Approaches for manufacture of domestic plasma - the WHO guidance

Yuyun Siti Maryuningsih
Team Lead for Blood and other Products of Human Origin
World Health Organization headquarters

No Disclosure

- I have no actual or potential conflict of interest in relation to this congress or this presentation.

OUTLINE

- WHO mandate for self-sufficiency of blood products
- Challenges for self-sufficiency of Plasma-derived Medicinal Products (PDMPs)
- WHO Efforts to overcome challenges
- WHO Guidance in increasing supply of PDMPs in LMICs through fractionation of domestic plasma
- Closing

WHO mandate for self sufficiency of blood products

- World Health Assembly Resolutions 58.13, 2005 on Blood Safety and 63.12, 2014 on Availability, safety and quality of blood products:
  - urge countries to ensure adequate availability of safe and quality blood, blood components and Plasma-derived Medicinal Products (PDMPs)
- Ensuring a safe, secure, sufficient and ethically obtained supply of PDMPs is an important public health responsibility
- Increasing collection of plasma for fractionation, better understanding of the plasma manufacturing processes, and its regulations, contribute to sufficiency of PDMPs.

GDBS 2015
Challenges in Blood Services

World Health Organization

Only 60-70% Member States with blood policy, legislation, oversight System in place

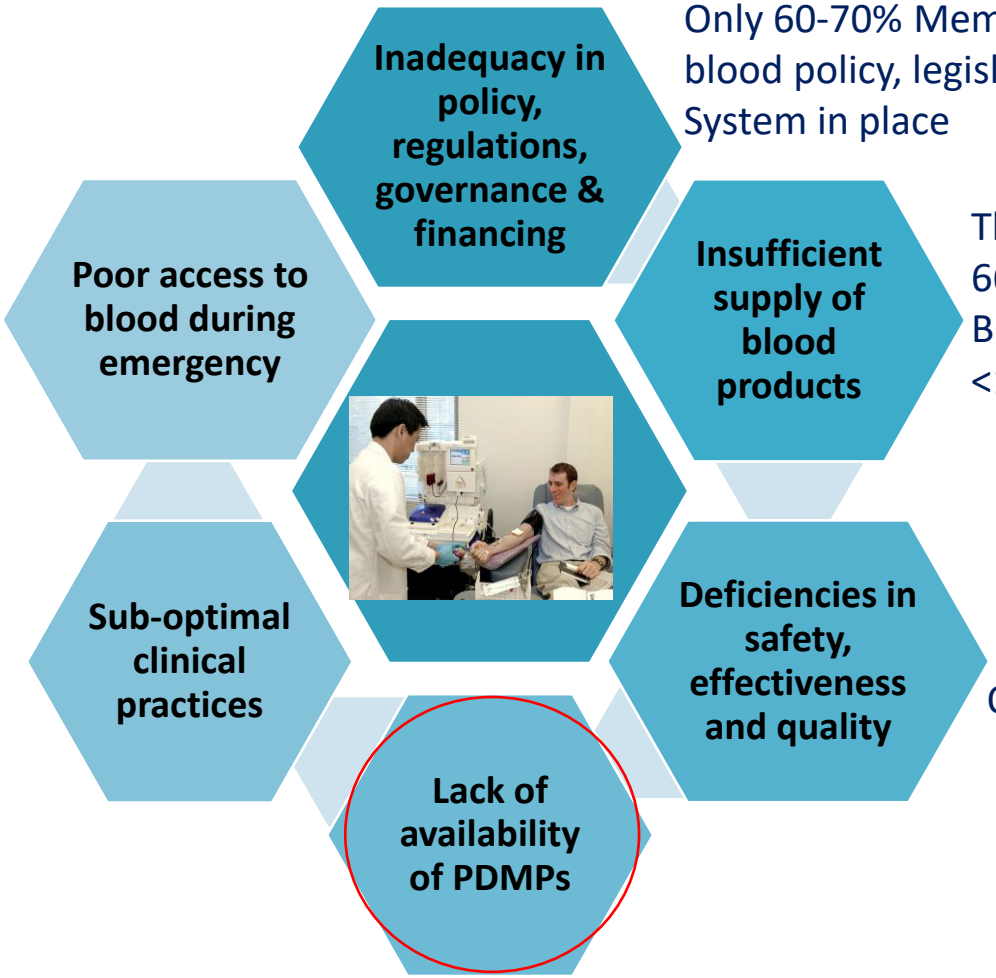
There are still 66 Member States with Blood donation rate <10/1,000 population

Only 80% of donated blood was tested in LMICs

Limited use of blood components → low volume of plasma for fractionation

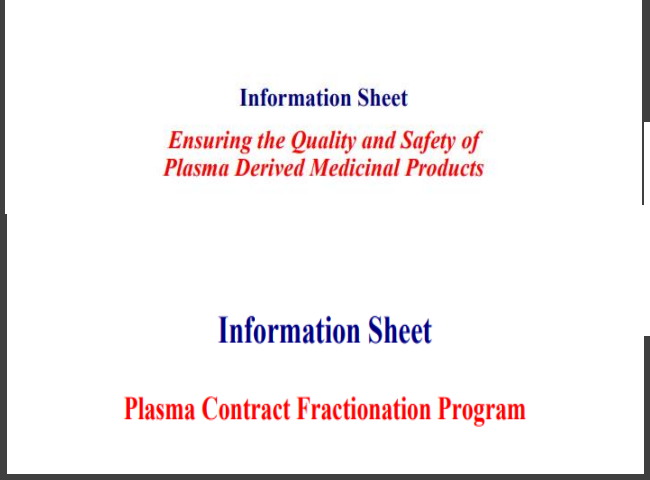
Clinical Use of Blood, Haemovigilance system and Patient Blood Management are not implemented yet

