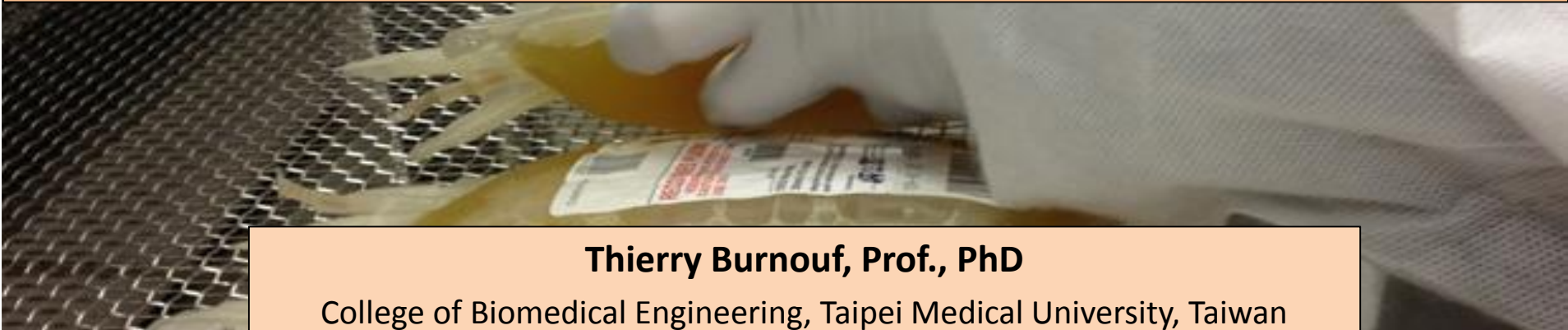


Plasma fractionation: “Setting the scene”



Thierry Burnouf, Prof., PhD

College of Biomedical Engineering, Taipei Medical University, Taiwan

Technical points to consider

Plasma fractionation technologies



Picture
Sources:

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



What makes plasma fractionation unique ?

Plasma fractionation uniqueness



Unique raw
material

Unique
manufacturing
technology

Plasma fractionation uniqueness



Unique raw
material

Unique
manufacturing
technology

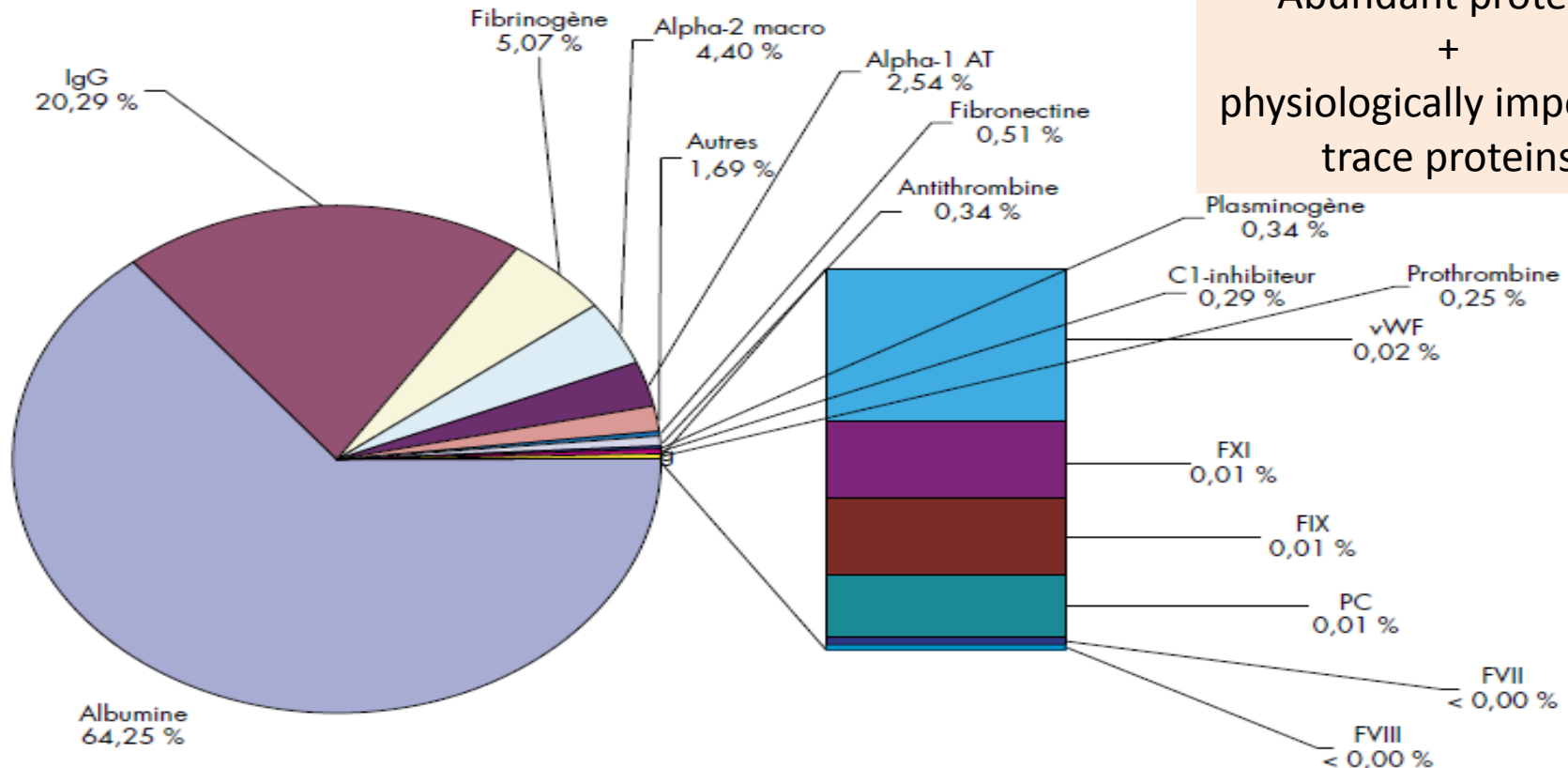
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Unique manufacturing technology

