Range of products available in developed and developing countries and gap-filling strategies

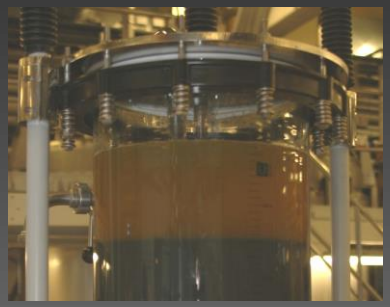
Thierry Burnouf, PhD
Graduate Institute of Biomedical Materials & Tissue Engineering
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Taipei, Taiwan
thburnouf@gmail.com

IPFA workshop – Cape Town – Dec 1 & 2, 2015









Historical perspectives:

Building-up a range of blood and plasma products at national levels



With my apologies
for some oversimplifications
in a world (or countries) facing disparities

Low income countries (case 1)



Blood*

Whole Blood

*WHO model list of essential medicines



Hemorrhage (pregnancy; childbirth)
Trauma (car accidents)
Anemia (malaria)

Emergency priority needs

Low income countries (case 2)



Blood

Blood separation

Blood

Red blood Cells

Plasma



Clinical Plasma

Hemorrhage (pregnancy; childbirth)
Trauma (car accidents)
Anemia (malaria)

Emergency priority needs

More specific clinical indications

Low-Medium income countries (case 1)

*WHO model list of essential medicines

Blood separation

Blood

Blood*

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) ?

- No freezing equipment
- No storage facility
- Quality criteria for fractionation are not met:
  - Traceability
  - testing criteria
  - Time between blood collection and plasma freezing
- 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)

Low-Medium income countries (case 2)

Blood separation

Blood

Blood

Red blood Cells

Platelets

Plasma

HOSPITAL

Clinical Plasma

Cryo

Plasma





Plasma for Fractionation

Storage

Contract fractionation
Domestic fractionation

« Compliance with specifications »

High income countries: recovered plasma

Blood separation

Blood

Blood

Red blood Cells

Platelets

Plasma



Cryo

Clinical Plasma

Plasma





Plasma for Fractionation

Storage

Contract fractionation
Domestic fractionation

« Compliance with international regulations »

No plasma wasted

High income countries: Apheresis plasma collection in blood centers



Apheresis collection

Hyperimmune plasma and standard plasma

Red blood Cells

Platelets

Plasma



Clinical Plasma

Plasma





Plasma for Fractionation

Storage

Hyperimmune IgG IVIG

Contract fractionation
Domestic fractionation

« Compliance with international regulations »

High income countries: Apheresis plasma centers



Apheresis collection

Plasma

Plasma centers







Plasma for Fractionation

Plasma fractionation plant

« Global » fractionation

« Compliance with international regulations »