No blood supply preparedness system



Lack of availability of PDMPs

- Availability of PDMPs is insufficient in LMICs and shortages still occur in HICs
- Extensive use of locally prepared and non-pathogen-reduced cryoprecipitate
- World Federation of Haemophilia: 70-75% hemophilia patients do not receive appropriate treatment
- Over 9 million liter of plasma collected in LMICs are not produced or are discarded for lack of acceptability for fractionation
- Production of PDMPs faces numerous technical and regulatory challenges
- In many LMICs, recovered plasma is categorized as waste material and destroyed



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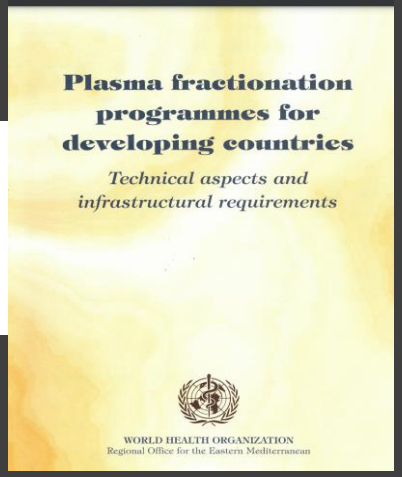

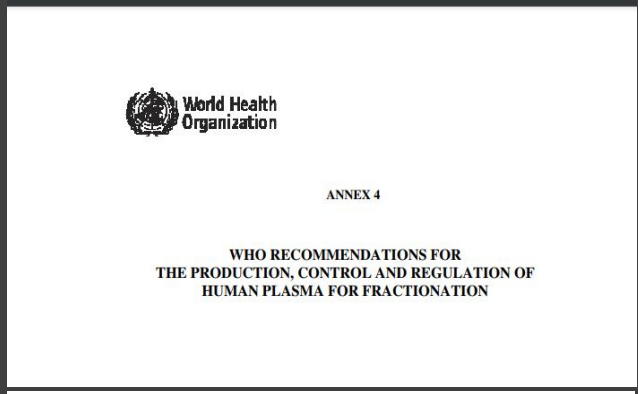

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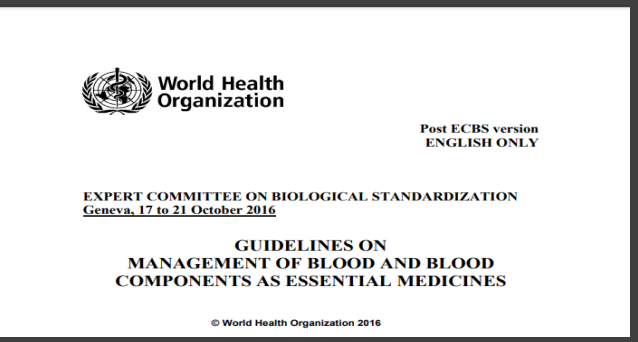

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Countries that implement WHO Resolutions and guidance documents on blood (mostly developed countries) are making progress in providing a sufficient supply of safe blood products

BUT

Progress in establishing and strengthening national blood systems including improvement of plasma quality has been **slow** in many LMICs

Action framework to advance universal access to safe, effective and quality-assured blood products

2020–2023

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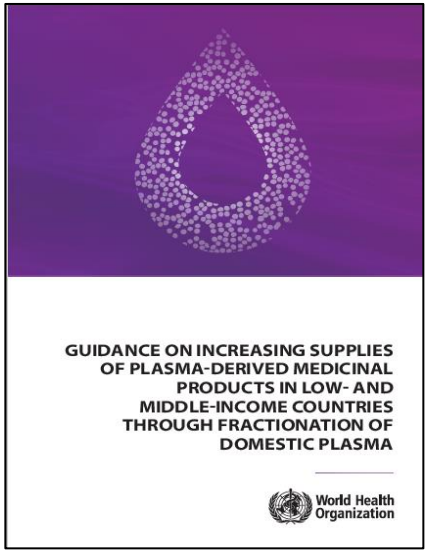

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WHO RECENT EFFORTS

World Health Organization

- **The Action Framework for blood products:**
  - is **a strategic direction** to global efforts to address present barriers to safe blood
- **Strategic objective 3: "Functioning and efficiently managed blood services"**
  - "Guidance on Increasing supply of PDMPs in LMICs through fractionation of domestic plasma"
  - "High-level" recommendations to **Prioritize actions to reduce wastage of domestic plasma that could be fractionated to make the PDMPs that are urgently needed in LMICs**

Motivations for the Guidance

Up to now situation in LMICs with regards to PDMPs

1. Insufficient supply of safe PDMPs due to:
   a. Global shortages
   b. Cost of imported PDMPs
   c. Failure of local plasma to meet requirements for contract/toll or domestic fractionation
   d. Insufficient volume of quality plasma for fractionation
2. Patients are treated with crude plasma or plasma fractions (e.g. cryoprecipitate) and are at high risk of acquiring TTI
3. Increase in whole blood collection (to meet RBC needs)
4. Increasing volume of plasma recovered from whole blood collection is wasted and destroyed

Producing PDMPs from domestic plasma resources is one way to improve the quality and safety of treatment of patients in LMIC

Structure of the Guidance

- Executive summary
- Glossary

1. **Background**
2. **Ensuring an adequate supply of plasma-derived medicinal products**
3. **Strategies to obtain plasma for fractionation**
4. **Recruitment, retention and protection of blood and plasma donors**
5. **Standards and quality management in blood establishments**
6. **Country bilateral and regional cooperation**
7. **Production of plasma for fractionation**
8. **Economics of plasma collection and domestic manufacture of PDMPs**
9. **Stepwise approach to domestic manufacture of virus-inactivated plasma, plasma components and immune globulin concentrates**
10. **Conclusion**