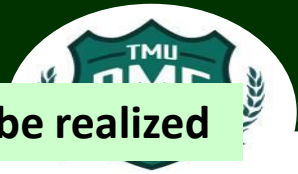
Plasma: a rich biological material



Abundant proteins
+
physiologically important
trace proteins



Plasma fractionation: Unique biotechnology



The technological difficulties of the plasma fractionation process should be realized

VACCINE

Start material

Purification step

Purification step

Finishing

Vaccine

RECOMBINANT

Cell cultures

Chromatography

Chromatography

Chromatography

Finishing

Rh-FVIII

ANTIVENOMS

Plasma pool

Precipitation
enzymatic treatment

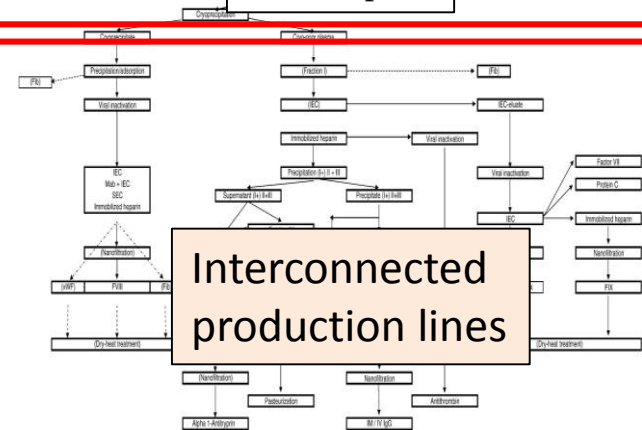
Precipitation

Finishing

IgG/
IgG fragments

HUMAN PLASMA PRODUCTS

Plasma pool



Finishing

FVIII

PCC

Alb

IgG

Clinical fields covered by plasma products



Diversity in the clinical indications covered by plasma products

Products	Clinical Indications	
Polyvalent immunoglobulins	Substitutive therapy (IgG deficiency) Immunomodulation	Immunological disorders
Hyperimmune Immunoglobulins	Treatment and prophylaxis of infectious disease, Prevention of hemolytic disease of newborn	Infectious diseases Hemolytic disease
Coagulation factors (VIII, IX, vWF, VII)	Coagulation factor deficiency	Coagulation & bleeding disorders
Fibrinogen	Congenital or acquired deficiency	
Prothrombin complex	Coagulation defects due to liver disease	
Antithrombin	Congenital deficiency	
Alpha 1-antitrypsin	Lung panacinar emphysema due to congenital deficiency	Metabolic diseases
Albumin	Blood volume replacement / oncotic pressure	Traumas, ...

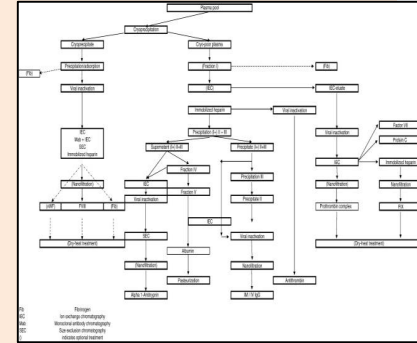
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- [illegible]

