

Safety and Global Availability of Plasma-Derived Medicinal Products



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Background facts: Global situation



Proven therapeutic importance of PDMPs

Several are on the WHO Model List of Essential Medicines

Global shortage of PDMPs

Leading, established, plasma fractionators are located in HIC

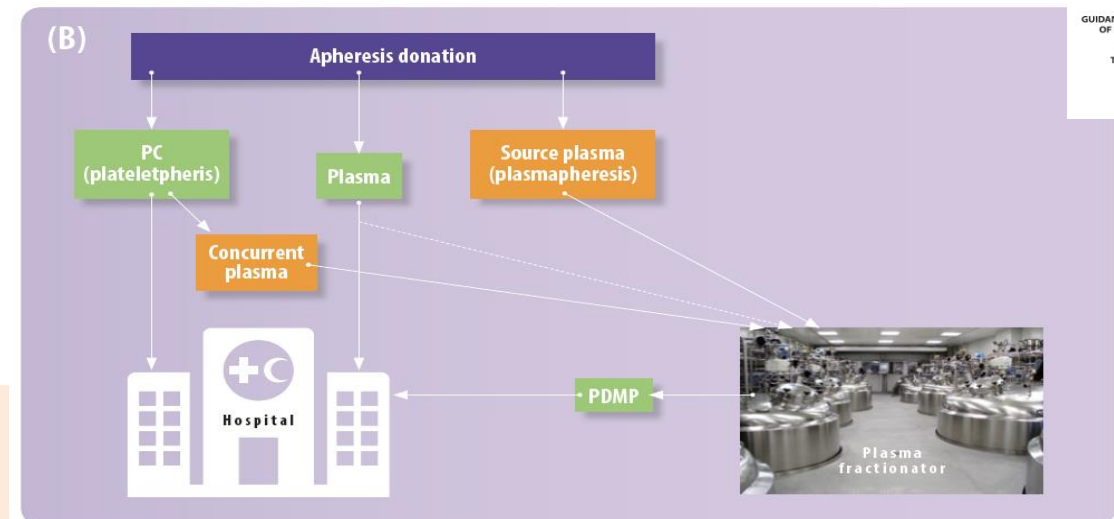
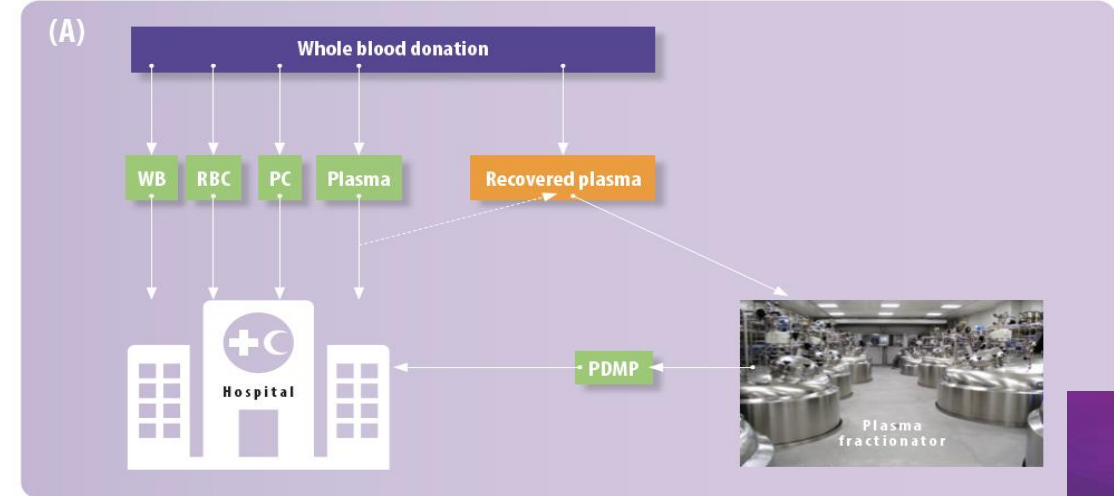
Volume of plasma fractionated worldwide is largely driven to cover clinical needs in HIC ... not LMIC

LMIC patients lack access to safe PDMPs, face supply shortages.

Plasma for fractionation (PFF) in HIC



Fig. 2. Approaches to obtain plasma for fractionation from whole blood donations (A) or apheresis donations (B)



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

World Health
Organization

WB = whole blood; RBC = red blood cell concentrate; PC = platelet concentrate.

