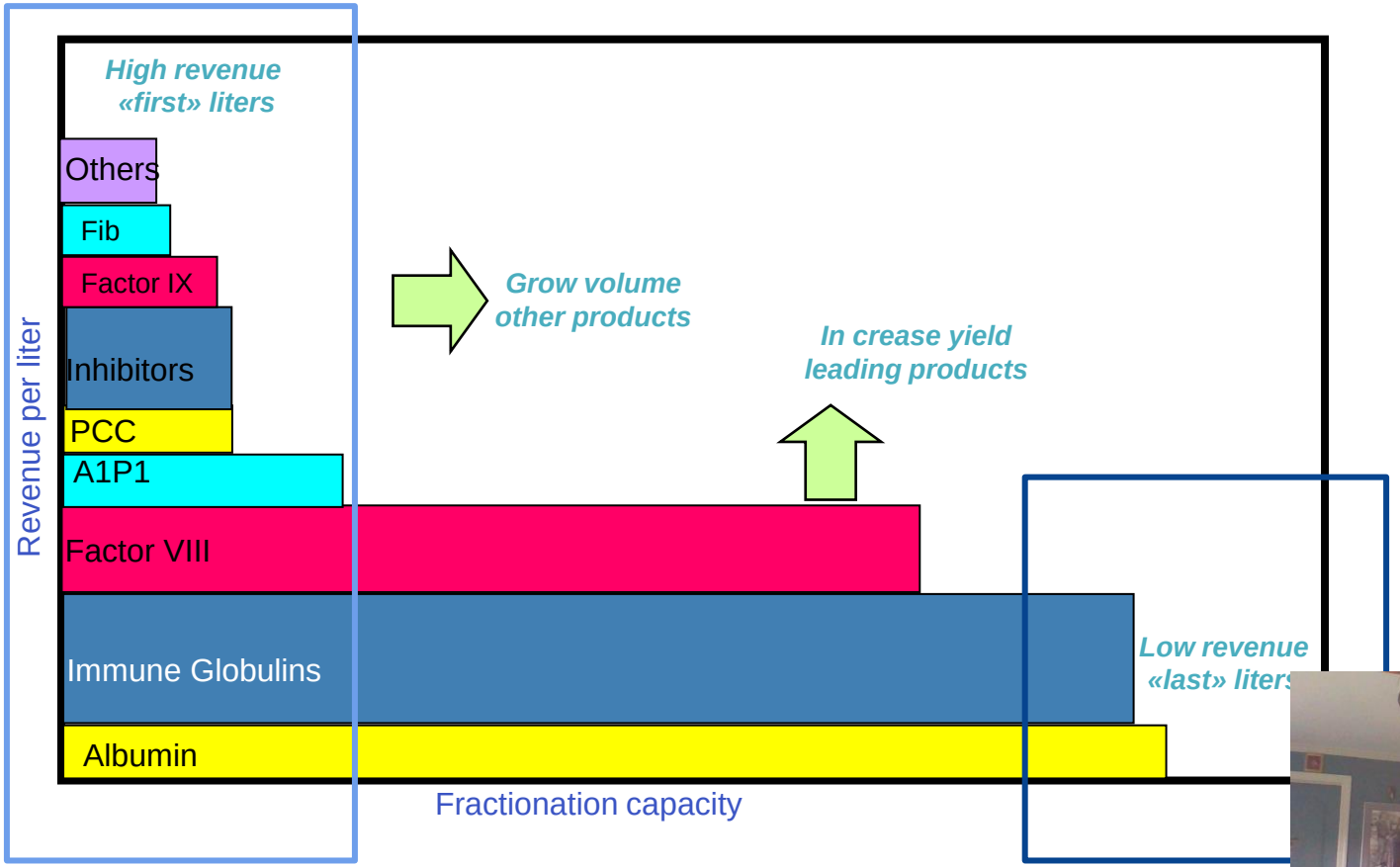
ZLB

Plasma: Unique and Complex Biological Material

Source: Production of plasma proteins for therapeutic use, Wiley 2013, page 452

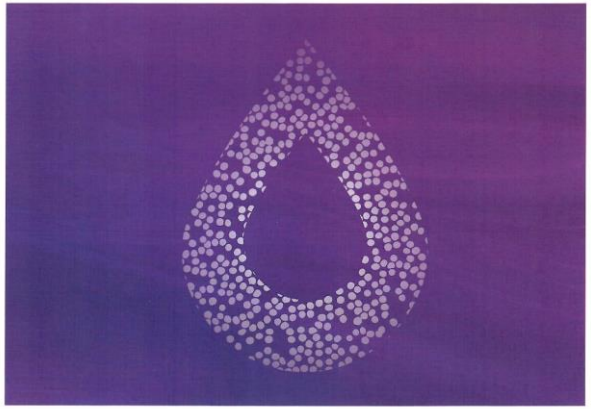


More Economics of Fractionation