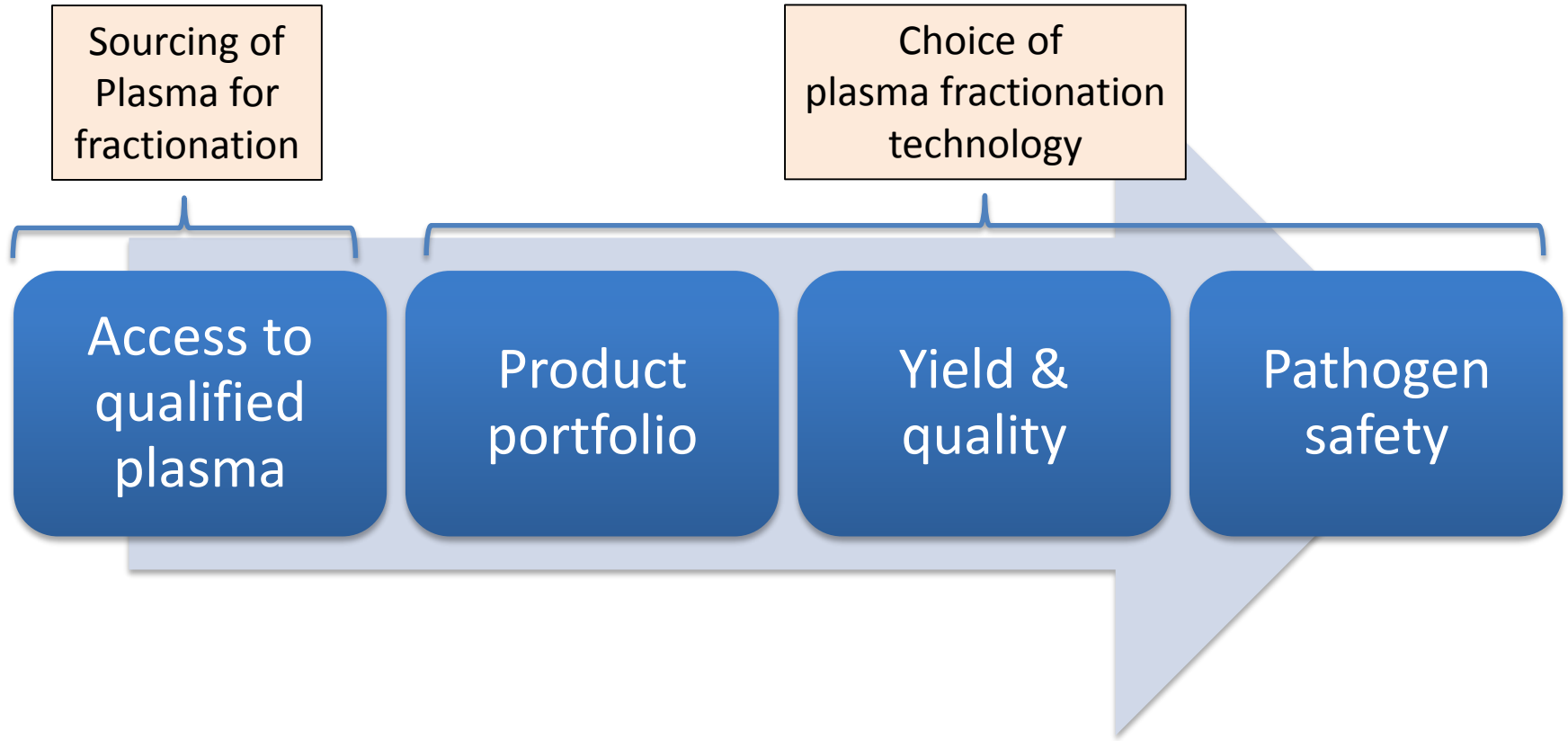
Unique technological requirements



- **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



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



*Picture
Source:*

Global Database on Blood Safety



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



Picture
Source:

Global Database on Blood Safety

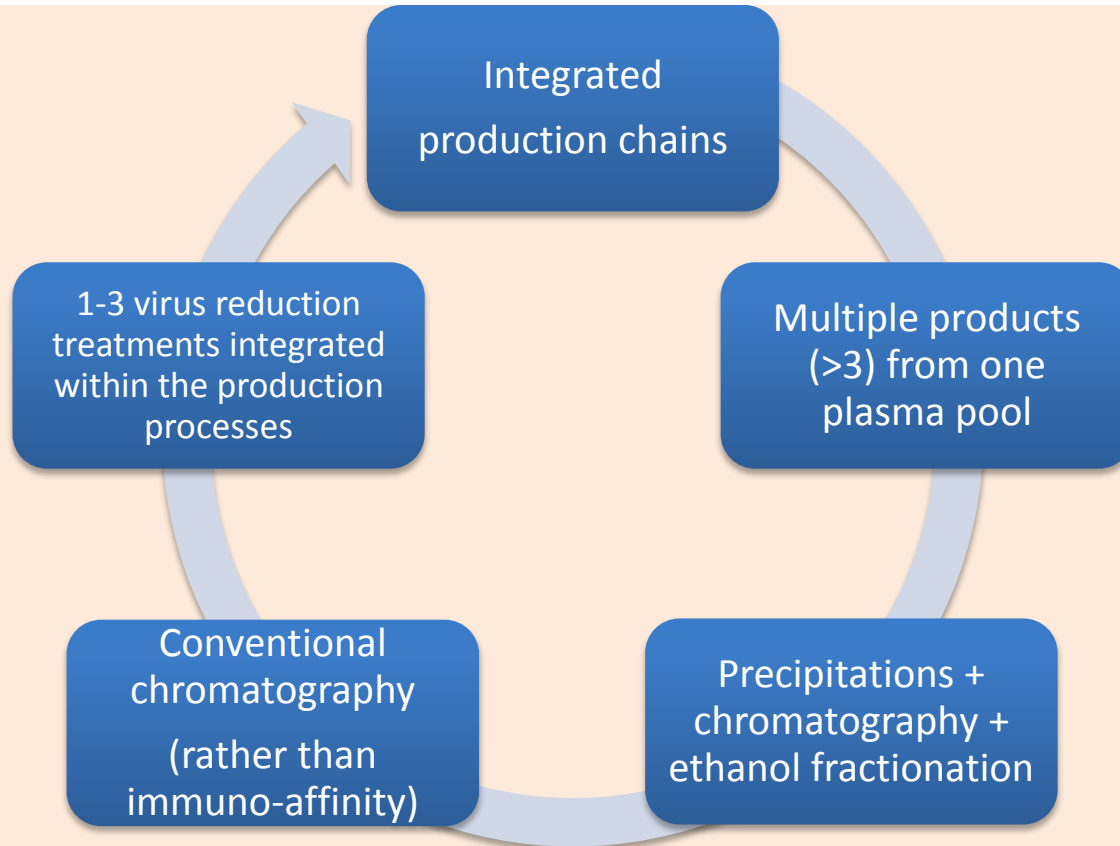


The answer is ? Yes or No



Not necessarily !