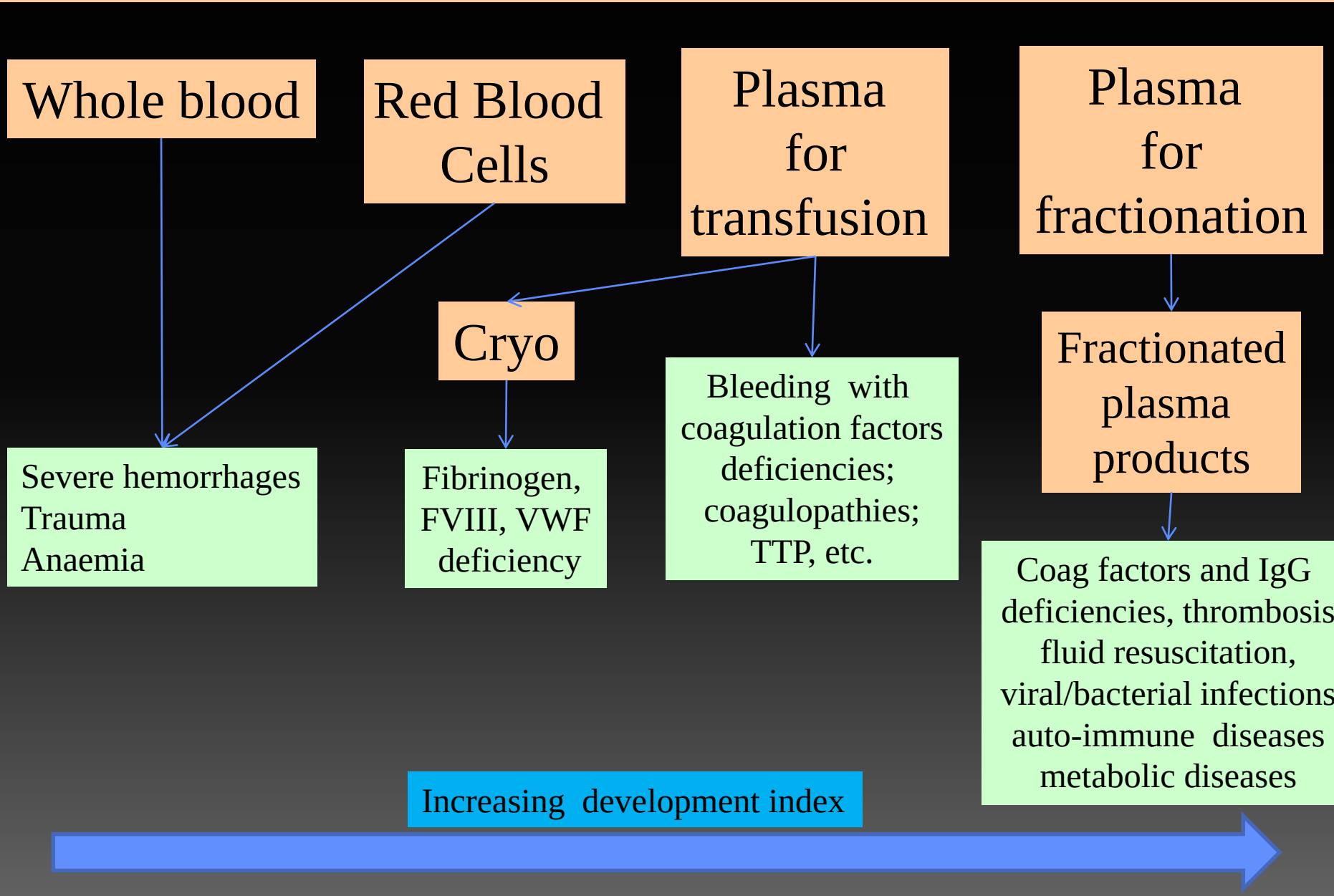
Plasma for fractionation in 2012

Worldwide

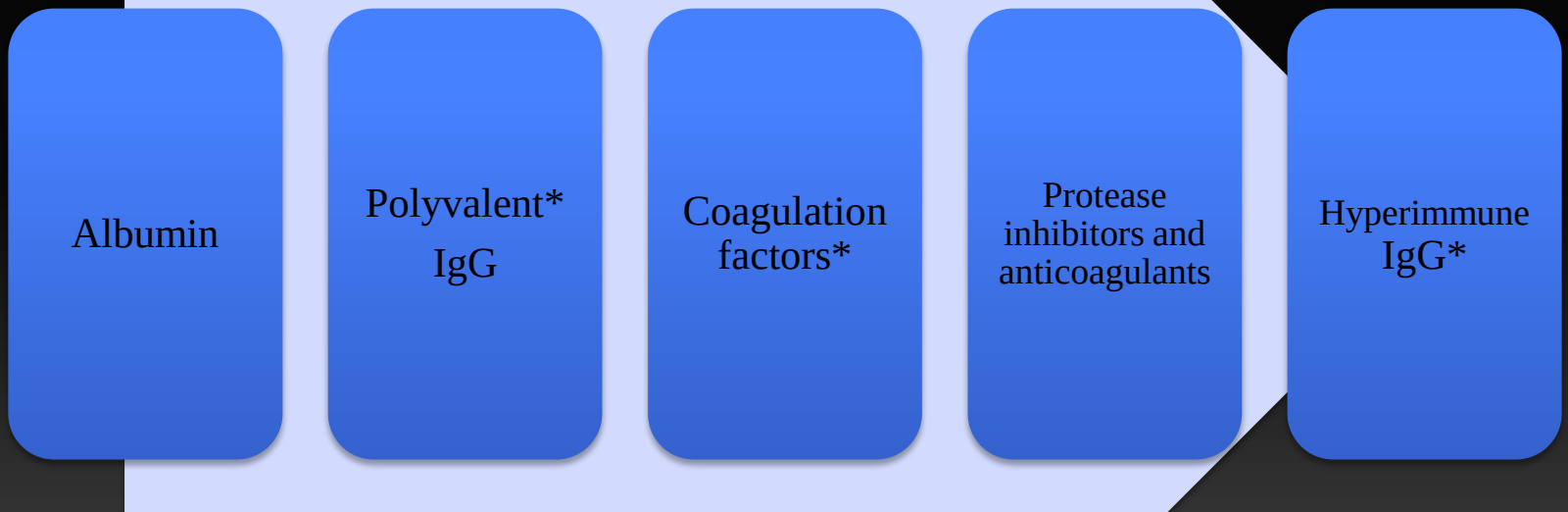
	Volume (million liters)
Recovered	8.9
Apheresis (« Source »)	27,9
Total	**36.8**

Source: Marketing Research Bureau, Directory of plasma fractionators, 2012

Towards selective hemotherapy



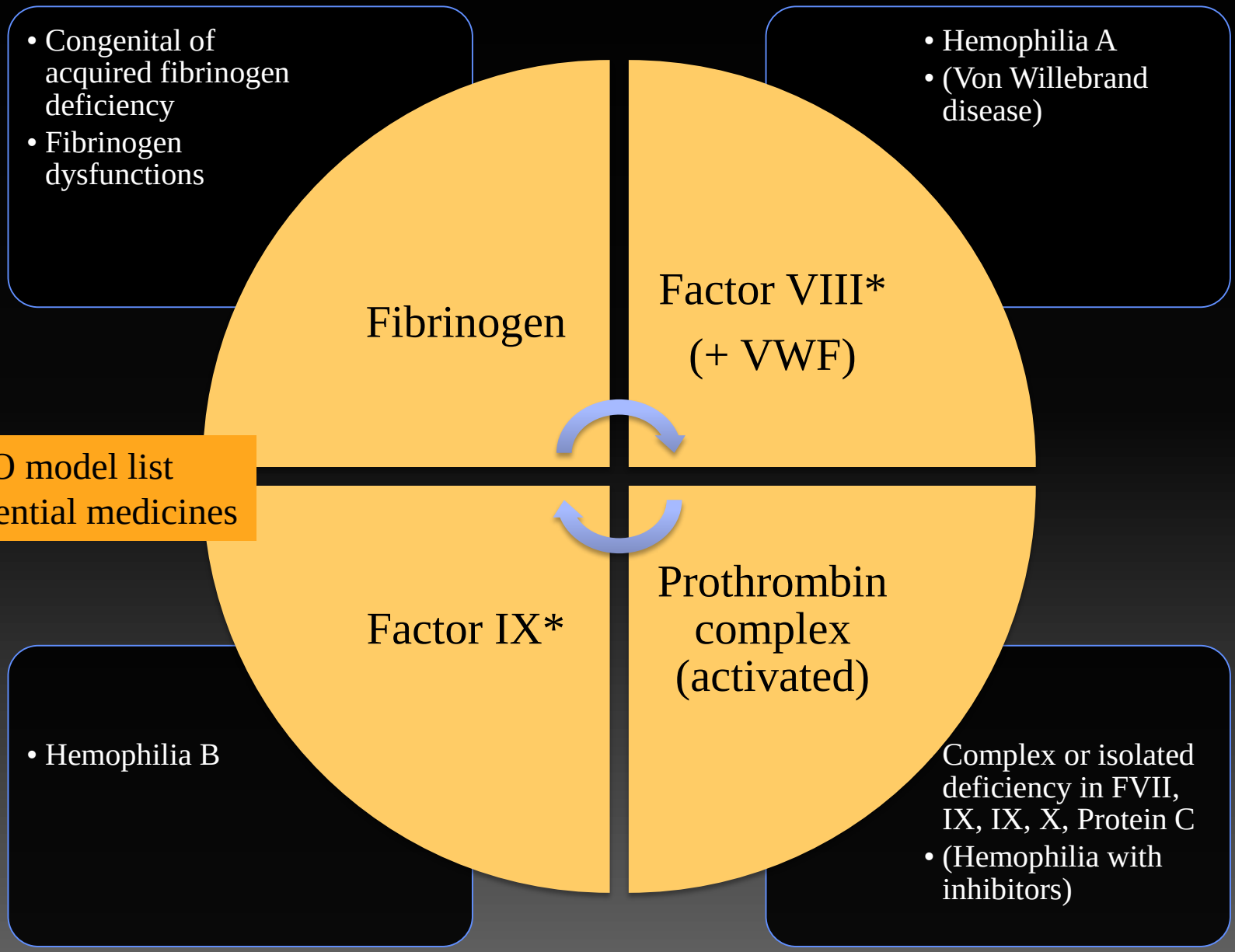
Range of fractionated plasma products produced or available in high-income countries



