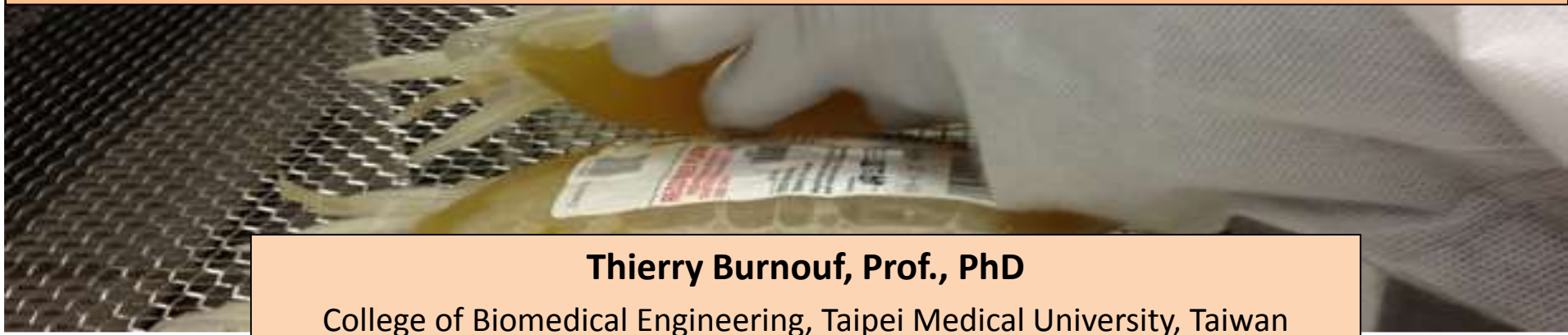
Plasma fractionation: Technical and organisational points to consider



Thierry Burnouf, Prof., PhD

College of Biomedical Engineering, Taipei Medical University, Taiwan

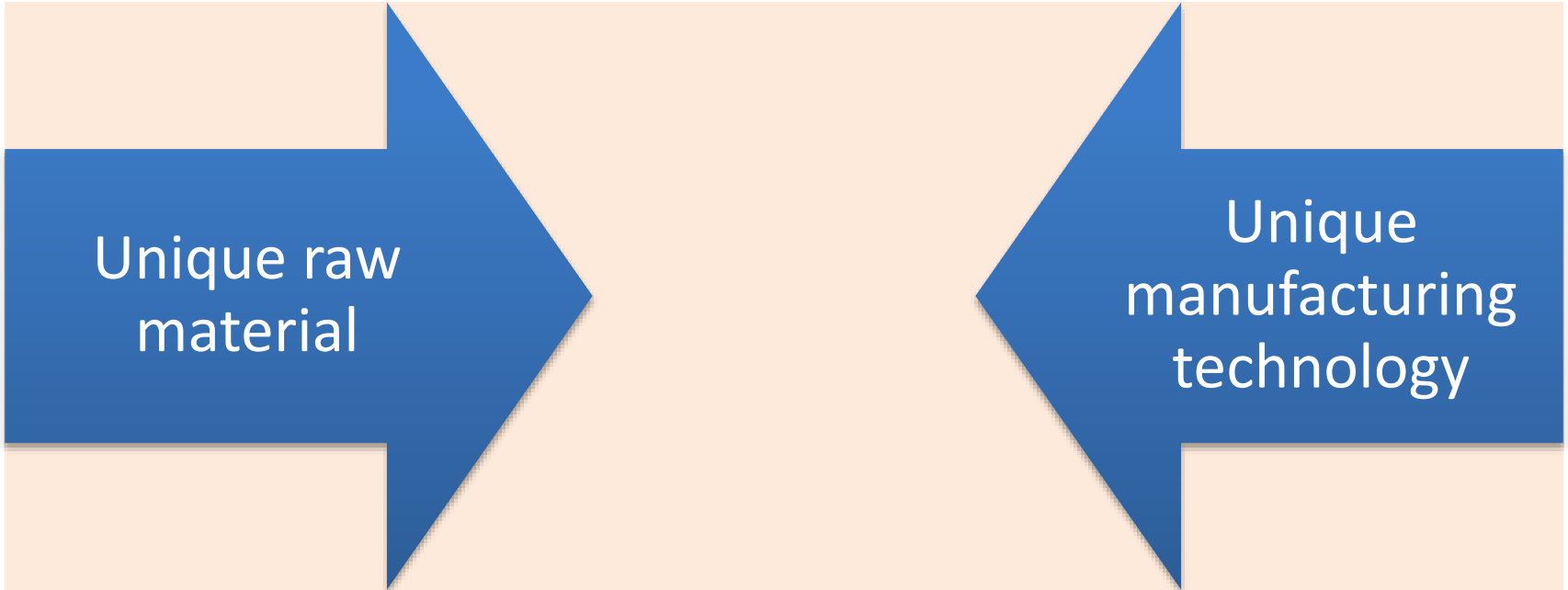
Technical points to consider

Plasma fractionation technologies

Picture Source:

What makes plasma fractionation unique ?