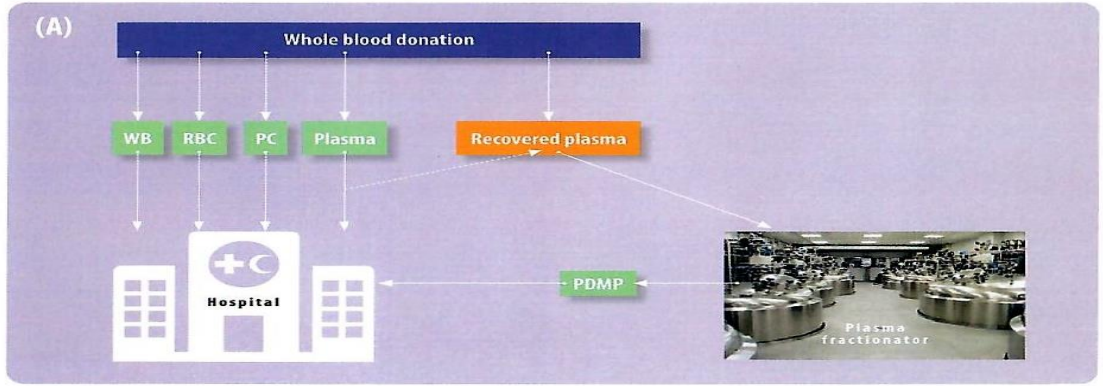
Proposed Solution Step-by-Step

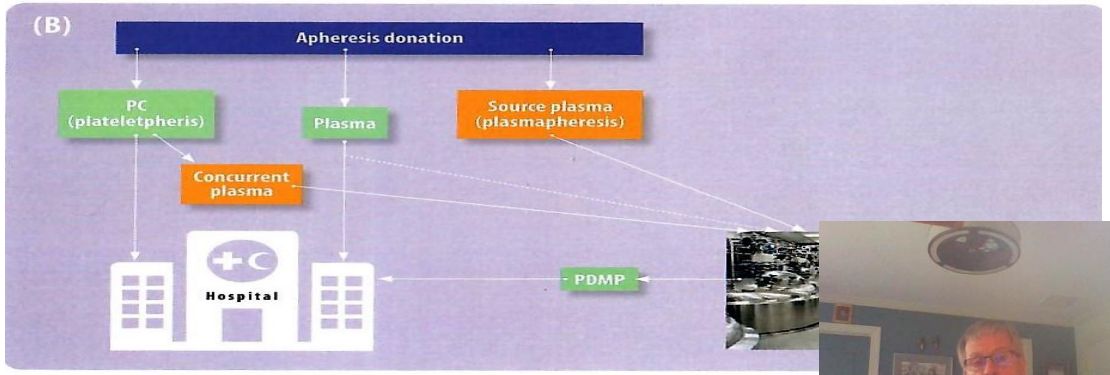
From 2021 WHO Guidance



GUIDANCE ON INCREASING SUPPLIES OF PLASMA-DERIVED MEDICINAL PRODUCTS IN LOW- AND MIDDLE-INCOME COUNTRIES THROUGH FRACTIONATION OF DOMESTIC PLASMA