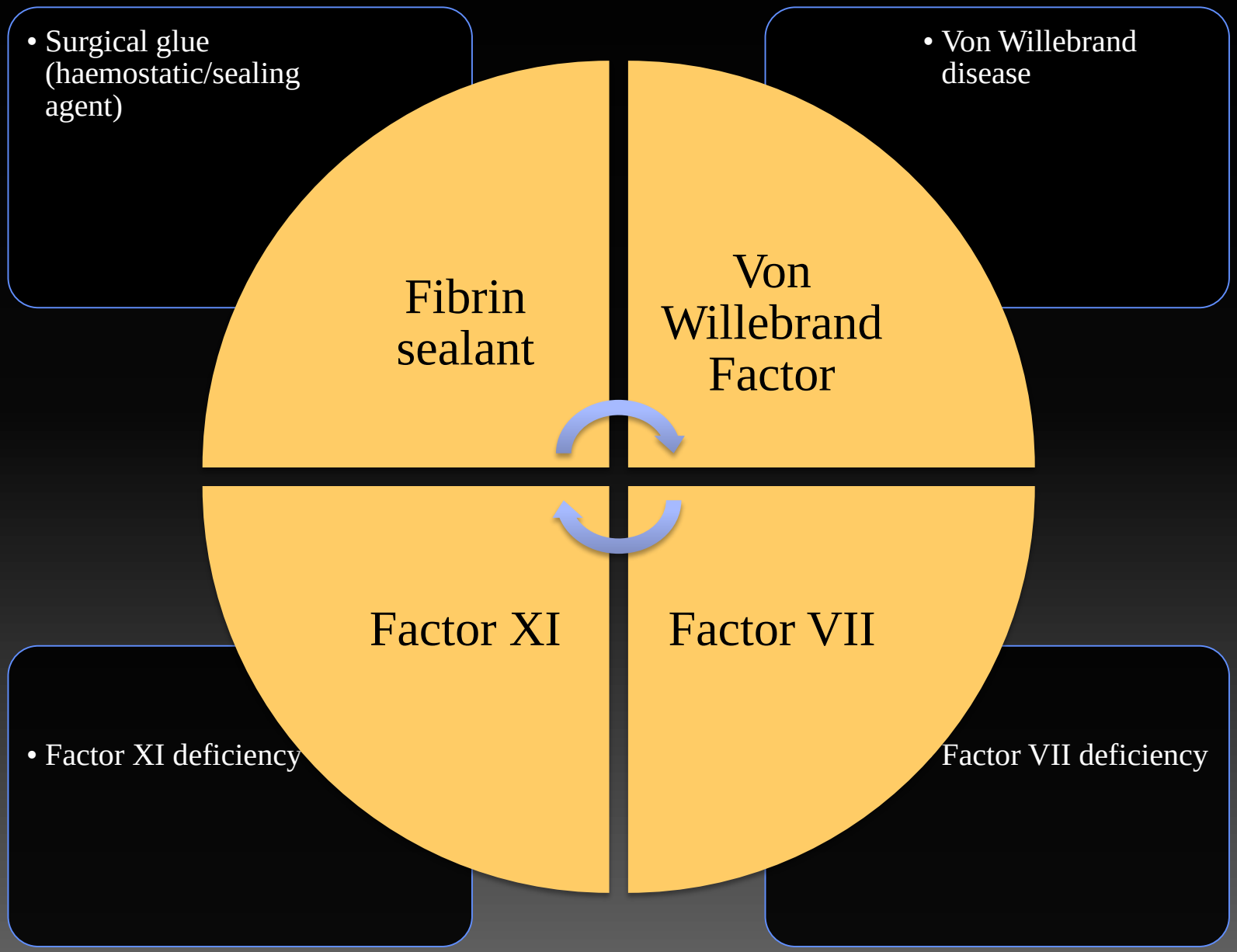
* WHO model list of essential medicines

Close to 20 protein therapeutics !