Recovered plasma: available after preparation of RBC from whole blood and when plasma is not needed for transfusion.

Low wastage of recovered plasma in HIC:
used for fractionation

Source plasma: collected by plasmapheresis for manufacture of PDMPs

Concurrent plasma: surplus plasma available after preparation of platelets by apheresis

+/- 80% to cover needs in PDMP, and increased collection is driven by the needs in IgG in HIC

Quality PFF in HIC: highly regulated



<https://www.who.int/publications/m/item/annex4-ecbs-human-plasma-fractionation>



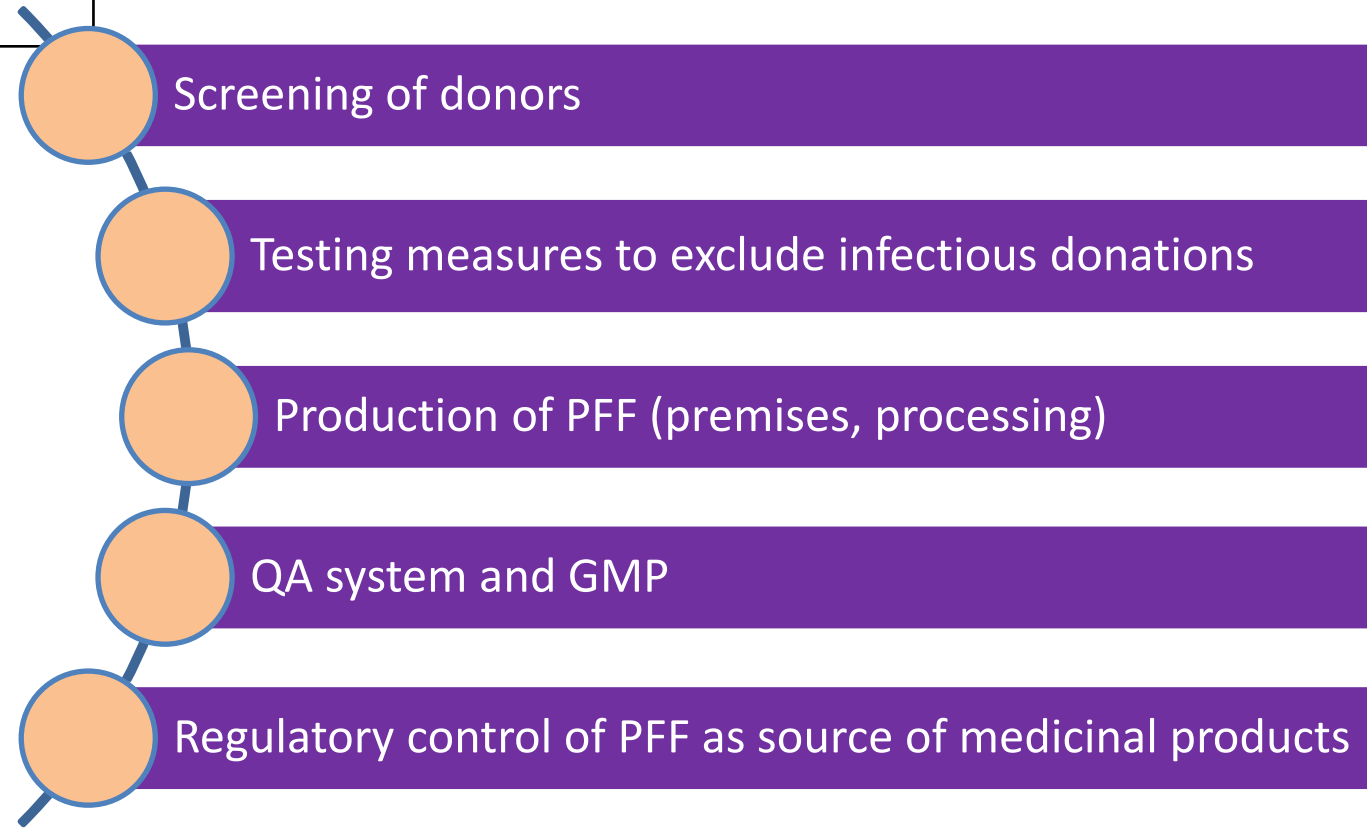
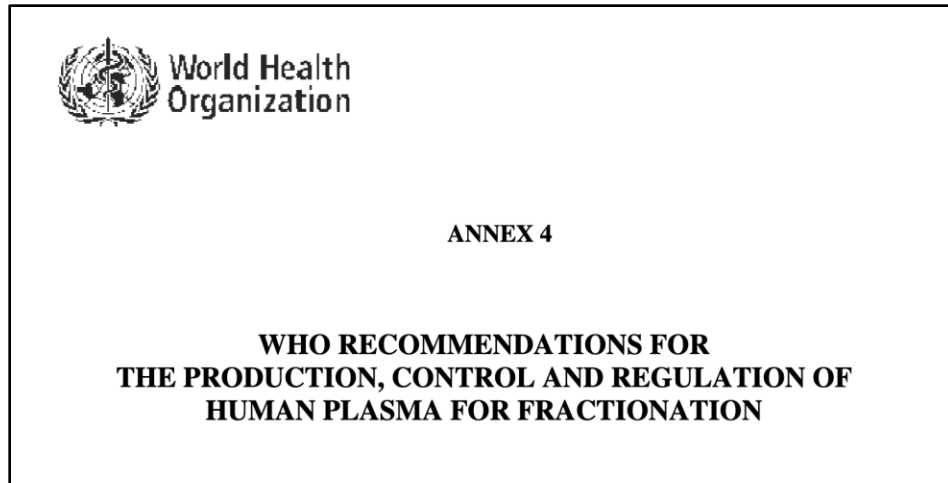
World Health Organization