Technological features of plasma fractionation



Plasma fractionation technologies

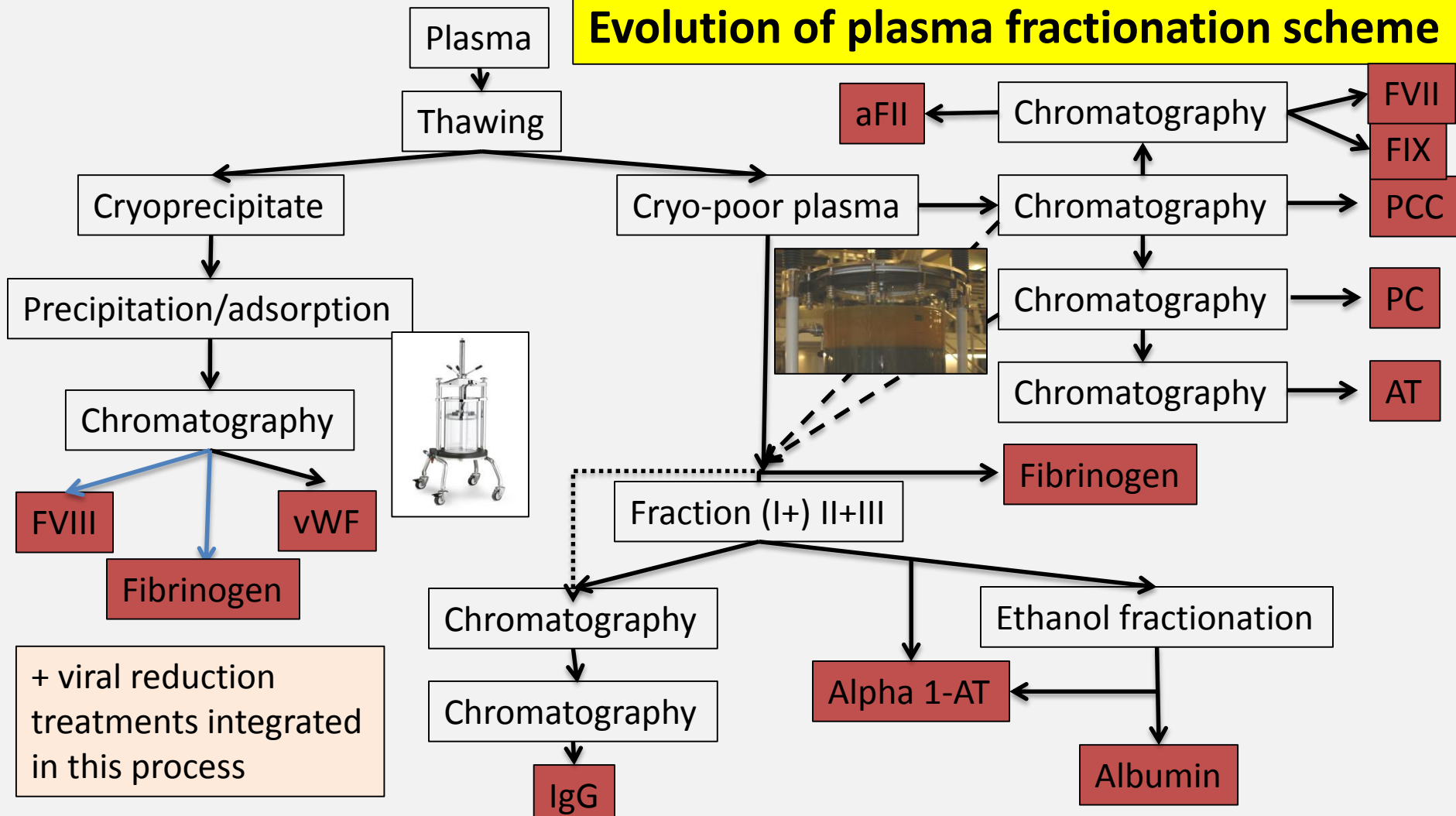


Current technology is typically based on combination of ...

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

... and continues to evolve gradually to improve product yield and quality

Evolution of plasma fractionation scheme



Virus safety in plasma fractionation

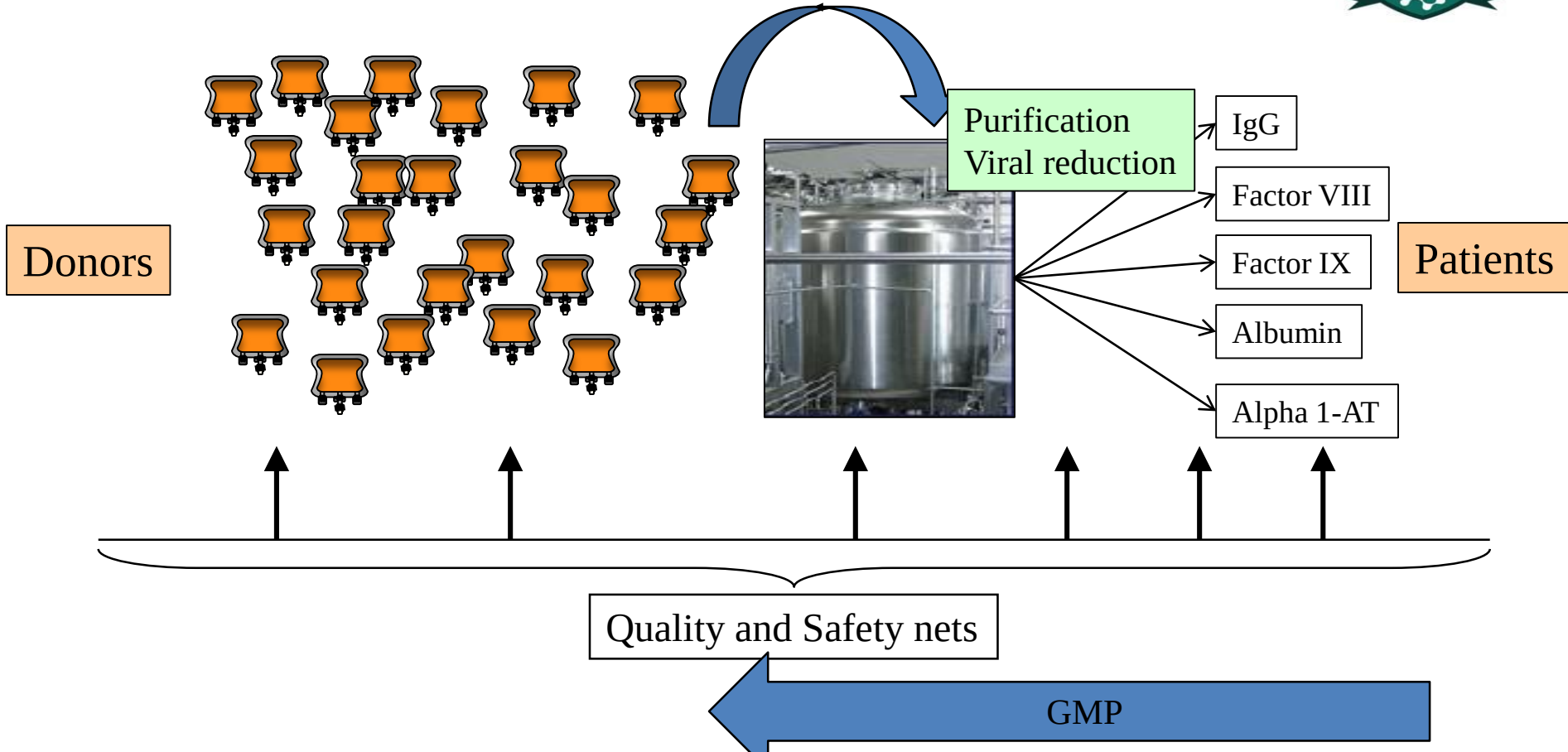


Improving access to safe blood products
through local production and technology
transfer in blood establishments