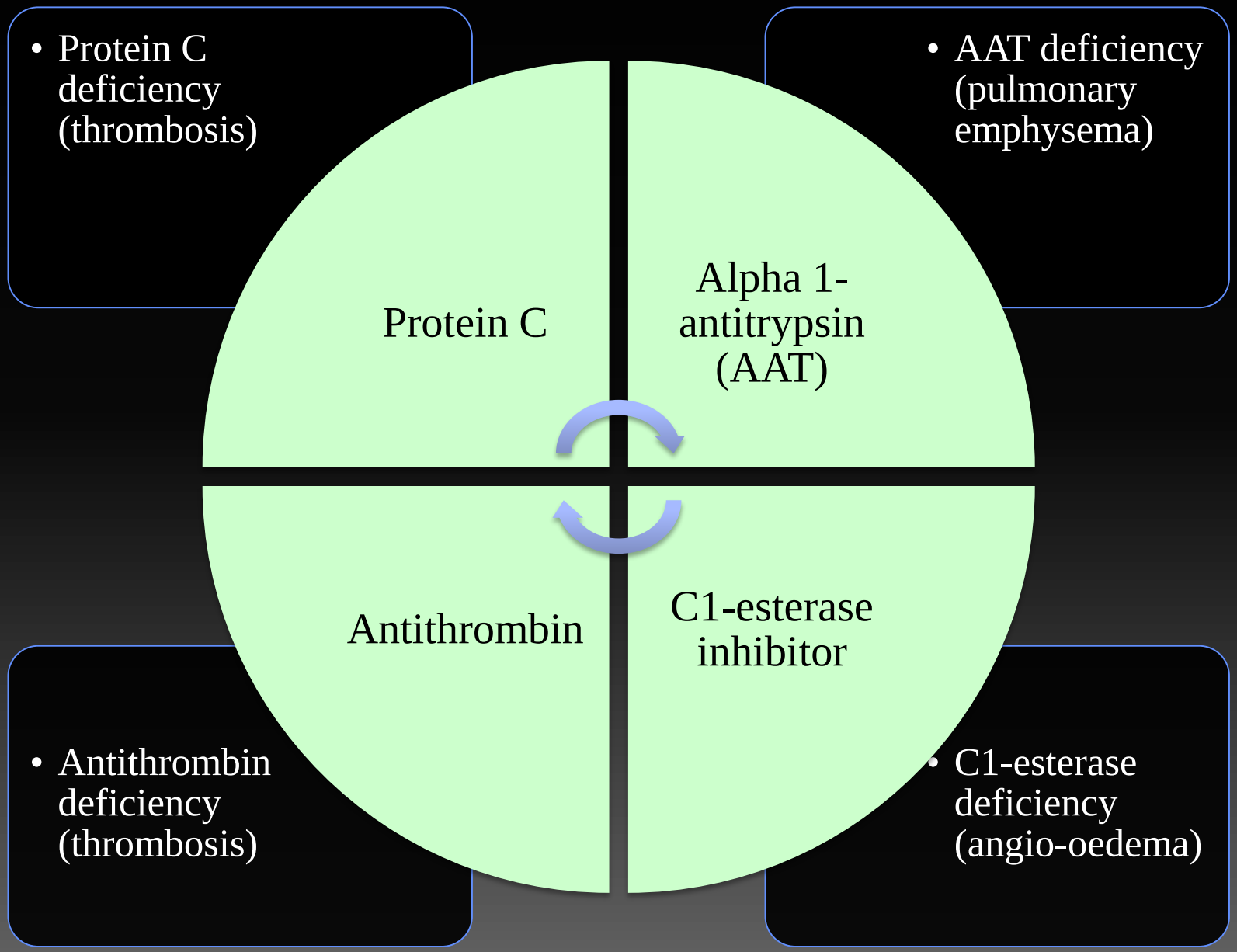
Main coagulation factor products



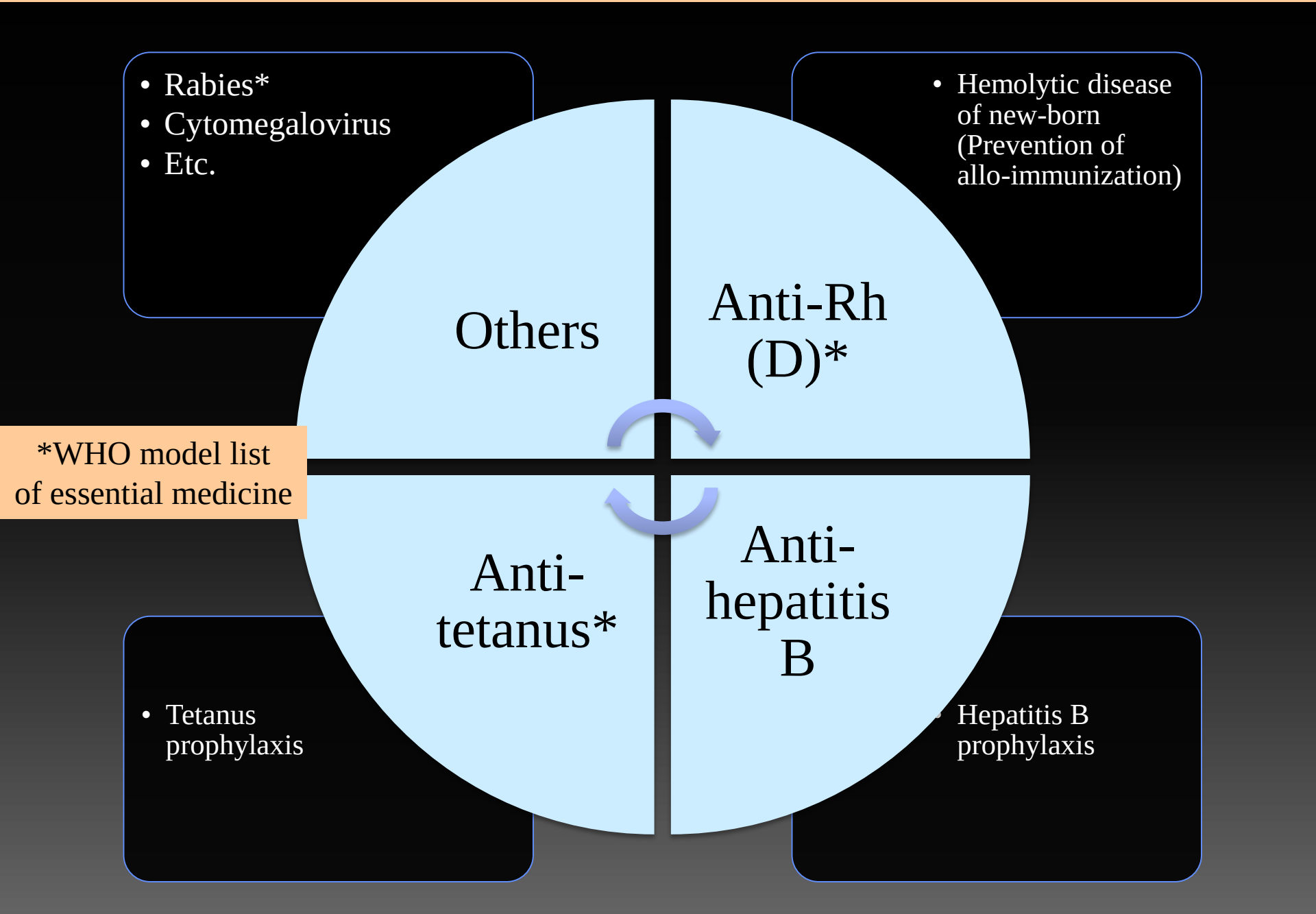
Other coagulation factor products



Protease inhibitors / anti-coagulants



Hyper-immune immunoglobulins G



Current range of plasma products

Coagulation factors	Protease inhibitors and anticoagulants	Albumin	Immunoglobulins	Others, in development
Factor VIII*	Antithrombin		**Polyvalent***	Factor II
Von Willebrand Factor	Alpha 1-antitrypsin		**Anti-D***	Factor V
Fibrinogen	C1-esterase inhibitor		Anti-Hepatitis B	Factor X
Fibrin sealant (fibrinogen + thrombin)	Protein C		**Anti-tetanus***	Haptoglobin
Prothrombin complex			Anti-CMV	Inter-alpha-trypsin inhibitor
Factor IX*			**Anti-rabies***	Plasminogen
Factor VII			Anti-hepatitis A	Factor H
Factor XI				Anti-HCV IgG
Factor XIII				HDL

*** WHO Essential Medicines**

Existing of protein products in search of new indications

Plasma fraction	New indications (?)
IVIG	Neurological diseases (multiple sclerosis etc.)
Albumin	Alzheimer (therapeutic apheresis)
Alpha 1-antitrypsin	Cystic fibrosis Type 1 diabetes mellitus
Fibrinogen	Coagulopathic bleeding in cardiac surgery Regenerative medicine

How to fill the gap ?