Home / Publications / Overview / WHO recommendations for the production, control and regulation of human plasma for fractionation, Annex 4, TRS No 941

WHO recommendations for the production, control and regulation of human plasma for fractionation, Annex 4, TRS No 941

28 October 2005 | Publication

- Comprehensive framework for ensuring the quality and safety of plasma for fractionation ... and thus PDMPs.
- The WHO recommendations: valuable resource for regulatory authorities, industry stakeholders, and healthcare professionals.



Plasma fractionation technology in HIC



- Complex--- > wide range (>25) of PDMPs
- Sub-optimal recovery of some proteins

- Well mastered and highly regulated
- > robust quality/safety of PDMPs

- Capacity primarily targeting needs in HIC
- > only the excess products are sold in LMIC

- Sporadic shortages in PDMPs (e.g. IgG) still occur in HIC
- Occasional difficulties in meeting the demand for PDMP-based therapies



<https://www.who.int/publications/i/item/9789240021815>

(Lack of) treatment of patients in LMIC



- PDMPs are unavailable, unaffordable, or available in insufficient quantities
- Some lack of understanding on clinical value and use of PDMPs

Most obviously affected: patients with bleeding disorders and primary immunodeficiencies (role of patients' organizations asking better access)

Lack of access to safe PDMPs leads to patients' morbidities, associated with societal costs

Humanitarian aid programs are valuable, help to meet increasing and diversified therapeutic needs, and represent an intermediary, but not sustainable, solution

Rationale to use LMIC plasma resources as a source of PDMPs

Domestic plasma in LMIC: realistic?



Collection driven by whole blood collection to meet the needs for RBC

Increasing proportion of whole blood separated into components

Increasing volume of plasma in excess of the needs for direct transfusion

Increasing volume of recovered plasma that is discarded instead of being processed into safe therapeutic plasma proteins = wastage

Wastage of recovered plasma in LMIC



Several million L of plasma each year

Plasma not produced, or discarded as it does not fit various requirements for industrial fractionation