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

GMP from Z to A



Plasma products overall viral safety nets

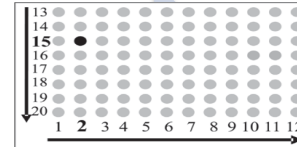
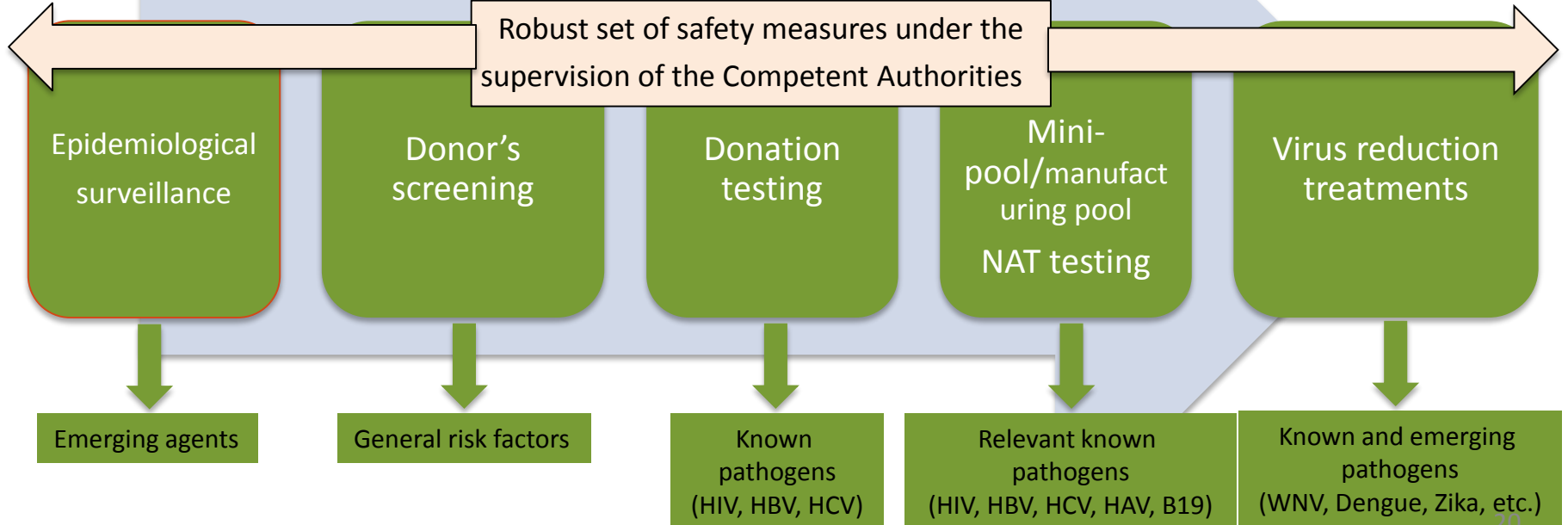
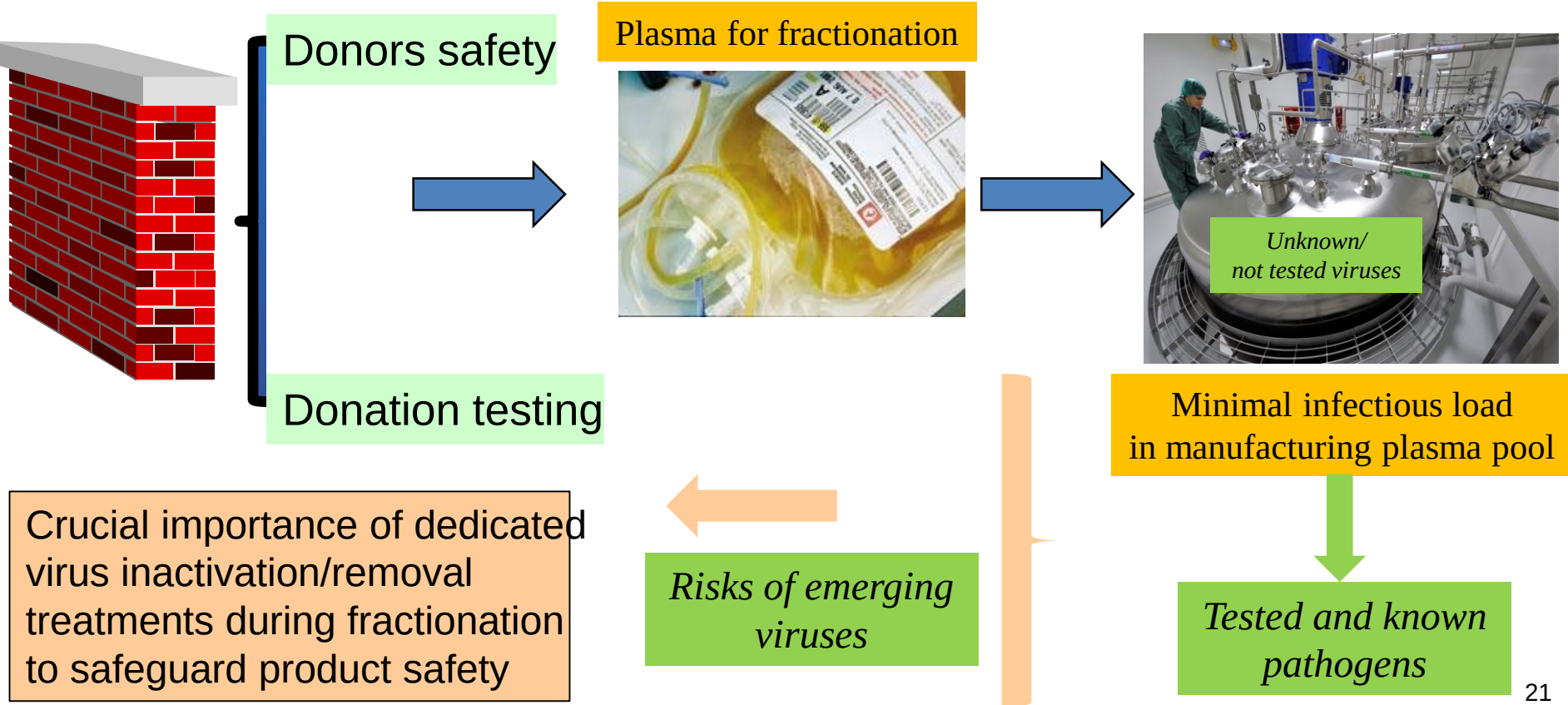