Plasma fractionation uniqueness



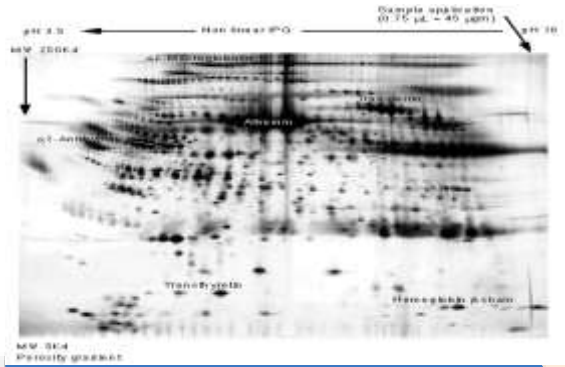
Plasma fractionation uniqueness

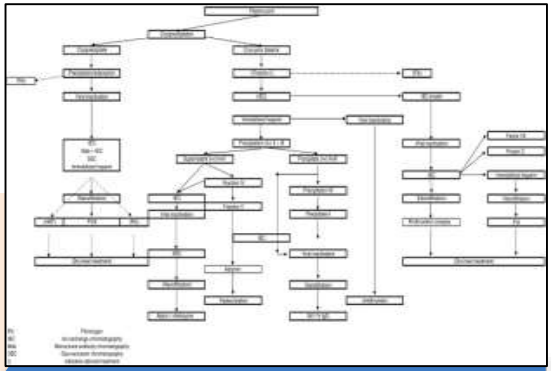
Unique raw material

Unique manufacturing technology

Plasma fractionation uniqueness

http://world-2dpage.expasy.org/swiss-2dpage/images/publi/plasma-total.gif

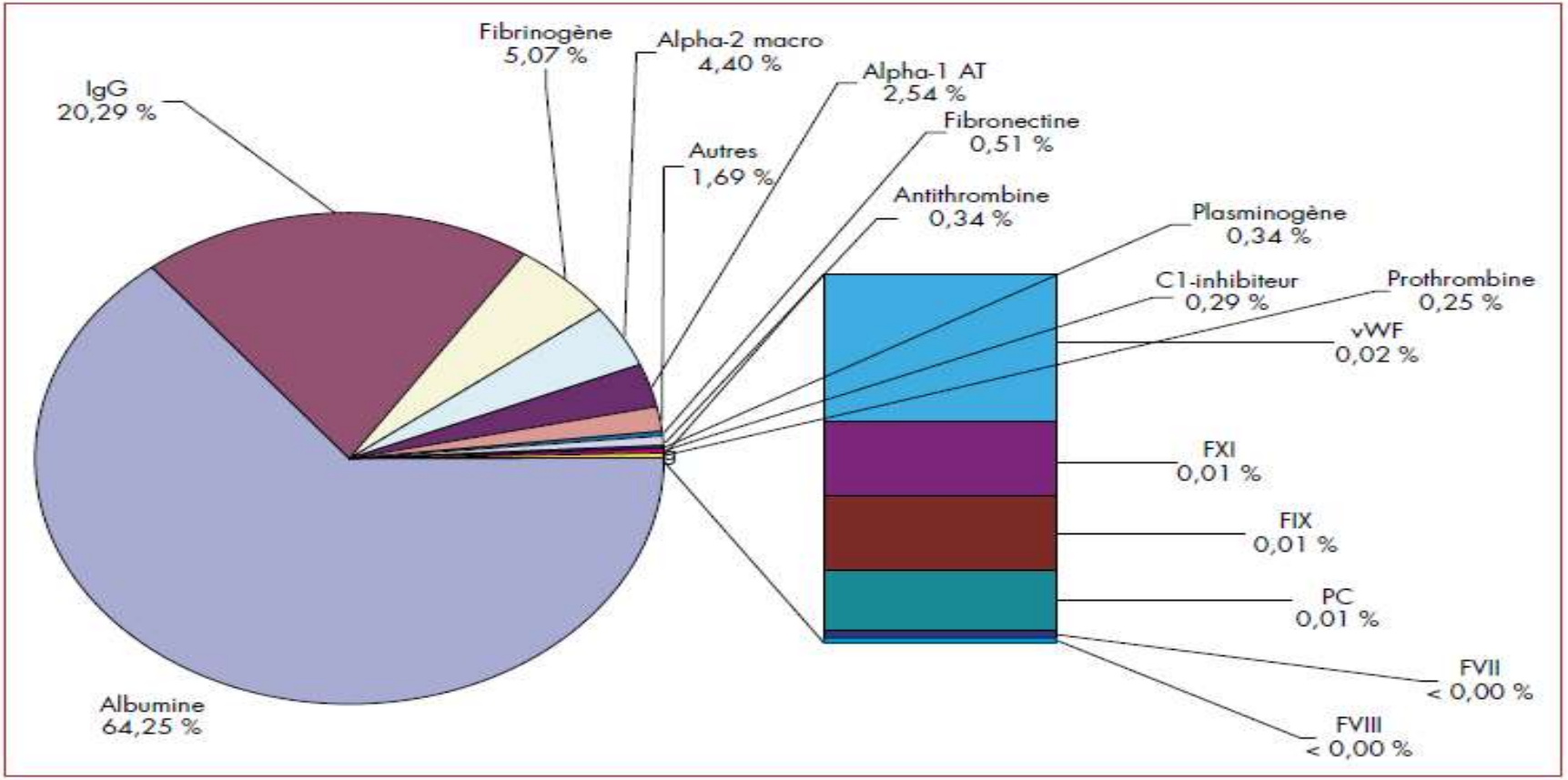




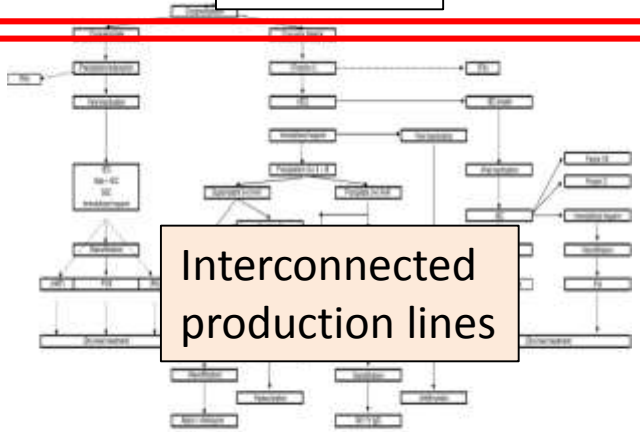
Unique raw material

Unique manufacturing technology

Plasma: Rich biological material



Plasma fractionation: Unique technology

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

Clinical fields covered by plasma products