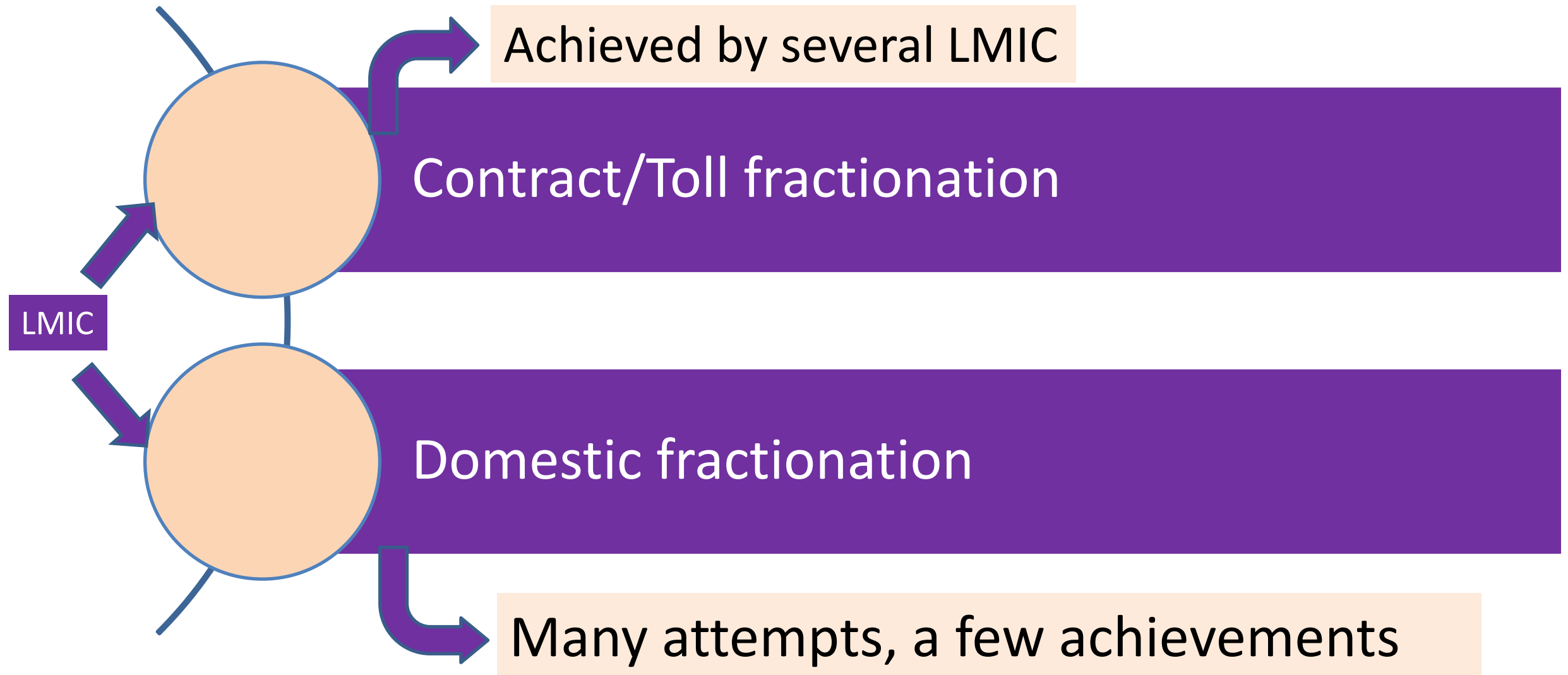
LMIC

Reasons: fragmented collection system, absence of regulation, deficient testing, inadequate infrastructure for freezing, storage and transport...