Fig. 1 - Scheme of the pooling strategy for NAT testing. Each circle corresponds to one donation. Horizontal (12 pools, 1-12) and vertical pools (8 pools, 13-20) are identified by Arabic successive numbers. A hypothetical NAT reactive donation is represented by a dark circle, which corresponds to pools 2 and 15, which would allow only one sample to be simultaneously present in both pools, rendering an automatic identification of the putative positive sample.



Donors and donations safety





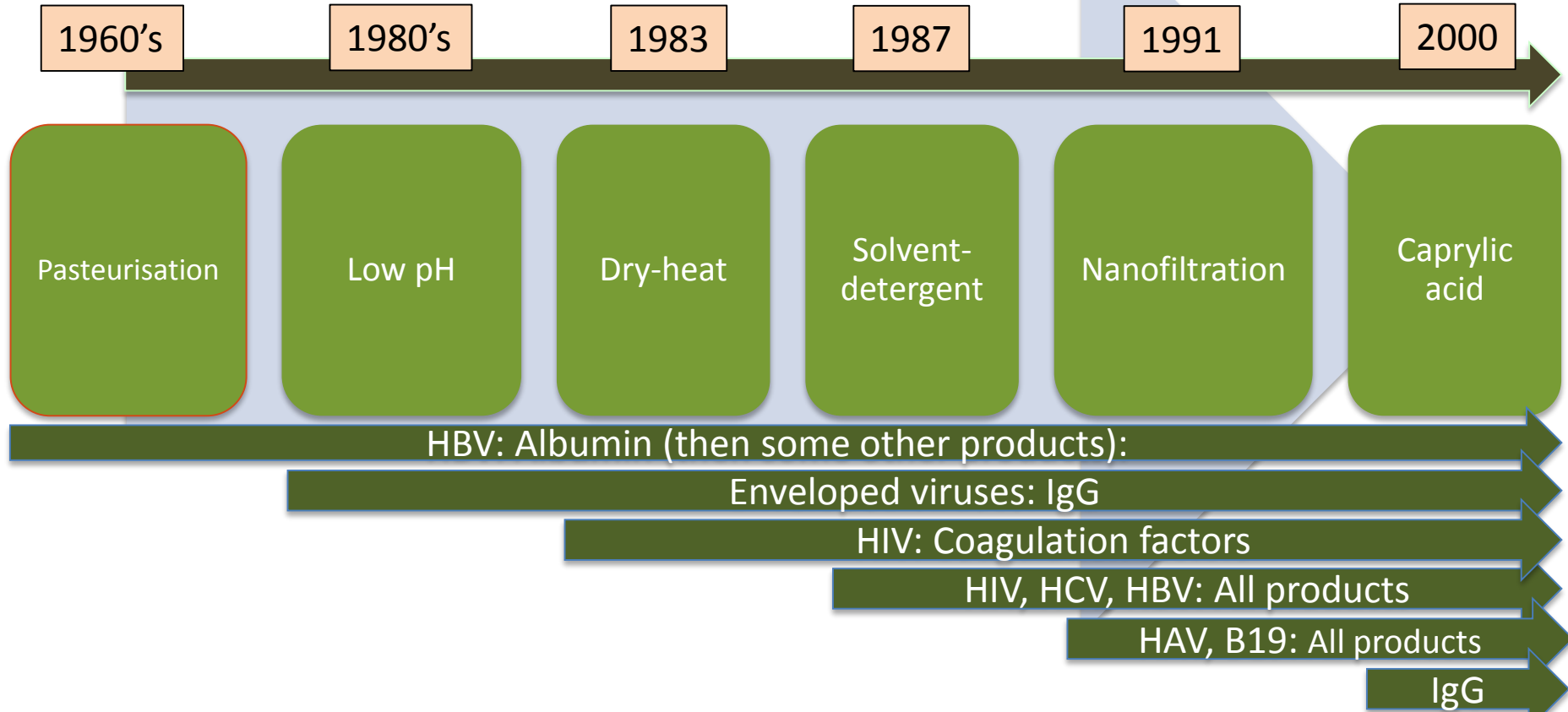
- Broad spectrum of inactivation/removal efficiency of viruses
- Optimal protein recovery and no protein denaturation (neoantigens)

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



Fractionated plasma products have never been so safe with regards to risks of HIV, HBV, HCV



Picture
Source:

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



The answer is ? Yes or no?



yes

What about emerging viruses?

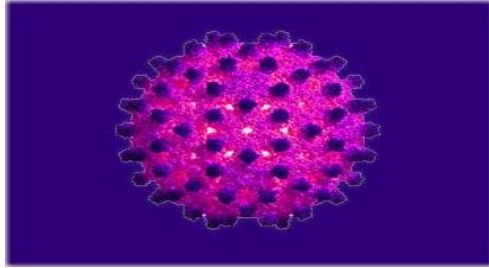


NYIV

Not Yet Identified Virus

?