Products	Clinical Indications
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

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Alpha 1-antitrypsin	• Lung panacinar emp al deficiency
Albumin	• Blood volume repla contic pressure

Immunological disorders

Infectious diseases

Hemolytic disease

Coagulation & bleeding disorders

Metabolic diseases

Traumas

Unique technological requirements

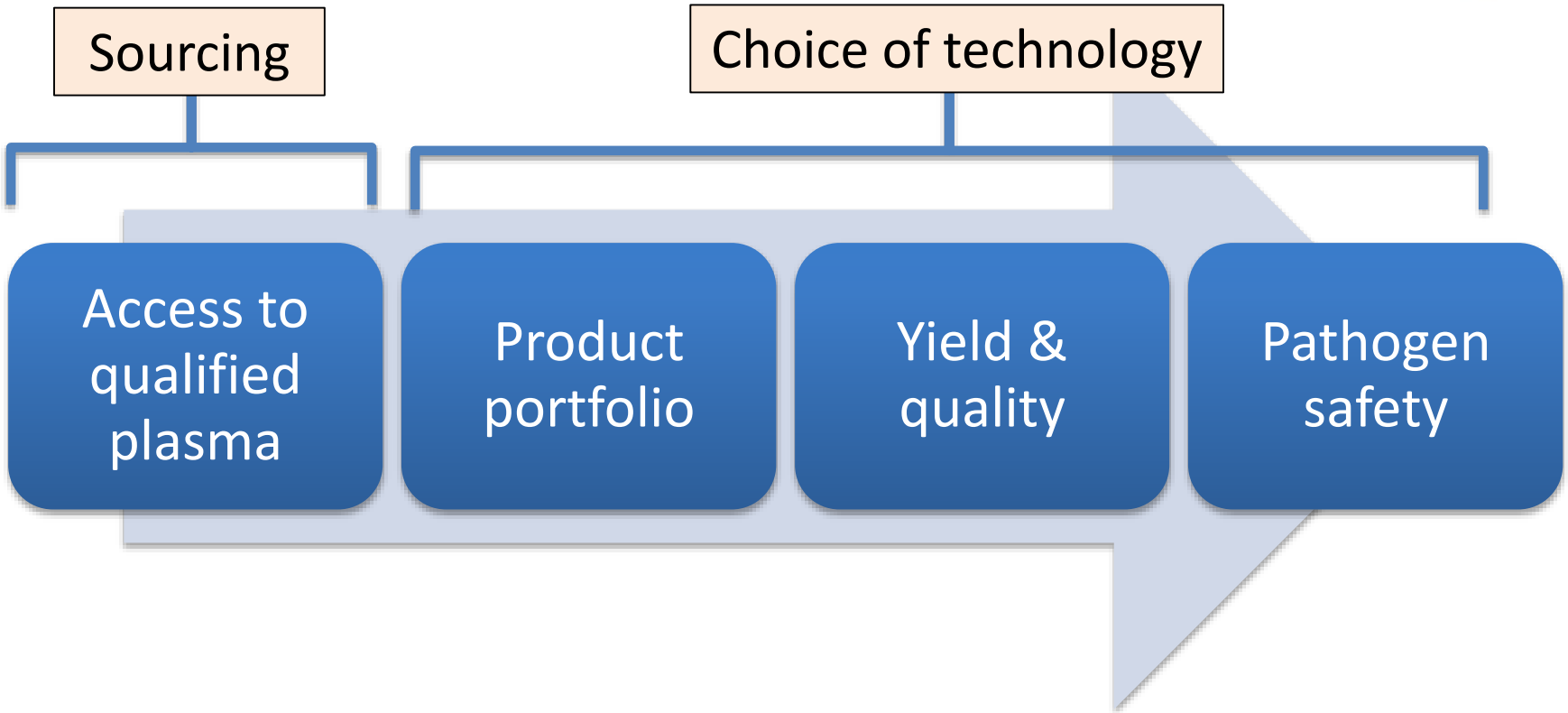
- **Variability of the plasma raw material**
  - Each plasma unit and each pool are different
  - Risk of emerging (known and unknown) infectious agents