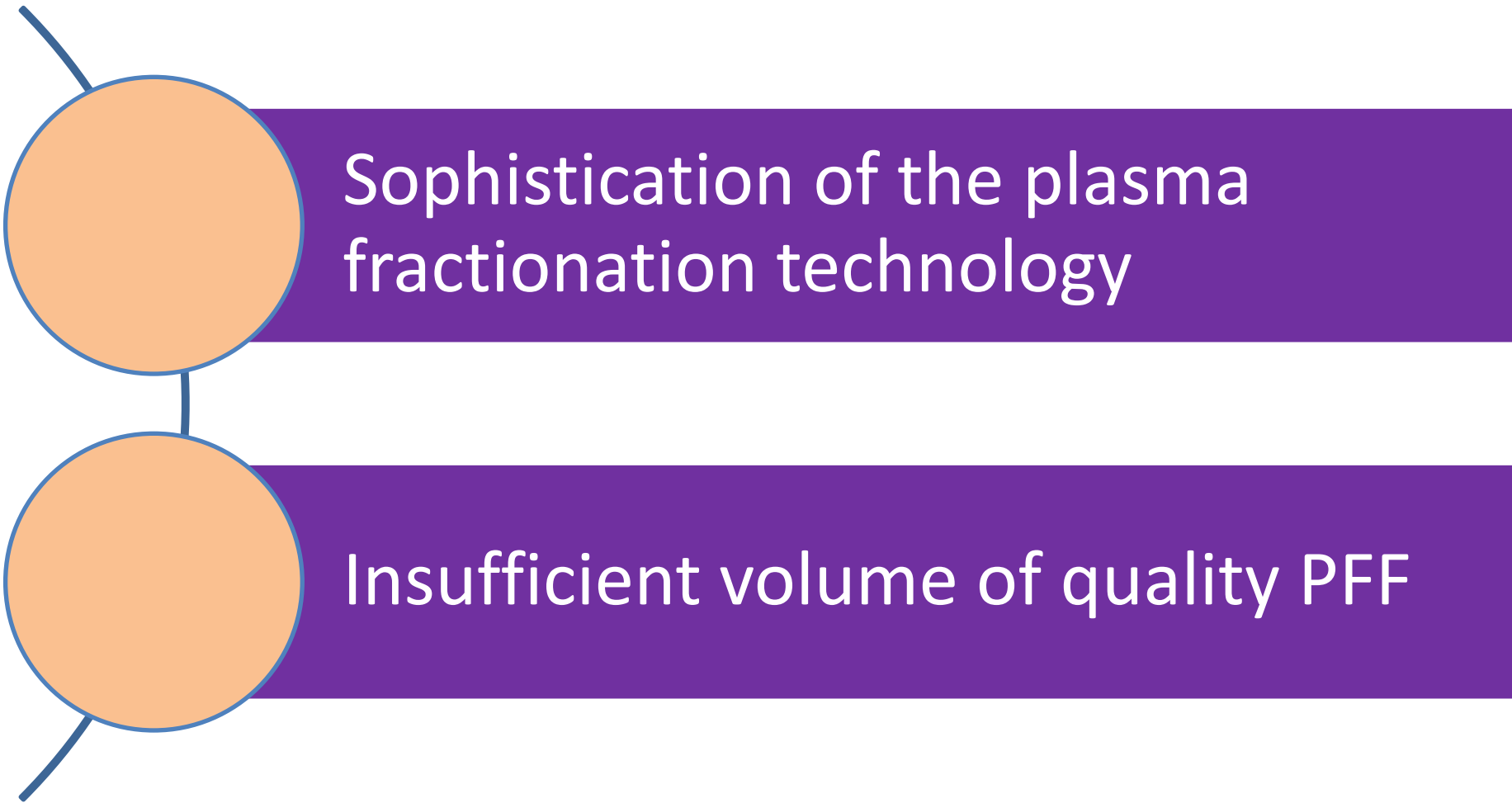
Steady increase in WB collection (to meet RBC needs) is leading to larger volumes of plasma available in LMIC

Steady implementation of GMP principles in blood establishment is increasing plasma suitability for fractionation

What are the industrial options in HIC?



Obstacles to using domestic plasma as the industrial source of safe plasma proteins in LMIC



A diagram consisting of two orange circles connected by a vertical line. From the top circle, a line extends upwards and to the left, ending in a blue arrow pointing towards the top-left obstacle text box. From the bottom circle, a line extends downwards and to the left, ending in a blue arrow pointing towards the bottom-left obstacle text box.

Sophistication of the plasma fractionation technology

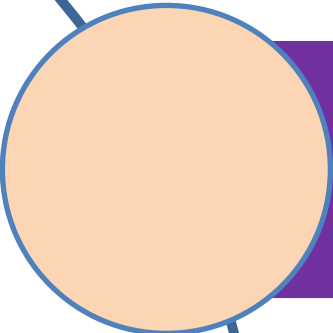
Insufficient volume of quality PFF



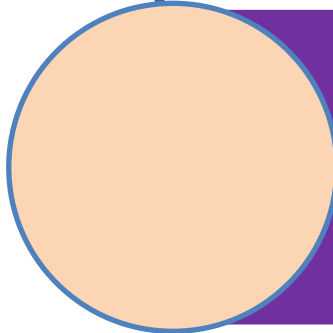
Industrial plasma fractionation obstacles



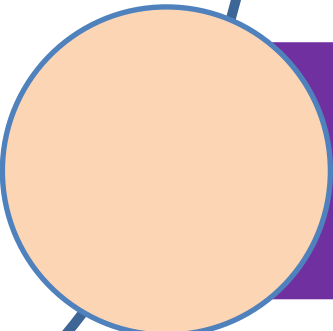
To name just a few



Economics require multiple proteins to be made from the same plasma pool



Complex, specialized know-how for protein purification and virus reduction requiring extensive training and process validation



Complex engineering

Plasma volume obstacles



Options for using domestic quality plasma for fractionation or processing into virally-safe fractions

Domestic facility?