- References

Executive Summary: rationale

1. Guidance in line with resolutions WHA58.13 and WHA63.12 urging countries to ensure adequate availability of safe and quality blood, blood components and Plasma Derived Medicinal Products (PDMPs)
2. This Guidance focuses on PDMPs:
    1. Essential medicines to treat congenital or acquired deficiencies in coagulation factors, haemorrhagic and septic shock, immunological disorders, and viral or bacterial infections
    2. Global shortages affecting LMICs, in part due to their insufficient volume of domestic quality plasma and their current lack of technical and financial capacity to implement a domestic plasma fractionation programme
    3. Wastage of plasma in LMICs that could be used to make PDMPs either through contract (i.e. foreign) or domestic fractionation

Executive Summary: targets & objectives

1. High-level overview of actions to increase access to PDMP in LMICs through use of locally-produced plasma
2. Roadmap for policy-makers, NRA, blood collection organizations, blood donors & associations, clinicians, & patients, on how to:
    1. Reduce plasma wastage
    2. Increase the volume of quality and safe plasma
    3. Use plasma for production of PDMPs
3. Eventual sufficiency of PDMPs in LMICs, enhanced public health and resilience of the blood system in situations of crisis, including pandemics

1 BACKGROUND

1.1 Scope and objectives of the guidance

- Identification of major barriers to using domestic plasma for fractionation, considerations and actions … to assist countries in developing policies and strategies to increase the supply of PDMPs
- Primary audience: policy-makers, national regulatory authorities, blood collection organizations, blood donors and their associations, clinicians and patients … and plasma collectors and fractionators.
- Blood components for transfusion (whole blood, red blood cells, platelets, plasma, cryoprecipitate and cryoprecipitate-poor plasma) and plasma for fractionation

BACKGROUND

1.2 Blood: source of blood components for transfusion and purified protein products from plasma fractionation

Two major types of production procedures of plasma for fractionation

"Recovered"(prepared from whole blood donation)

+ "concurrent" plasma

"Source" (dedicated collection by apheresis)

- Standard plasma used to make all PDMPs
- Hyperimmune plasma used to make hyperimmune IgG

1 BACKGROUND

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1.3 PDMP therapies

Table 1. Main PDMPs and their clinical indications

Products	Main indications
Albumin	
Human serum albumin	Volume and protein replacement
Blood coagulation factors	
Factor VIII[a*+]	Haemophilia A
Prothrombin complex (PCC/PPSB)[b*]	Complex liver diseases; warfarin or coumarin derivatives reversal[c]
Factor IX*+	Haemophilia B
Factor VII	Factor VII deficiency
von Willebrand factor	Von Willebrand factor deficiency (type 3 and severe forms of type 2)
Factor XI	Haemophilia C (FXI deficiency)
Fibrinogen	Fibrinogen deficiency
Factor XIII	Factor XIII deficiency
Activated PCC	Haemophilia with anti-FVIII (or FIX) inhibitors
Protease inhibitors	
Antithrombin	Antithrombin III deficiency
Alpha-1 antitrypsin	Congenital deficiency of alpha-1 antitrypsin with clinically demonstrable panacinar emphysema
C1-inhibitor	Hereditary angioedema
Anticoagulants	
Protein C	Protein C deficiency/(thrombosis)
Fibrin sealant (fibrin glue)[d]	Topical haemostatic/healing/sealing agent (surgical adjunct)
Intramuscular immunoglobulins (IMIG)	
Normal (polyvalent)*+	Prevention of hepatitis A (also rubella, and other specific infections)
Hepatitis B	Prevention of hepatitis B
Tetanus*+	Treatment or prevention of tetanus infection
Anti-Rho(D)*	Prevention of haemolytic disease of the newborn
Rabies*+	Prevention of rabies infection
Varicella/zoster	Prevention of chickenpox infection

Table, divided into the main classes of PDMPs, presenting their main clinical indications

Products	Main indications
Intravenous immunoglobulins (IVIG)	
Normal (polyvalent)*+	Replacement therapy in immune deficiency states Immune modulation in immune disorders
Hepatitis B	Prevention of HBV infection (e.g. liver transplant)
Anti-Rho(D)*	Prevention of haemolytic disease of the newborn
Intravenous immunoglobulins M	
	septic shock; binding of endotoxins