- **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



Can a donor donating plasma for transfusion also donate plasma for fractionation ?

Picture Source: Global Database on Blood Safety

World Health Organization

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*

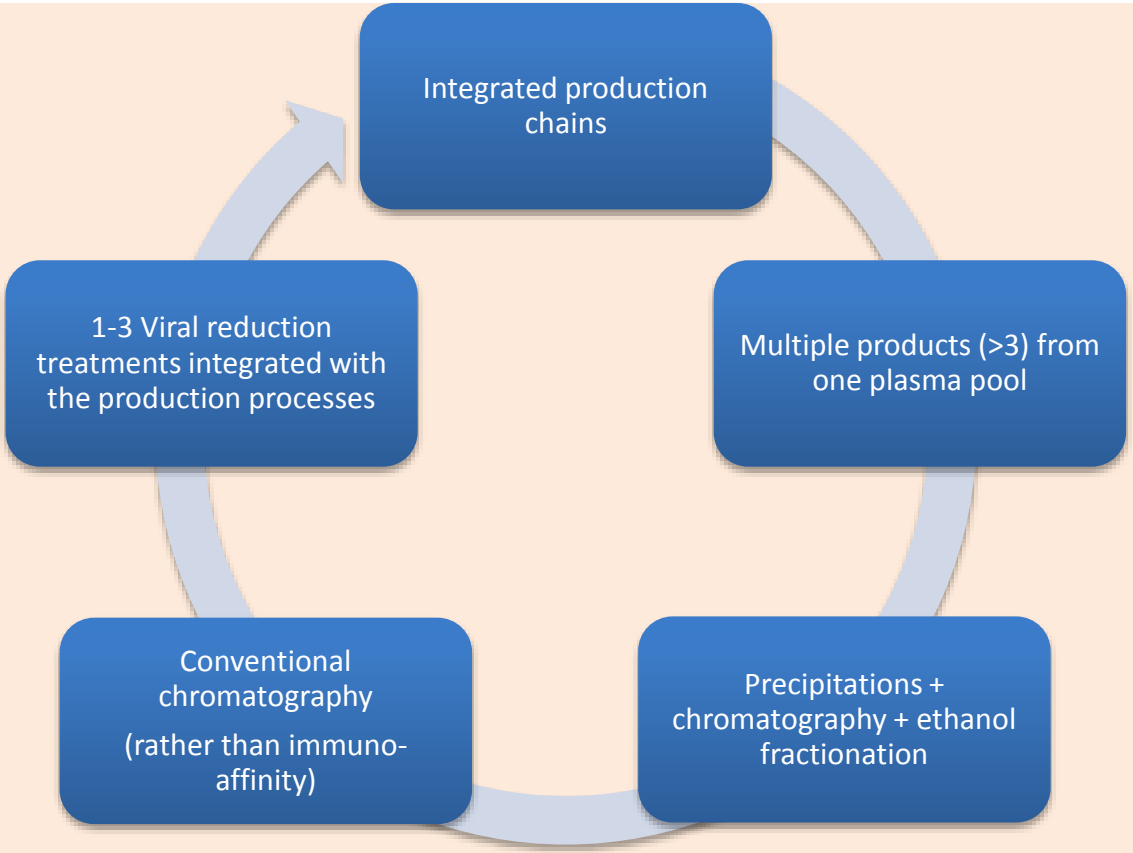
Picture Source: Global Database on Blood Safety

World Health Organization

The answer is ? Yes or No

Not necessarily !