Contract/Toll fractionation



No industrial option

What to do not to waste plasma?



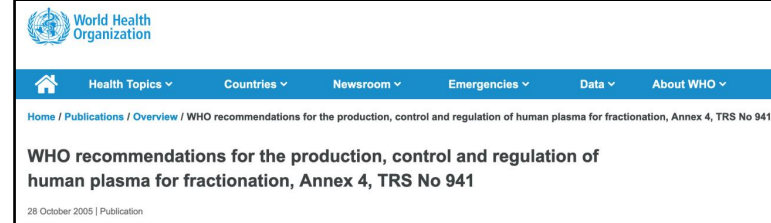
Phase 3
> +/- 300'000L

Phase 2:
+/- 50'000-250'000L

Phase 1: local small-scale production of safe plasma protein products
<50'000L



Volume of plasma available/year

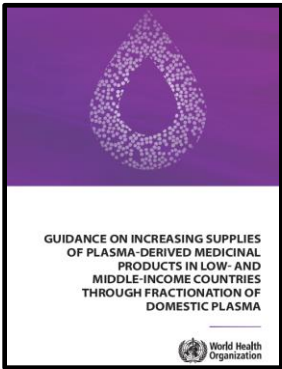


Stepwise improvements are needed and achievable, taking advantages of the solid knowledge in quality/safety of PDMPs

Rationale: Provide therapies for patients who otherwise are

- not treated
- or treated with unsafe crude plasma fractions (non-virally-inactivated FFP or cryoprecipitate)

Local “Mini-pool/Small-pool” processing



- Technological developments made possible thanks to the knowledge acquired over decades on quality and virus safety criteria of PDMPs

- Developed and implemented in Egypt
- Pilot-project at CNTS-Dakar, Senegal (ICSPP)
- Source of virus-inactivated FVIII, fibrinogen, vWF, FXIII

Production of “mini-pool” solvent-detergent treated virus inactivated cryoprecipitate in a single-use bag system

Dr. Jay Epstein’s presentation, tomorrow

Production of “small-pool” caprylic acid purified and virally-inactivated Immunoglobulins in single-use bag system or small vessels

- Developed and implemented in Egypt
- Caprylic acid process implemented in Pakistan to prepare SARS-CoV-2 IgG

Workshop



Workshop Stepwise Access to Safe Plasma Proteins in Resource-Constrained Countries: Local Production & Pathways to Fractionation

This workshop was held on September 21-23, 2021. The recordings and presentations are now available.

[Access the Workshop Content](#)

Vox Sanguinis

The International Journal of Transfusion Medicine



REPORT [Token Access](#)

Stepwise access to safe plasma proteins in resource-constrained countries: Local production and pathways to fractionation—Report of an International Society of Blood Transfusion Workshop

Thierry Burnouf ^{a,b}, Jay Epstein ^c, Jean-Claude Faber ^d, Martin Smid ^e

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Meeting Report

Rationale for supporting stepwise access to safe plasma proteins through local production in low- and middle-income countries: A commentary of an international workshop[☆]

Thierry Burnouf^{a,b}, Jay Epstein^c, Jean-Claude Faber^d, Claude Tayou Tagny^e, Daniel Somuah^f, W. Martin Smid^g

Local “mini-pool” processing: advantages



Domestic access to safe plasma proteins (when PDMPs are not available or insufficient) to treat patients

Implementable on small yearly volumes of plasma, requiring limited capital investment

Valuable learning/training phase on plasma processing, eventually compatible with industrial contract or domestic fractionation

Avoids wastage of plasma and contribute to GMP education in BE

Amenable to “South to South” sharing of experience and finding context-specific solutions to access to PDMPs

Key elements to build any industrial plasma program in LMIC



National blood policies

Centralized and harmonized blood collection services

Focus on the need for quality plasma collection and regulation

Estimates of the domestic needs in PDMPs

Access to options for plasma processing into PDMPs



Contract/Toll fractionation: how?