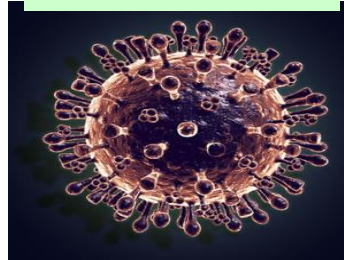
Hepatitis E virus



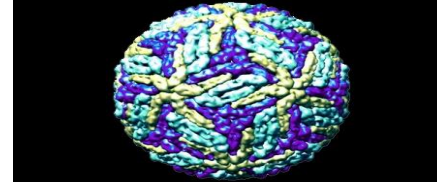
Ebola virus



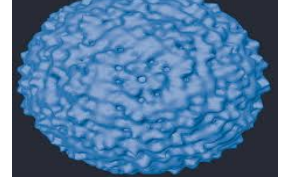
Avian flu virus



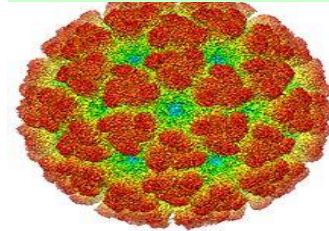
Dengue virus



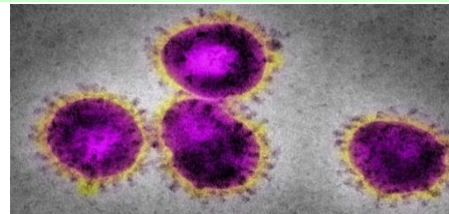
West Nile virus



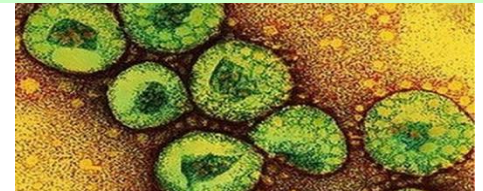
Chikungunya virus



SARS coronavirus virus



MERS- Coronavirus virus



Plasma products transmit emerging viruses ?



Picture
Source

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



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



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

**nano-
filtration**

Technologies in place can safeguard against recent “emerging” viruses



VIRUS

Safety against emerging viruses should be built in the manufacturing process

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, as with any biological products, one should not lower the guard

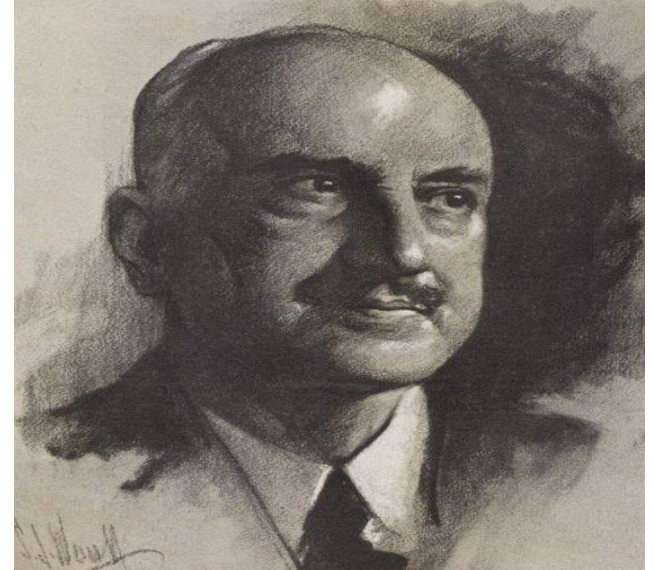


<http://www.leblogfinance.com>

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

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



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

Essential
medicines

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 ?



Picture
Source:

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



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



Picture
Source:

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



Minimum



50'000 – 100'000 donations

Maximum



1'250'000 donations

Excess products of contract fractionation must be destroyed by plasma fractionator



Picture
Source:

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



The answer is ? Yes or 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)

Plasma fractionator's audits role



- “Gap analysis” between:
 - its collection criteria of plasma for fractionation
 - and current collection practices by the local 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 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



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

Minimum



300'000 L

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



Classification: WH 23)