Technological features of plasma fractionation



Technological features of plasma fractionation

Current technology is typically based on combination of:

Technology	Comments
Cryoprecipitation	• Still used to isolate cryoprecipitate for Factor VIII isolation
Chromatography	• Mostly ion-exchange and affinity • Used for most proteins
Ethanol fractionation	• Still used for albumin • Decreasing use for IgG

Evolution of plasma fractionation scheme

Plasma

Thawing

Cryoprecipitate

Precipitation/adsorption

Chromatography

FVIII

vWF

Fibrinogen

+ viral reduction treatments integrated in this process

Cryo-poor plasma

Fibrinogen

Fraction (I+) II+III

Chromatography

Chromatography

IgG

Ethanol fractionation

Alpha 1-AT

Albumin

Chromatography

aFII

FVII

FIX

Chromatography

PCC

Chromatography

PC

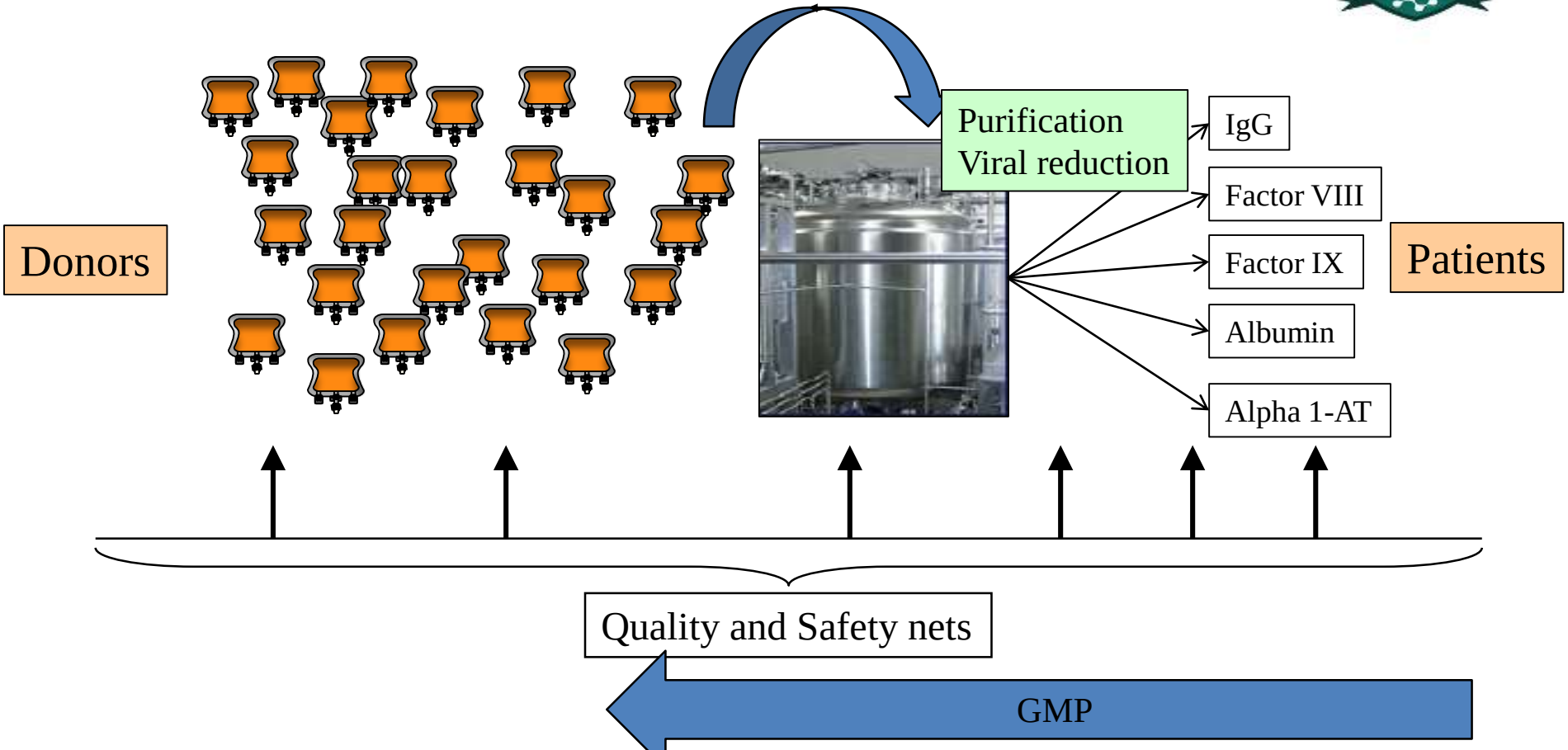
Chromatography

AT

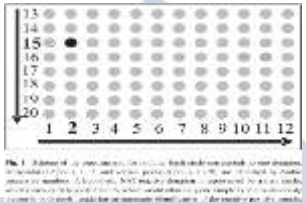
Viral reduction technologies in plasma fractionation