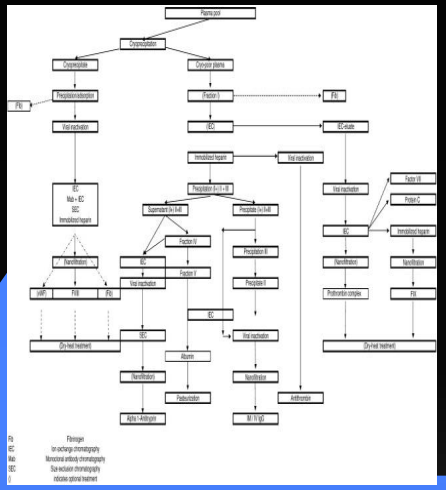




First… let’s have in mind that…

Plasma fractionation: unique biological product industry

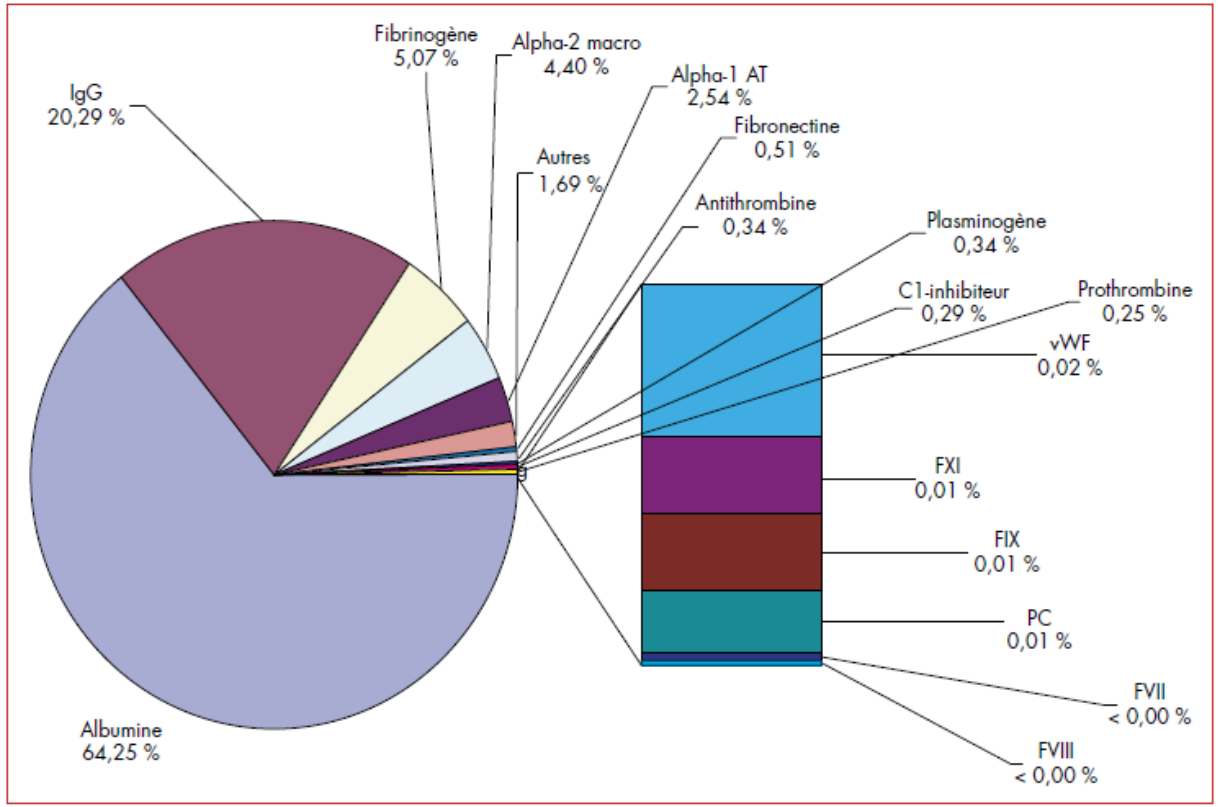


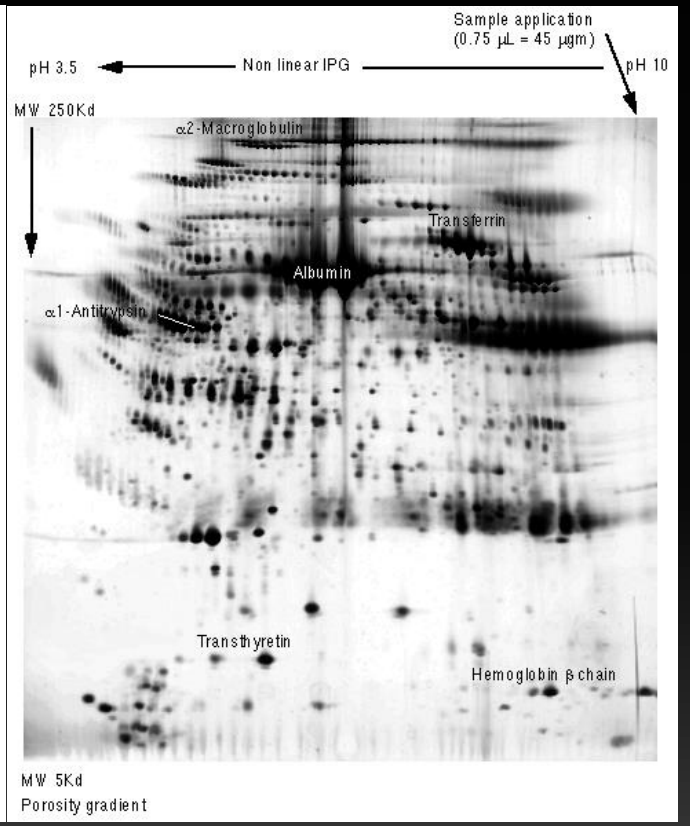


Unique raw material

Unique manufacturing technology

Plasma: Unique and complex biological material





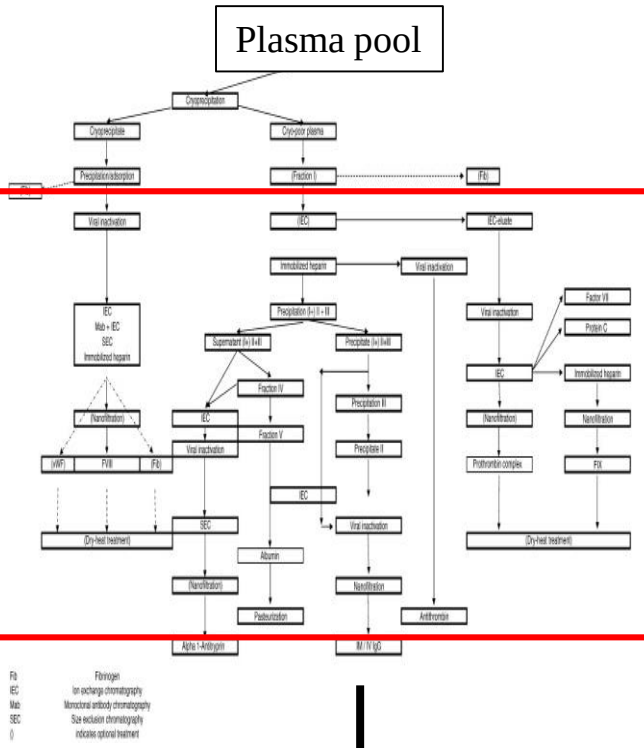
Unique combination of protein purification technologies to isolate abundant proteins (albumin, immunoglobulins) and trace Proteins (factor VIII, Factor IX)

Each industrial plasma pool size: 1000-4000 L

4000 – 20’000 donations



Plasma fractionation: Unique and complex technology

VACCINE	RECOMBINANT	ANTIVENOMS	HUMAN PLASMA PRODUCTS
Start material	Cell expression culture	Plasma pool	Plasma pool
Purification step	Chromatography	Precipitation enzymatic treatment	
Purification step	Chromatography	Precipitation	
Finishing	Chromatography	Finishing	Finishing
Vaccine	Finishing	IgG/ IgG fragments	FVIII PCC Alb IgG
	Rh-FVIII		

Plasma fractionation: Unique and complex technology

VACCINE

Start material

Purification step

Purification step

Finishing

Vaccine

RECOMBINANT

Cell expression culture

Chromatography

Chromatog

tography

Finishing

Rh-FVIII

ANTIVENOMS

Plasma pool

Precipitation
enzymatic treatm

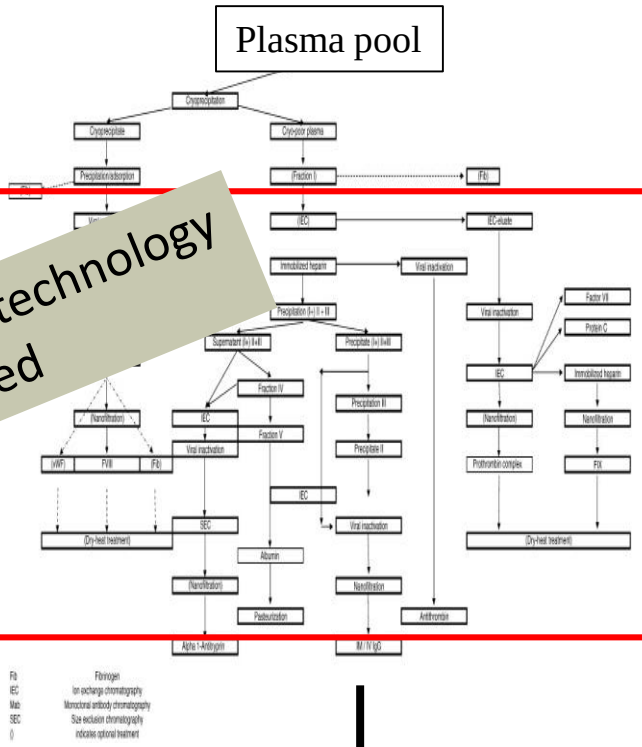
ipitation

Finishing

IgG/
IgG fragments

HUMAN PLASMA PRODUCTS

Plasma pool



Finishing

FVIII

PCC

Alb

IgG

The complexity of plasma fractionation technology should not be under-estimated

Unique technology

- **Plasma fractionation: technologically complex and highly regulated biotech industry:**
  - Variability of the plasma raw material
    - Each plasma unit and each pool are inherently different
    - Risk of emerging (known and unknown) infectious agents
  - Substantial process know-how required
    - Purification steps + Viral inactivation (+ other processing steps)
    - Stringent in-process and quality control
    - Extended process validation needed

Unique technology

- **Plasma fractionation:**
  - **technologically complex**
  - **highly regulated biotech industry:**
    - Several products made from same plasma batch (interconnected processes = process changes can affect several products)
    - Typically, 2 or 3 virus reduction steps for each product
    - Risks of crossed and downstream-contaminations to be avoided by careful facility design, SOP, extensive training, etc.