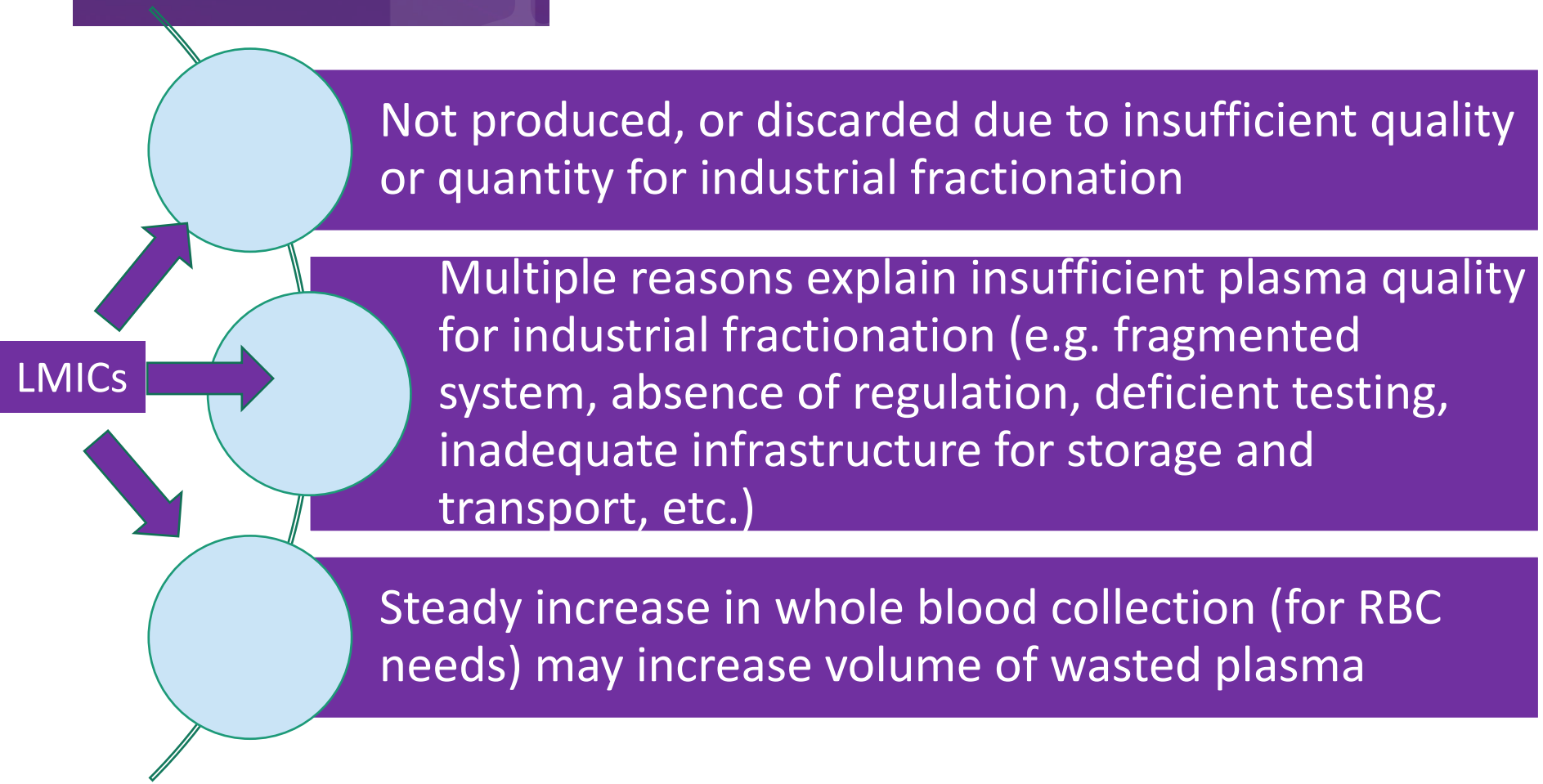
[a] Some factor VIII concentrates containing von Willebrand factor are effective for the treatment of von Willebrand disease.
[b] Prothrombin complex contains factor II, factor VII, factor IX, and factor X. The content of factor VII may vary depending upon products.
[c] Prothrombin complex may be used, in the absence of purified plasma products, for substitutive therapy in factor VII, factor X, or protein C deficiency. Whenever available, purified factor IX should be used to treat haemophilia B.
[d] Fibrin sealant is obtained by mixing a concentrate rich in fibrinogen and a concentrate rich in thrombin.
* Products on WHO Model List of Essential Medicines *(4)*.
+ Products on WHO Model List of Essential Medicines for Children *(5)*.
Source: WHO recommendations for the production, control and regulation of human plasma for fractionation *(3)*.

Listed as Essential Medicines

1.4 Unmet needs for PDMPs

- Situation recognized by WHA
- LMICs: critical chronic supply difficulties in PDMPs
- LMICs: Use of crude, non-virus safe blood components