Last 40 years:
from “no” to “multiple” viral inactivation treatments

Fractionation technology selection criteria



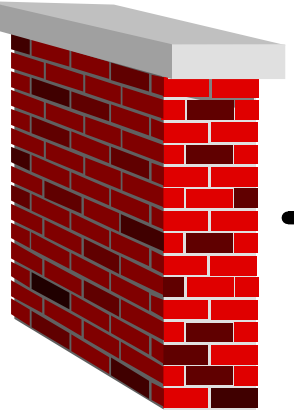
Plasma products
overall viral safety nets



A robust set of safety measures under Regulatory Authorities supervision

Epidemiological surveillance	Donor's screening	Donation testing	Mini-pool NAT testing	Viral reduction treatments
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

Tested and known pathogens

Risks of emerging pathogens

Crucial importance of dedicated virus inactivation/removal treatments during fractionation

Selection criteria of viral reduction methods

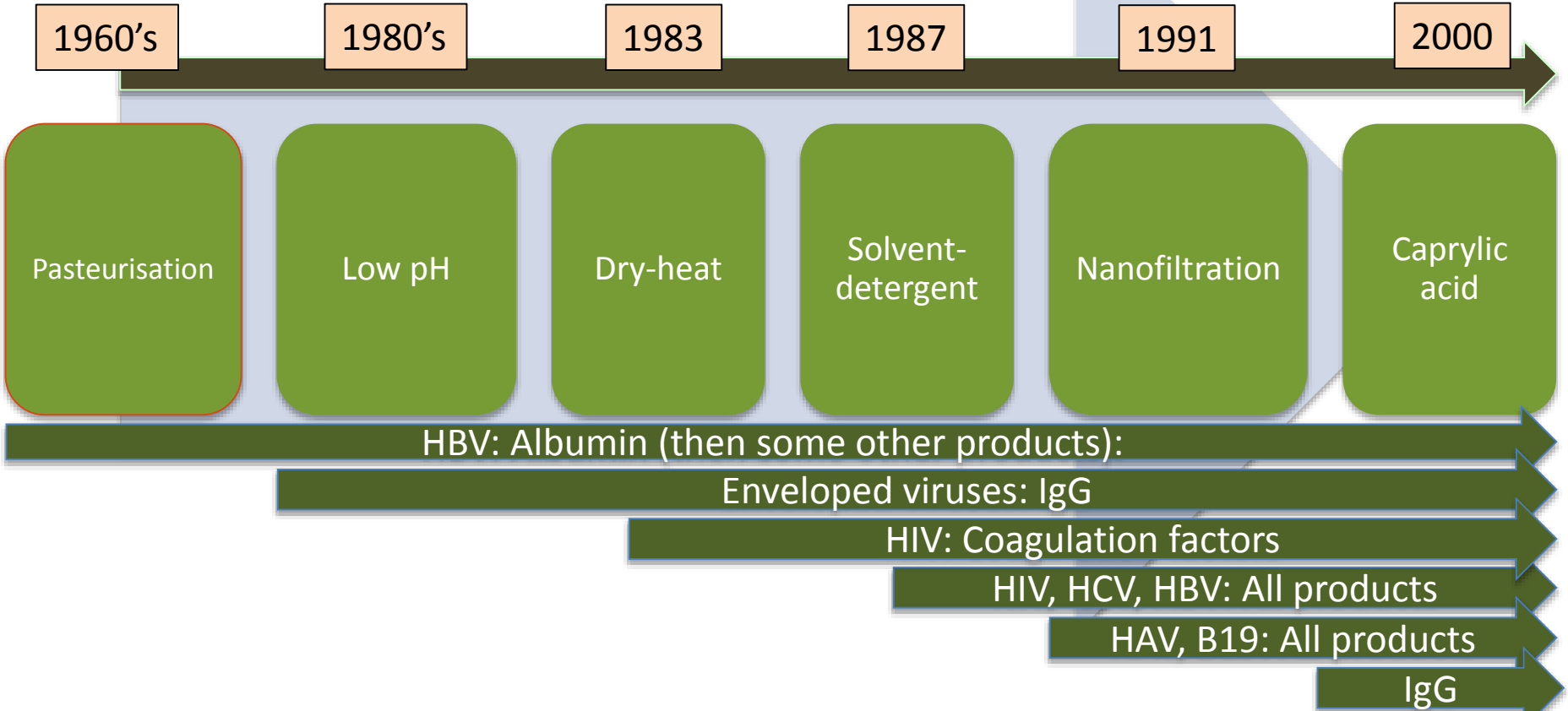
- Broad spectrum of inactivation/removal efficiency
- Optimal protein recovery
- Absence of protein denaturation

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



Fractionated plasma products have never been safer for HIV, HBV, HCV ?