World Health Organization 2016

Domestic fractionation: points to consider



- 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



Plasma



L
O
C
A
L



Final products

CONTRACT FRACTIONATOR



A
B
R
O
A
D

Domestic fractionation: possible phasing



Plasma



**LOCAL
Bulk fractionation**

Intermediates



L
O
C
A
L

Final products

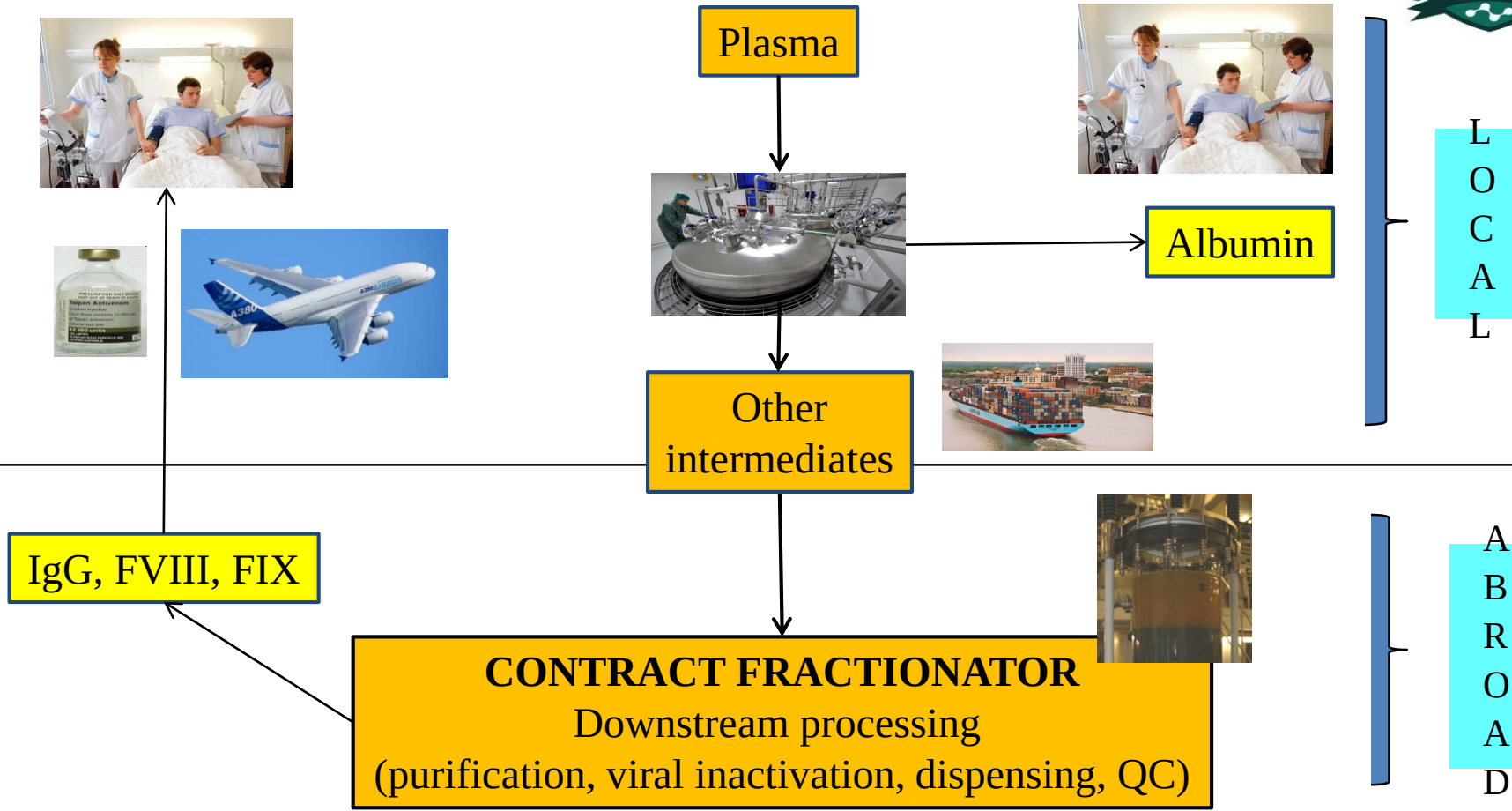
CONTRACT FRACTIONATOR

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

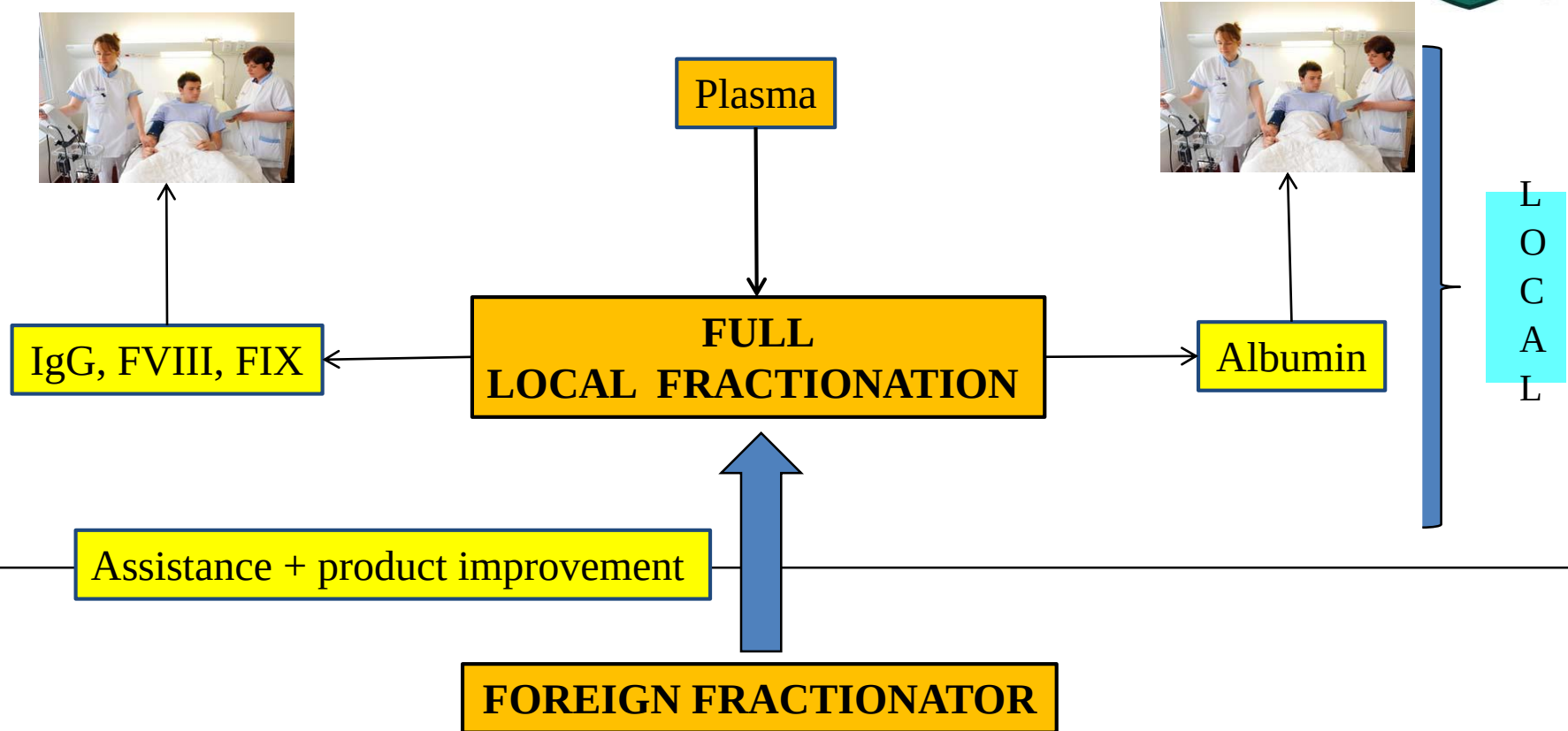


A
B
R
O
A
D

Domestic fractionation: possible phasing



Domestic fractionation: possible phasing



TMU
BME
2015

 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