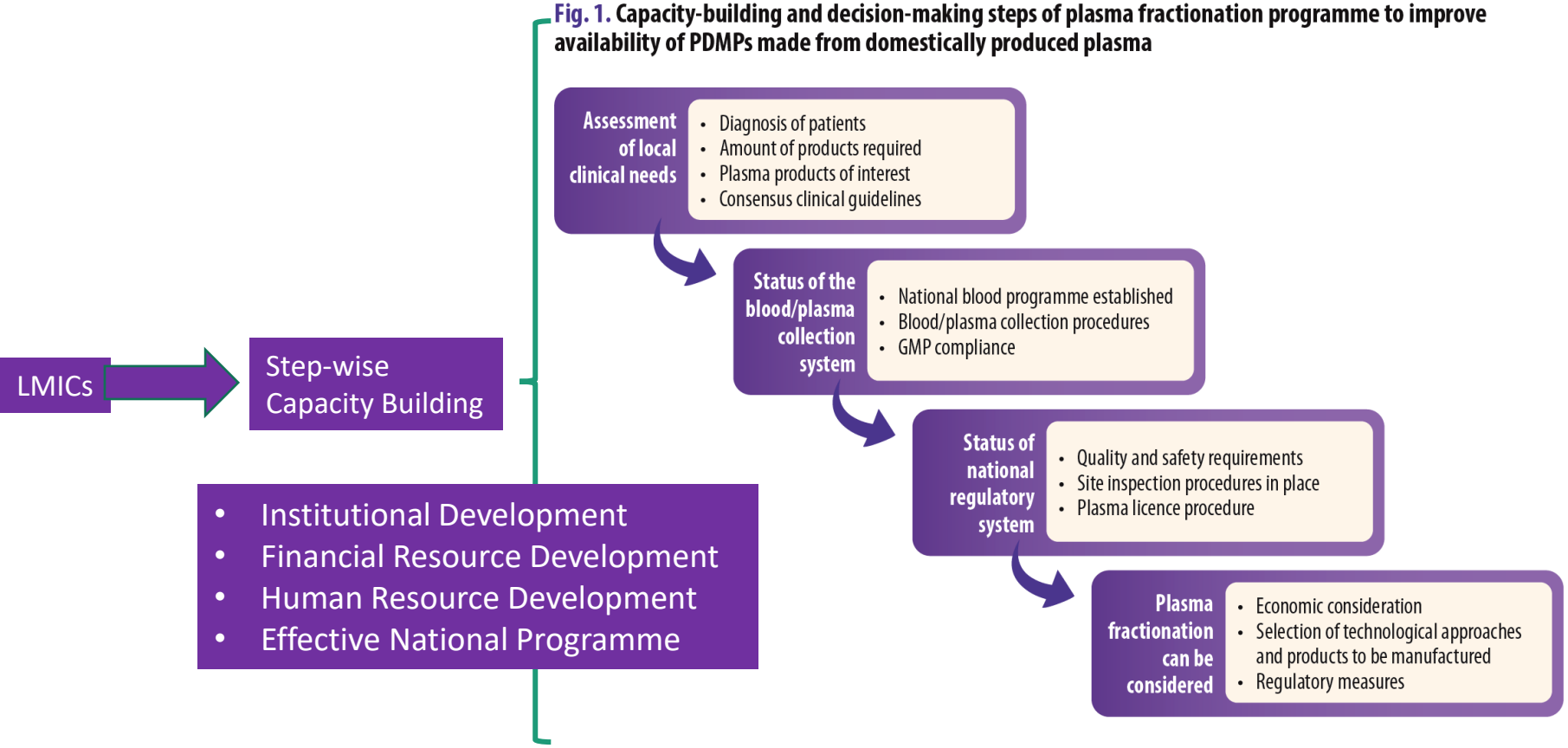
1.5 Wastage of recovered plasma



1 BACKGROUND

1.6 Urgent need for capacity-building in LMIC

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



1 BACKGROUND

1.7 Optimal use of PDMPs

1.8 Concerted action in utilizing surplus protein products

- Sound medical practices
- Evidence-based clinical use
- Cooperation among countries can help improve the supply of some PDMPs (e.g. sharing of surplus products)

2 ENSURING AN ADEQUATE SUPPLY OF PLASMA-DERIVED MEDICINAL PRODUCTS

- 2.1 Barriers to supply of suitable plasma for fractionation – issues of quality and volume
- 2.2 Requirements for a nationally organized, regulated and stably funded system – National Blood Policy as a foundation
- 2.3 Establishment and enforcement of standards – quality based on compliance with pre-established standards
- 2.4. Regulatory authorization of blood and plasma collection, testing, and processing – maturity of blood regulation defined in the WHO Global Benchmarking Tool
- 2.5.GMP audits by the fractionator – comprehensive assurance of plasma quality
- 2.6. Haemovigilance and pharmacovigilance – monitoring, reporting, investigation and analysis of adverse events and adverse reactions

3 STRATEGIES TO OBTAIN PLASMA FOR FRACTIONATION

Recognizing the medical value and ethical significance of all human donations, efforts need to be made to ensure that plasma is used in the most efficient way and not discarded as waste.

3.1 Recovered and concurrent plasma

3.2 Source plasma

development of a national programme of plasmapheresis should be part of a stepwise advancement of the blood system to provide quality and safe blood for transfusion.

4 RECRUITMENT, RETENTION AND PROTECTION OF BLOOD AND PLASMA DONORS

- 4.1 Culturally sensitive promotion of blood and plasma donation and social marketing
- 4.2 Sensitization and education of blood and plasma donors on the specific value of plasma and its products
- 4.3.Protection of donors' health and rights

5

STANDARDS AND QUALITY MANAGEMENT IN BLOOD ESTABLISHMENTS

5.1 Standards for donor selection

5.2 Standards for quality-assured laboratory testing for evidence of transfusion-transmissible infection

5.3 GMP and quality management

- Suitable organization and trained personnel
- Suitable facility and equipment
- System of documentation and traceability
- Validation of operating procedures and quality monitoring

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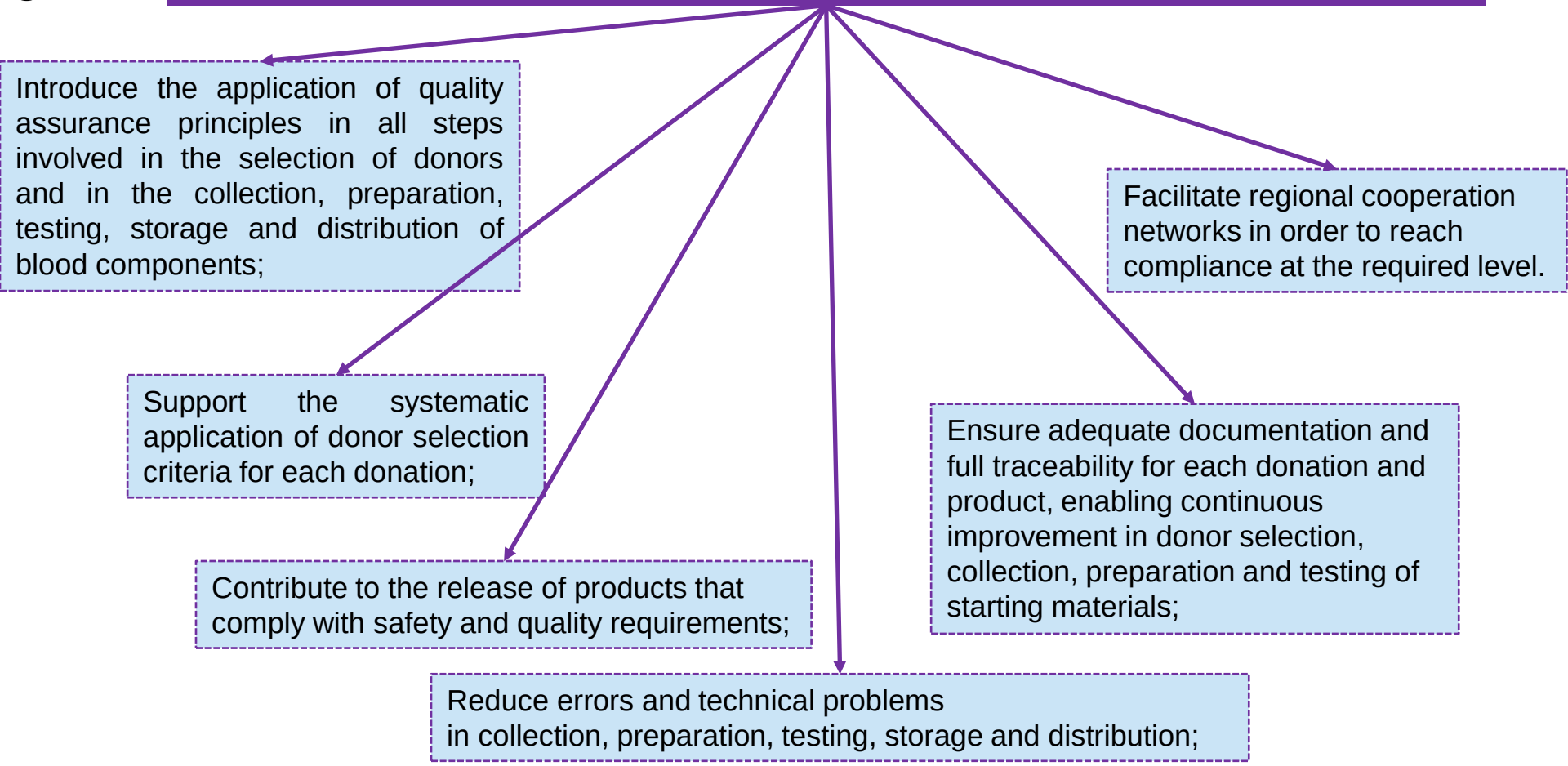
The implementation of GMP in blood establishments aims to:



6

COUNTRY BILATERAL AND REGIONAL COOPERATION

- A pragmatic way to avoid wastage of recovered plasma and potentially make use of plasma obtained from plasmapheresis is to contract with a plasma manufacturer from another country to perform the fractionation, which involves sending a country's plasma supply to a licensed fractionator.
- Contract fractionation can be set up in a relatively short time and with a relatively low volume of plasma (10 000 to 50 000 litres).
- A national process roadmap for the supply of plasma should be developed and followed.

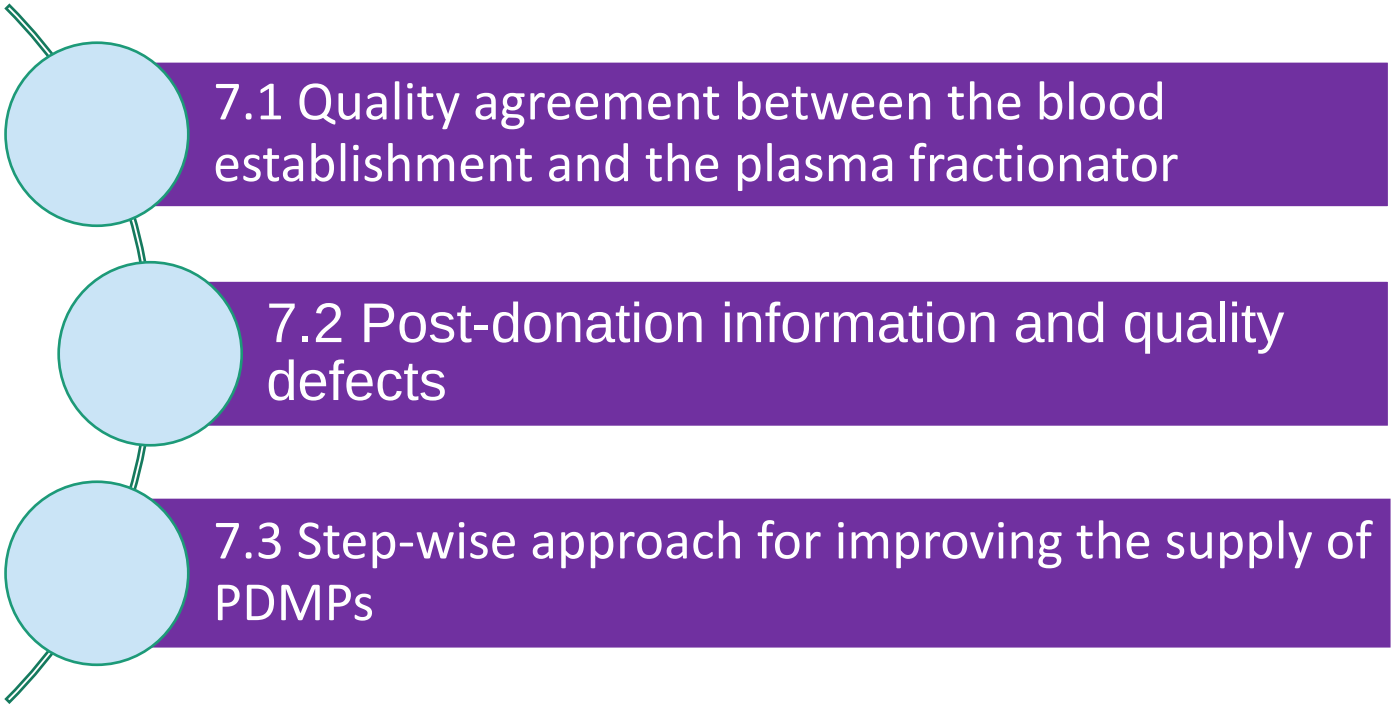
6

COUNTRY BILATERAL AND REGIONAL COOPERATION

Business Considerations

- Cost of compliance with the plasma specifications of the fractionator, including the availability of funding for infrastructure development;
- Net value of recovered plasma, and possibly source plasma (cost per litre collected versus revenue from the sale of plasma);
- Transport and logistics costs of providing plasma to the fractionator;
- Duration of the supply contract
- Product supply chain and distribution model (including consideration of legal, product registration and legislative issues);
- Cost–benefit ratio of the entire process, and regulatory compliance