The answer is ? Yes or no?

yes

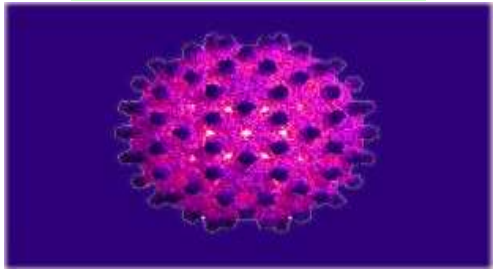
What about emerging viruses?

NYIV

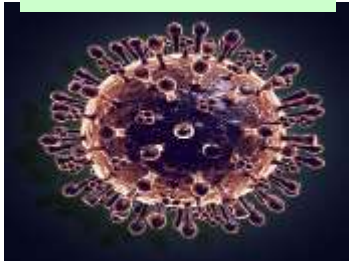
Not **Y**et **I**dentified **V**irus

?

Hepatitis E virus



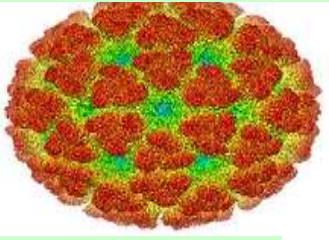
Avian flu virus



Dengue virus

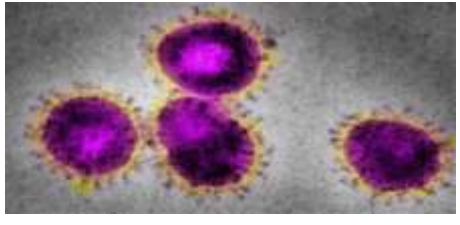
West Nile virus

Chikungunya virus



Ebola virus

SARS coronavirus virus



MERS- Coronavirus virus

Plasma products transmit emerging viruses ?

Picture Source:

The answer is ? Yes or No

Technologies in place safeguard against recent “emerging” viruses

VIRUS	Enveloped (E)	Size (nm)
Avian Flu	E	80-120
SARS	E	80-90
Chikungunya	E	60-70
Dengue	E	40-45
West Nile	E	40-45
MERS-coronavirus	E	80-90
Ebola	E	120
Hepatitis E	NE	27-34

S/D

nano-filtration

Technologies in place can safeguard against recent "emerging" viruses

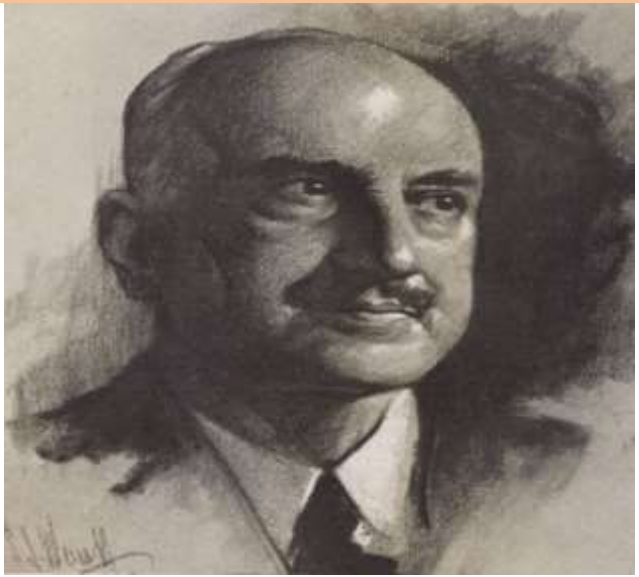
Safety against emerging viruses should be built in the manufacturing process

VIRUS						
Avian Flu		E			80-120	
SARS		E			80-90	
Chikungunya		E			60-70	
Dengue		E	**S/D**		40-45	**nano-filtration**
West Nile		E			40-45	
MERS-coronavirus		E			80-90	
Ebola		E			120	
Hepatitis E		NE			27-34	

However, with any biological products, One should not lower the guard

http://www.leblogfinance.com

"Those who do not remember the past are condemned to repeat it" (George Santavana)



https://en.wikipedia.org/wiki/George_Santayana#/media/File:George_Santayana.jpg

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

Slide inspired from Dr. Thomas Kreil presentations on viral safety

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 maximun volume of plasma for contract fractionation ?