World Health Organization

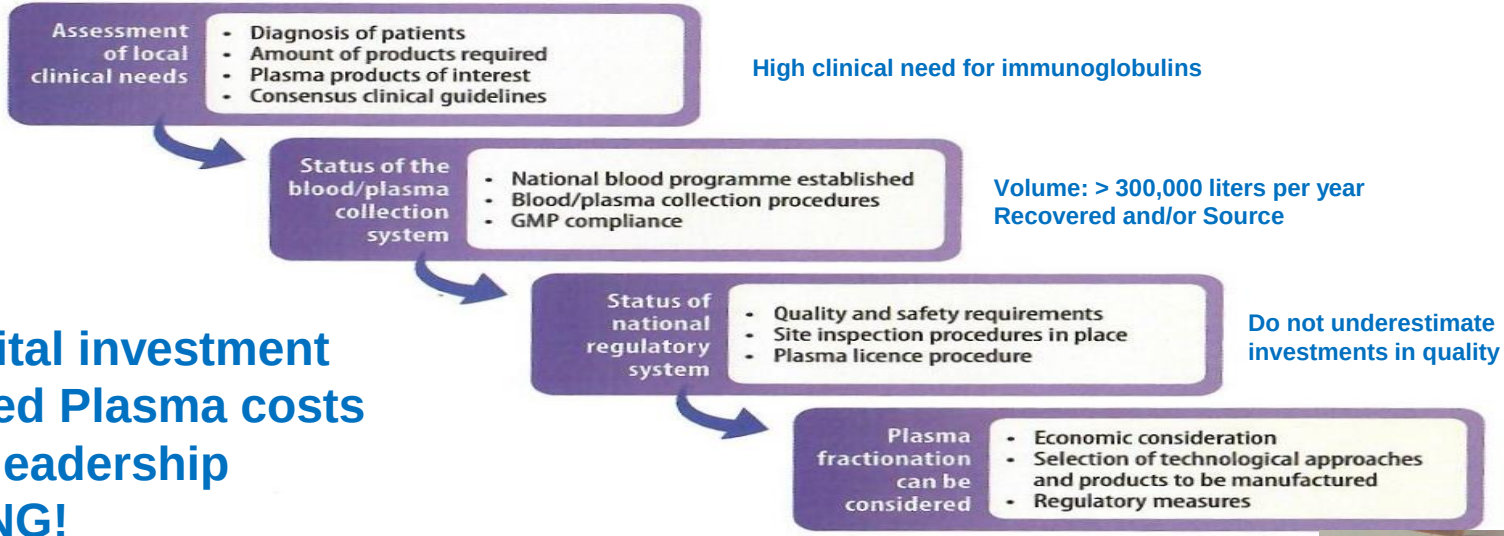




Plasma Fractionation Technologies Benefits and Limitations

Step–by–Step Approach

Fig. 1. Capacity-building and decision-making steps of plasma fractionation programme to improve availability of PDMPs made from domestically produced plasma



Big capital investment
Increased Plasma costs
Strong leadership
TRAINING!

Must have: Albumin and Immunoglobulin
Maybe: Factor VIII
Nice to have: Others

What Else?

- Determine minimum fractionation capacity, should be more than 200,000 liter per year

- Economics not favorable with e.g. 200,000 liter
  - 4-5 million gram albumin
  - approximately 800,000 gram immunoglobulin
  - approximately 40 million units FVIII

- Long term sourcing of plasma needs to be secured

- After decision for domestic fractionation several steps need to be taken
  - Select experienced, trust-worthy party for technology transfer
  - Facility design by engineering company with plasma protein experience
  - Equipment decision: design, qualification and validation
  - Process and Product qualification and validation
  - Personnel training programs
  - Clinicals
  - Ensuring c-GMP
  - Implementation of Quality Systems e.g. Self-auditing, Deviation reports, Tre

Key Points Learned

Take Home Messages

- ✓ Building a fractionation plant requires serious capital
- ✓ Technology transfer should mean that well known technology is transferred
- ✓ Complex technology requires in depth training
- ✓ Process modifications can increase yield but also impurities
- ✓ Process change can affect multiple products
- ✓ Do not ignore the risk of thromboembolic active substances due to process modifications
- ✓ Focus on quality is paramount
- ✓ Each donation and each pool are different
- ✓ Constant risk of emerging pathogens
- ✓ More products per liter is economically important

- ✓ Not all products are the same: THE PROCESS IS THE PRODUCT

WALK BEFORE YOU RUN

Thank You

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www.PPTAGlobal.org
www.DonatingPlasma.org

@PlasmaProteins
@PPTAEurope