7 PRODUCTION OF PLASMA FOR FRACTIONATION

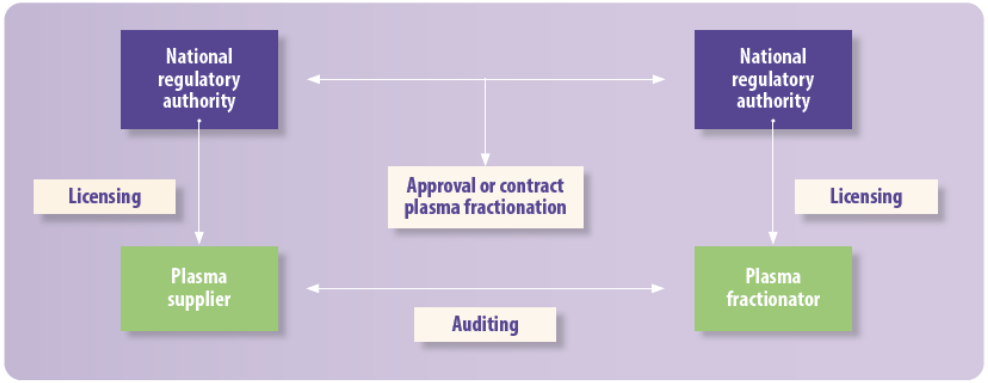


7

PRODUCTION OF PLASMA FOR FRACTIONATION

7.1 Quality agreement between the blood establishment and the plasma fractionator

Fig. 3. Parties involved in a plasma fractionation agreement



Source: Adapted from the WHO *Information sheet: plasma contract fractionation program (49)*.

Table 2. Areas of particular relevance for a quality agreement between a blood establishment and a fractionator

No.	Topic	Explanation
1	Donor selection	In accordance with the national regulatory authority, evidence-based donor selection criteria need to be agreed. Donor selection procedures typically include: • strategy to recruit donors at low risk of transfusion-transmissible infections • provision of donor candidates with educational material • assessment of donor eligibility.
2	Exclusion or acceptance of donors	Schedule of requirements for donor acceptance or exclusion will include: • donor identification • donor deferral and exclusion criteria • criteria for self-exclusion.
3	Tests to ensure donor safety	Plasma protein and IgG levels of frequent plasma donors should be monitored at specified intervals.
4	Epidemiology of the donor population	Arrangements need to be made for monitoring and reporting the epidemiology of the donor population. This should include at least HIV, hepatitis B and hepatitis C.
5	Location of blood establishments	The location of blood establishments needs to be convenient for donors and for personnel. Infrastructure must exist that allows transportation of plasma to the fractionator. The premises for collection should follow WHO recommendations (3).
6	Frequency of donation	Donations can be done at intervals approved by the national regulatory authority. The blood establishment needs to have a system that ensures that the donor does not exceed the approved frequency of donation.
7	Donor screening and donation testing	Requirements need to be established, including: • donor screening for risk factors of transfusion-transmissible infections • donation testing using national regulatory authority approved tests • preparation and testing of mini-pools.
8	Validation test reagents	A procedure should be in place for validation and approval of relevant test reagents and kits.
9	Record keeping	The blood establishment and the fractionator need to have a document management system in compliance with the agreed quality management system, including: • donor selection criteria and epidemiology • collection procedures • quality records of laboratory testing • manufacturing standard operating procedures • quality assurance procedures • lot release process • change control • audit and inspection procedures • retention periods.
10	Specifications of plasma	Plasma specifications need to be supplied, including: • volumes of collected plasma • yield of the PDMPs made from domestic plasma • documentation of compliance.
11	Specifications of containers	Each donation is stored in specific containers, authorized by the national regulatory authority and approved by the fractionator.
12	Labelling	Detailed requirements for labelling of individual plasma units and traceability need to be in place.
13	Freezing, storage and shipment	Arrangements need to be made for quality-assured freezing, storage and shipment of plasma.
14	Quality defects, post-donation notification	Requirements for notifiable events should be specified, including the arrangements for quality defects and post-donation notification.
15	Change	The procedure for review and approval of any proposal for procedural change will be described.
16	Audit	The procedure and agreed frequency for audit of the blood establishment by the fractionator will be specified.
17	Regulatory inspection	Arrangements need to be made on how to notify the blood establishment or the fractionator about an expected regulatory inspection, how often this occurs, and how the outcome of that inspection should be communicated.
18	Roles and responsibilities	Key personnel, contact persons.

Source: Adapted from WHO recommendations for the production, control and regulation of human plasma for fractionation (3).

7

PRODUCTION OF PLASMA FOR FRACTIONATION

7.2 Post-donation information and quality defects

- PDMP manufacturers are obliged to provide information to the national regulatory authority when adverse events related to their PDMPs are spontaneously reported. Adequate responses depend on the existence of bidirectional traceability of the entire chain.
- In the case of an unexpected adverse event or any other important information, the fractionator needs to review all documents related to the manufacturing process. The process for addressing such a situation needs to be described in the contract.

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7

PRODUCTION OF PLASMA FOR FRACTIONATION

7.3 Step-wise approach for improving the supply of PDMPs

Table 3. Stepwise approach to improving the supply of PDMPs at national level

Phasing	Description	Action
Phase 1	• There is insufficient quality and volume of recovered plasma for fractionation available at national level	• Estimate need for PDMPs • Import of PDMPs • Prepare pathogen-reduced plasma protein fractions using validated technologies preserving product efficacy
Phase 2	• Recovered plasma meeting quality and quantity requirements for fractionation is available • Establishment has an auditable quality system based on current GMP • Blood and blood component demand is being fully satisfied	• Initiate a programme for fractionation of recovered plasma (e.g. contract fractionation) • Produce more plasma for fractionation by apheresis, including concurrent plasma and source plasma, to meet stepwise clinical demand for PDMPs • Decrease the quantity of imported PDMPs
Phase 3	• Volume of plasma for fractionation produced at national level is sufficient	• Consider a national or regional facility for fractionation • Import PDMPs that are not produced domestically