Picture Source:

Minimum

Maximum

+/- 10’000 – 20’000 L

250’000 L

Minimum and maximun number of plasma donations (200 mL) needed for contract fractionation

Picture Source

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

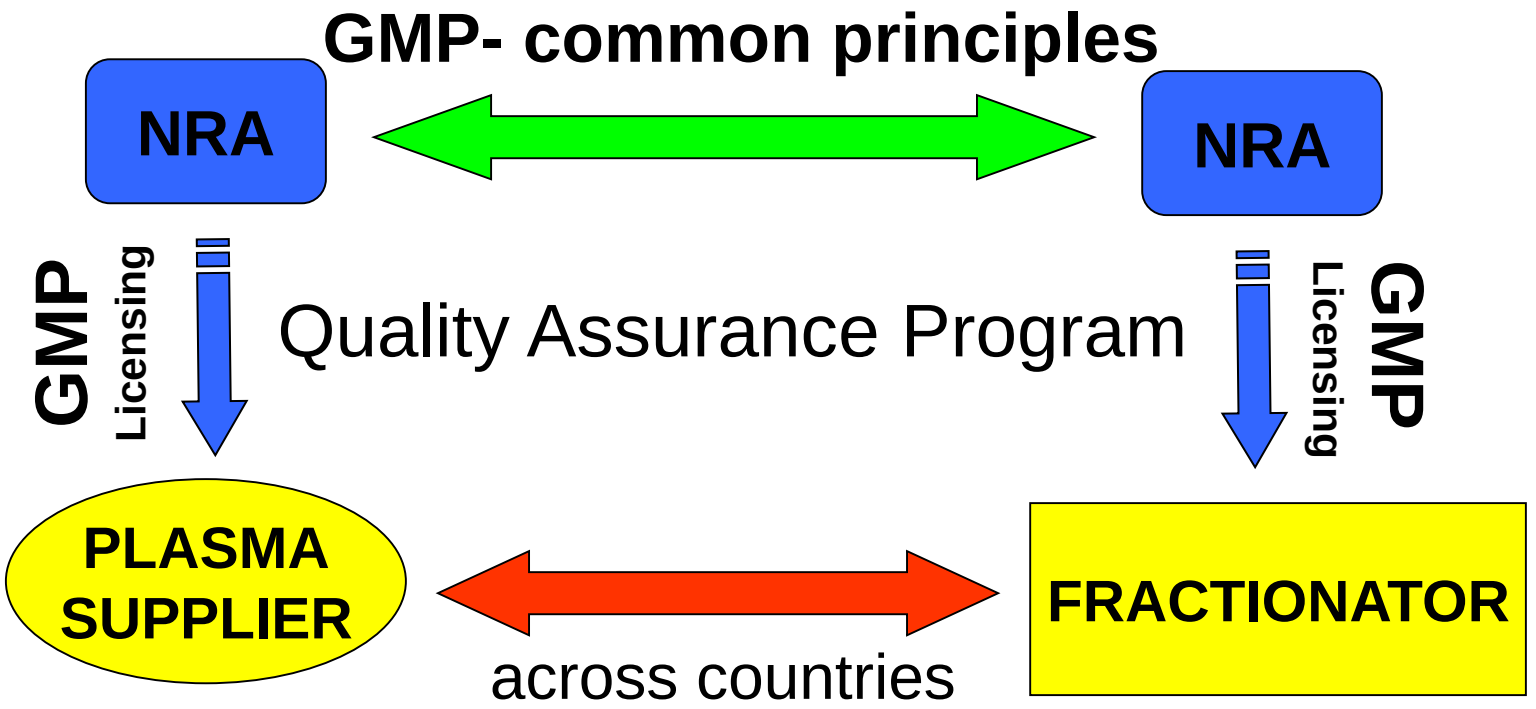
Plasma supplier’s NRA roles

- 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



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

Plasma

LOCAL

ABROAD

Final products

CONTRACT FRACTIONATOR

Domestic fractionation: possible phasing

Plasma

LOCAL
Bulk fractionation

Intermediates

L
O
C
A
L

Final products

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

A
B
R
O
A
D

Domestic fractionation: possible phasing

Plasma

Albumin

L
O
C
A
L

Other intermediates

IgG, FVIII, FIX

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

A
B
R
O
A
D

Domestic fractionation: possible phasing

Plasma

L
O
C
A
L

IgG, FVIII, FIX

FULL
LOCAL FRACTIONATION

Albumin

Assistance + product improvement

FOREIGN FRACTIONATOR

Further reading

© World Health Organization
WHO Technical Report Series No 941, 2007

Annex 4

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

© World Health Organization
WHO Technical Report Series, No. 961, 2011

Annex 4

WHO guidelines on good manufacturing practices for blood establishments

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 foreseable future, justifying efforts to avoid wasting plasma

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