    - Complex engineering to build a GMP facility
    - A set of 15-20 specialized quality control tests on each product

Plasma fractionation: unique economics

Range of products



Three traditional ways to get access to plasma products to fill therapeutic gaps

Supply of plasma products: points to consider

Imports of products

- Local product license
- Plasma-derived or recombinant plasma products
- No guarantee of continuous supply of the same products (shortages)
- Cost (national tenders may help lower the cost)
- Donations from international organizations (e.g. WFH)

Contract fractionation

- Volume > 10’000-50’000 L / year
- Regulatory requirements
  - Plasma meets quality requirements of plasma fractionator and regulatory authorities
  - Licensing of plasma products by NRA
- Selection of a plasma fractionator interested in contract fractionation
- There are fractionation costs

Domestic fractionation

- Volume > 300’000 L / year
- Selection and transfer of plasma fractionation technology
- Heavy capital investment
- Trained and skilled top management and manpower
- Regulatory requirements
  - Facility license
  - Products license

Use of local plasma for fractionation:
Currently: 3 good reasons (at least)

At least 3 good reasons to fractionate local plasma

- Increase plasma product supply and guarantee of supply to treat more patients or provide better treatments

- Increase the diversity in the type of plasma products available locally

- Improve the sustainability of blood establishments by making more products from blood

Added benefit:
producing plasma meeting international quality requirements for fractionation enhances the quality and safety of all blood components

Points to consider to produce recovered plasma for fractionation

- **Blood collection should preferably be coordinated at national levels**
  - **Harmonization in blood collection and donation testing criteria**
  - **Ensures minimal volume of plasma meeting the same quality criteria**
  - **Facilitates auditing by the plasma fractionation organization**
  - **Facilitates approval and inspection/supervision by the national regulatory authorities (local and, directly or indirectly, foreign)**
- **Plasma generated should meet quality requirements for fractionation**
  - **Audits by fractionator (usually foreign)**
  - **Inspections by National Regulatory Authorities**