Domestic

Country of
plasma collection



Transportation



Abroad

Country of
plasma fractionation



Several forms of contractual arrangements
are possible



Home
treatment



Contract/Toll fractionation: Requirements



Plasma quality (donor screening, donation testing, processing) must comply with fractionator's specifications and regulatory requirements

Audits of BE/plasma collection practices by plasma fractionator

Licensing of the BE by the local NRA (collection of plasma for fractionation)

Licensing of the contract fractionator and fractionated products by local NRA



Contract/Toll fractionation: advantages



Good means to use domestic plasma and avoid wastage

Guarantee of some stable supply in PDMP supply

Sustainability of blood establishments (optimal use of blood plasma)

Learning phase: quality criteria of plasma for fractionation (progressive GMP improvements at BE benefiting all blood components)

Learning phase (e.g. training on plasma fractionation) prior to potential technology transfer for domestic fractionation

Domestic fractionation: how?



National level

Abroad

Blood establishments



Transportation



Domestic plasma fractionator



Supplier of technology



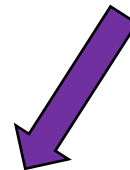
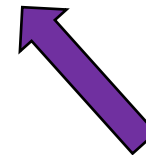
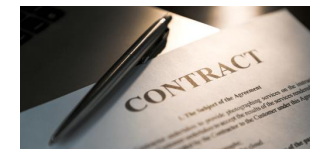
Ideally the one that performed contract fractionation



PDMPs



Engineering company



Pharmacy

Home



Domestic facility: requirements



Provide yearly volume target of quality plasma: 300'000L*

Find a supplier of technology and training of local manpower

Involve a skilled engineering company

Heavy capital investment (often under-estimated)

Recruit and retain skilled and stable manpower

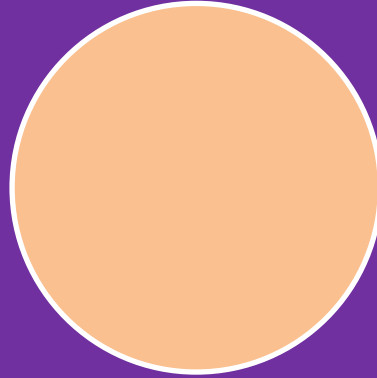
Get government support and relevant regulatory system in place

* WHO report: <https://www.who.int/publications/i/item/9789241564892>

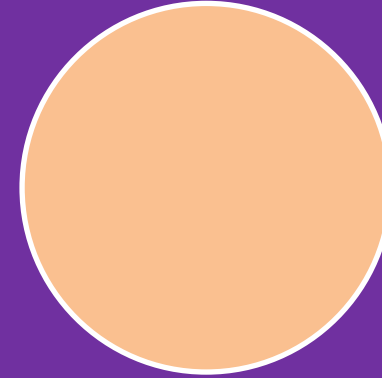
Domestic Facility: Advantages



Some strategic
independence
in PDMP supply



Better control
of PDMP price



Experience with
the biotech
industry



Conclusions/Summary



Safety and Global Availability of Plasma-Derived Medicinal Products

PDMPs are essential therapeutic products

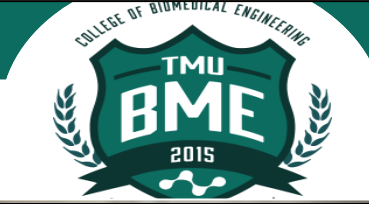
Shortages of PDMPs at global levels affect more particularly patients in LMIC

Quality and safety criteria of PFF and PDMPs are well understood in HIC and can be introduced, monitored, and regulated in LMIC

Stepwise mini/small pool plasma processing approaches can be developed and introduced in LMIC through South to South partnership to enhance supply and prime local technological developments

Contract fractionation of LMIC plasma by licensed fractionators is a meaningful manner to improve PDMP supply without major capital investment and to test the rationale for domestic fractionation

International initiatives (e.g. ICSPP) can provide vital guidance and support to facilitate stepwise access to safe plasma proteins



Safety and Global Availability of Plasma-Derived Medicinal Products

A close-up photograph of a medical device, possibly a dialyzer or a filter, with a yellowish, mesh-like structure. A white rectangular box with the text "Thank you !" is overlaid on the image.

Thank you !

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