8

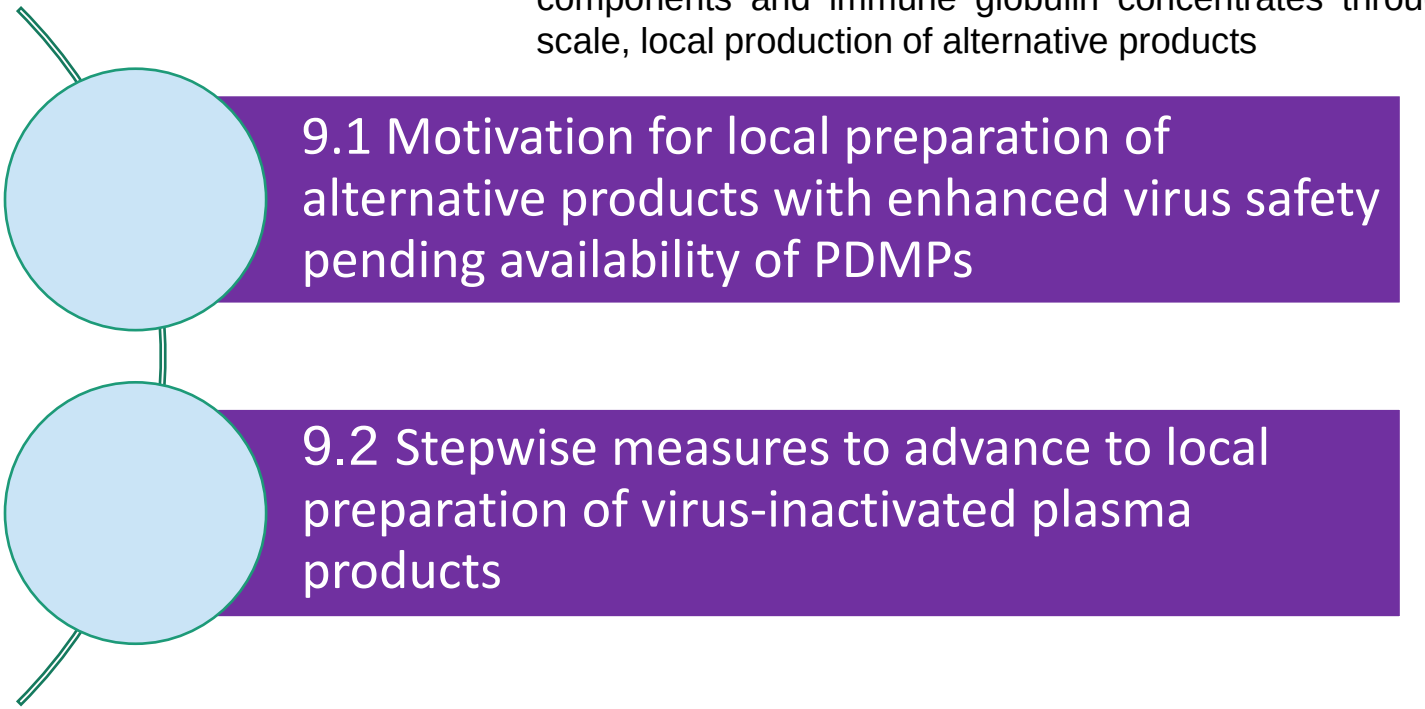
ECONOMICS OF PLASMA COLLECTION AND DOMESTIC MANUFACTURE OF PDMPs

- 8.1 Good manufacturing practices
- 8.2 Cost considerations in plasma collection
- 8.3 Cost consideration in domestic plasma manufacturing and associated risks
- 8.4 Additional financial considerations for domestic fractionation projects
- 8.5 Contract manufacturing

9

STEPWISE APPROACH TO DOMESTIC MANUFACTURE OF PLASMA, PLASMA COMPONENTS AND IMMUNE GLOBULIN CONCENTRATES WITH ENHANCED VIRUS SAFETY

Pending industrial plasma fractionation, actions can be taken stepwise to improve the availability of safe plasma, plasma components and immune globulin concentrates through small-scale, local production of alternative products



9.1 Motivation for local preparation of alternative products with enhanced virus safety pending availability of PDMPs

9.2 Stepwise measures to advance to local preparation of virus-inactivated plasma products

9

9.2 Stepwise measures to advance to local preparation of **virus-inactivated plasma products**

- Stepwise measures to be taken

GMP to guarantee quality and safety requirements for blood donation

Increase and improve the separation of whole blood to generate FFP with preserved native quality, including the content in coagulation factors.

Enable preparation of single-donor native cryoprecipitate and single-donor native cryoprecipitate-poor plasma

3-6 months quarantine for plasma, cryo and cryo-poor plasma. If the donor does not return, the units can be repurposed for additional manufacturing into final products by methods that include virus inactivation; When a quarantine is not technically feasible, consider a holding period of two weeks.

9

9.2 Stepwise measures to advance to local preparation of **virus-inactivated plasma products**

- Stepwise measures to be taken

- Transfer of validated virus inactivation technologies of plasma, cryo, and cryo-poor plasma, and small pool size manufacturing methods of virus-inactivated plasma components
- Implementation of small facilities and of equipment for virus inactivation treatments of plasma, cryoprecipitate and cryoprecipitate-poor plasma.
- Expand number of blood establishments able to prepare virus-inactivated plasma, cryo, cryo-poor plasma and small-scale immunoglobulin concentrates while efforts to establish fractionation of domestic plasma are ongoing.
- Consider the use of plasma for small-scale or large-scale fractionation into immunoglobulins and albumin when its freezing and storage do not meet the standards for production of coagulation factors.

Closing

- WHA Resolutions urge Member States for self-sufficiency of blood products
- Numbers of WHO documents are available to guide improvement of quality of blood products
- Good blood regulatory system and well coordinated blood supply system need to be in place to be able to utilize plasma for fractionation
- WHO Guidance on Increasing supply of PDMPs in LMICs through fractionation of domestic plasma provide recommendation on stepwise approach to domestic manufacture of PDMPs
- Strong support from MoH, NRA and other relevant stakeholders is very important.

Thank you