Contract fractionation

Principles of contract fractionation

















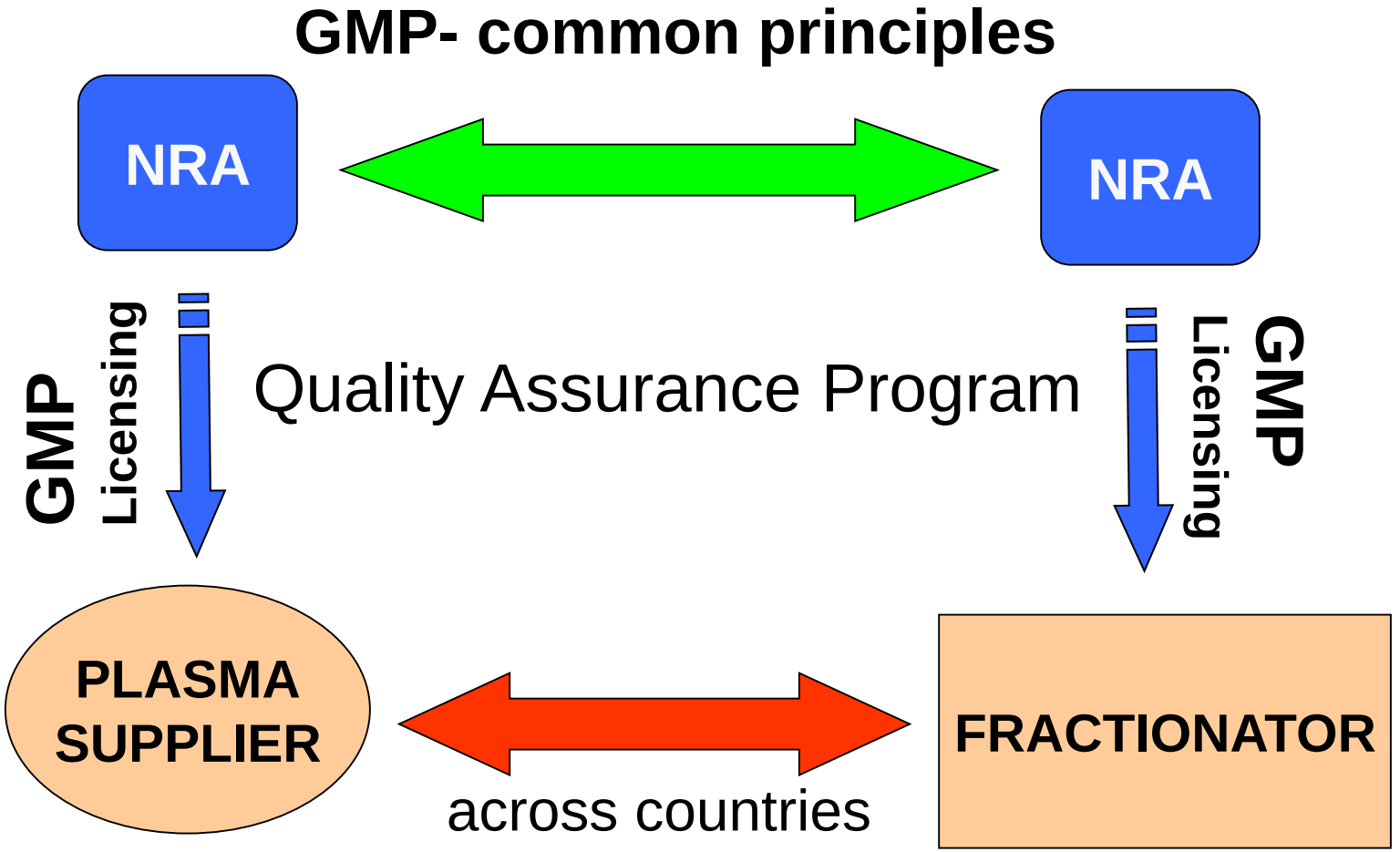
Several models exist and should be defined in the contract, in compliance with regulations

Contract fractionation agreements

- **Volume of plasma ?**
  - **>10’000**
  - **Up to ± 200’000 L / year**
  - **Continuous supply over several years**
- **Needs local leadership for professional management**
- **A financial and technical contract defining obligations ar should be signed between plasma supplier and contract fractionator**
- **Plasma fractionator interested in contract fractionation and able to prepare the needed product range should be identified**
- **Government support/endorsement is needed**
- **Needs regulatory approvals from National Regulatory authorities of plasma supplier and plasma fractionator**

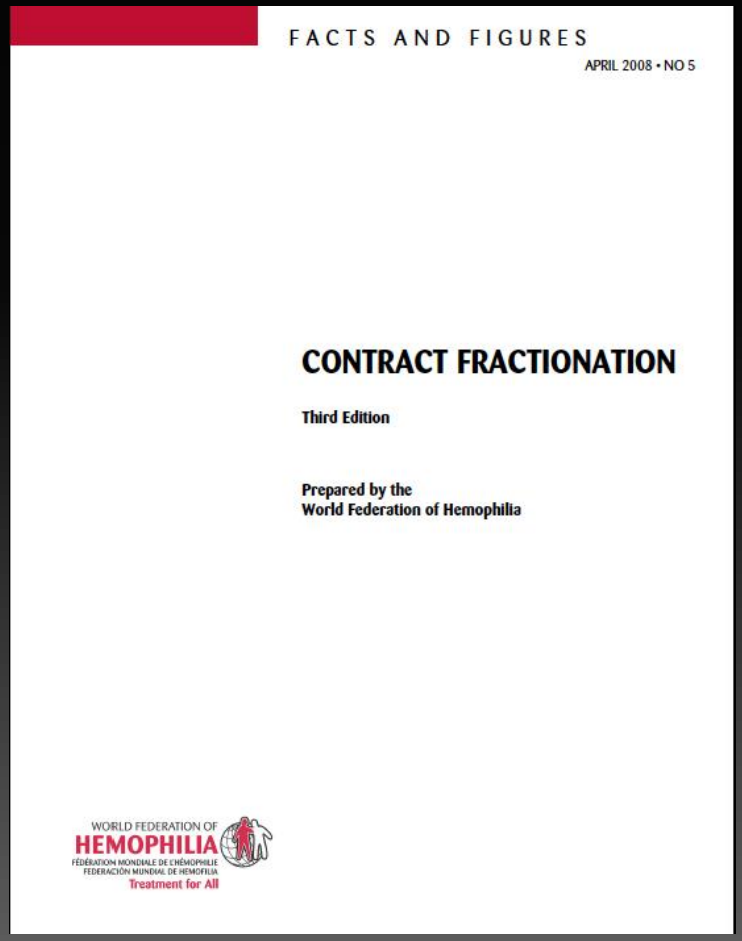
Brazil
Canada
Iran
Finland
Hong-Kong
Luxemburg
Malaysia
Morocco
New Zealand
Norway
Poland
Iran
Singapore
Taiwan
Tunisia
Etc.

Plasma Contract Fractionation Programs (parties involved)



A. Padilla, WHO, Geneva

Reference documents on contract fractionation



World Health Organization
Quality and Safety of Blood Products and related Biologicals
Department of Essential Health Technologies
20 Avenue Appia, 1211 Geneva 27, Switzerland
Fax: +41 22 791 4836
www.who.int/biologicals
www.who.int/eht

http://www.who.int/bloodproducts/publications/en/Infosheet_plasma_contract_fractionation.pdf

Information Sheet

Plasma Contract Fractionation Program

Reference documents

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



Domestic fractionation

Domestic fractionation: points to consider

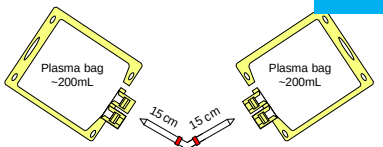
- **Volume of plasma to build new facility: from +/- 300'000/year**
- **Guarantee/continuity of plasma supply for 15-20 years**
- **Established long-term needs for plasma products**
- **A plasma fractionation technology supplier should be identified for transfer of technology and:**
  - **Basic and detailed design of facility**
  - **Design, qualification, and validation of equipment**
  - **Training of operators**
  - **Products' qualification and validation files**
  - **Standard operating procedures for production and QC**
  - **Pre-clinical and clinical studies**
  - **Marketing authorizations**
  - **etc**
- **Skilled management and manpower**
- **Financial support**
- **Government commitment/endorsement (NRA)**
- **Strong leadership**

Brazil
Iran
Russia
Thailand

Mini-pool viral inactivation and fractionation in medical devices

(Egyptian experience)

Plasma









20 cm

SD syringe

SD POOL Oval bag 1 750 ml

Sealed inlet (as close to bag as possible)

SD POOL Oval bag 2 750 mL

Syringe Prefilled with 40 mL oil

OIL BAG 3 750 mL

SD POOL 4 Oval bag 750 mL

10 cm

Transfusion filter

100 cm

Adsorption filter

20 cm

Bacterial filter

20 cm

15 cm

Collection bag 350mL A

Collection bag 350mL B

Two-stage viral inactivation by solvent/detergent

S/D agents removal by

- Oil extraction
- Filtration

Sterile filtration

Dispensing

Viral inactivation & fractionation in a bag system

V2.0A / 03.09.2008

Cryoprecipitate

spike

20 cm

double stopcock

20 cm

female

SD Syringe

SD POOL Oval bag 1 750 mL

Sealed inlet (as close to bag as possible)

20 cm

SD POOL Oval bag 2 750 mL

20 cm

15 cm tube

OIL BAG 3 750 mL

20 cm

Sealed inlet (2 cm)

SD POOL Oval bag 4 750 mL

10 cm

Transfusion filter

100 cm

Adsorption filter

20 cm

Bacterial filter

Sealed inlet (2 cm)

Oval collection bag 5

Roller clamp

Breakable valve (reversed sense)

Clamp

Connection Female luer lock

Connection Male luer lock

Mini-pool process

QC bag

1 bag for QC

7 bags for collection

SD POOL bag 75 mL Total : 8 bags

V2.0A / 03.09.2008

Minipool-S/D cryoprecipitate preparation

Cryo

30-40 cryo donations

Viral inactivation treatment

Plasma → Cryo → Pooling → S/D treatment → Oil extraction → Filtrations → S/D-cryo

Cryo





Final product after sterile filtration

- FVIII = 7 – 11 IU/ml
- Fibrinogen = 12 – 21 mg/ml
- VWF:

  RCo = 11 – 16 IU/ml

  CBA = 11 – 18 U/ml

  Ag = 15 – 18 IU/ml

  multimers > 15 mers and > 10 mers* = same as in starting cryo
- Anti-A, anti-B titer: 0 or 2

Labeled Final product





Production and clinical use in Egypt

March 2012 to Nov 2015

MINIPOOL S/D-CRYO

- 250 iu FVIII = 42384 doses
- 500 iu FVIII = 35216 doses

Total = ± 27.5 million IU FVIII

Maybe not very fancy… but it contributes to fill the gap

Minipool S/D-plasma: ±4000 units (200 mL)

Mini-pool immunoglobulin G

Treatment of immunodeficient patients

Preparation of “convalescent” hyperimmune IgG (Ebola, Dengue, SARS, etc.) ?

Mini-pool fractionation

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Minipool Caprylic Acid Fractionation of Plasma Using Disposable Equipment: A Practical Method to Enhance Immunoglobulin Supply in Developing Countries

Magdy El-Ekiaby[1], Mariángela Vargas[2], Makram Sayed[3], George Gorgy[1], Hadi Goubran[4], Mirjana Radosevic[5], Thierry Burnouf[6]*

1 Shabrawishi Blood Bank, Shabrawishi Hospital, Cairo, Egypt, 2 Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, San José, Costa Rica, 3 Environmental and Food Pollutant Laboratory, Fayoum University, Fayoum, Egypt, 4 Saskatoon Cancer Center, College of Medicine, University of Saskatchewan, Saskatoon, Canada, 5 Human Protein Process Sciences, Lille, France, 6 Graduate Institute of Biomedical Materials and Tissue Engineering, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

Quality of plasma for fractionation

World Health Organization

ANNEX 4

WHO RECOMMENDATIONS FOR THE PRODUCTION, CONTROL AND REGULATION OF HUMAN PLASMA FOR FRACTIONATION

Adopted by the 56th meeting of the WHO Expert Committee on Biological Standardization, 24-28 October 2005. A definitive version of this document, which will differ from this version in editorial but not scientific detail, will be published in the WHO Technical Report Series.



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9 million L plasma wasted/year

Options to improve access to plasma products

Cost consideration

Need for regulation

Conclusions: Gap filling strategies

- Local manufacture of virally-inactivated plasma fractions (Service center?)
- Limited capital investment
- One step towards control of supply and avoid wastage

Mini-pool Domestic Production

- National tenders & donations
- Access to specialized plasma and recombinant products
- Risks of shortages

Import of products



Thanks for your attention

Industrial Domestic fractionation

- Quality and quantity of plasma
- High capital and human investment
- Increased guarantee of supply
- Challenging

Industrial Contract fractionation

- Quality of plasma
- Some guarantee of supply
- Improved sustainability of blood establishment