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

World Health Organization

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PREFACE

Plasma-derived medicinal products (PDMPs) play a major role in health care, including treatment for haemophilia, immune diseases, certain infections, and a variety of other serious conditions. A number of PDMPs are included in the WHO Model List of Essential Medicines, emphasizing their importance in the health system and the need to facilitate access to these products in all countries. However, unequal access globally to PDMPs, especially scarcity in many low- and middle-income countries (LMIC), leaves many patients with severe congenital and acquired disorders without adequate treatment. A major factor limiting the global availability of PDMPs is an inadequate supply of plasma meeting internationally recognized standards for fractionation. In response to this situation, the World Health Assembly in 2010 adopted resolution WHA63.12, which urges Member States "to take all the necessary steps to establish, implement and support nationally-coordinated, efficiently-managed and sustainable blood and plasma programmes according to the availability of resources, with the aim of achieving self-sufficiency, unless special circumstances preclude it".

Medical treatment using blood components rather than whole blood is gradually increasing in developing countries. This results in production of plasma in excess of clinical need. Such "surplus plasma" recovered from whole blood donations (recovered plasma) could be made available for fractionation into PDMPs to help address unmet patient needs. However, in LMIC, good manufacturing practice often is not in place, rendering recovered plasma unacceptable for fractionation, with considerable wastage of plasma as a result.

The WHO guidance on *Increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma* provides a strategic framework to assist Member States in increasing their volume of quality plasma for fractionation. The guidance was developed under the WHO Action Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood Products 2020–2023 to advance the objective of "functioning and efficiently managed blood services". This guidance is complementary to the WHO guidance on centralization of blood donation testing and processing, which assists Member States in deciding whether to centralize blood donation testing and processing and provides practical guidance in that area. Centralization of blood donation processing can play an important role in increasing the availability of quality plasma for fractionation.

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LIST OF ABBREVIATIONS AND ACRONYMS

ELISA	enzyme-linked immunosorbent assay
GMP	good manufacturing practices
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HTLV	human T cell lymphotropic virus
IgG	immunoglobulin G
NAT	nucleic acid amplification testing
PDMP	plasma-derived medicinal product
WHO	World Health Organization

GLOSSARY

Apheresis	The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation or filtration into its components, and returning those not required to the donor. The term plasmapheresis is also used for a procedure dedicated to the collection of plasma.
Blood establishment	Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release or distribution of human blood or blood components (including source plasma) when intended for transfusion or further industrial manufacturing. It encompasses the terms blood bank, blood centre, plasma collection centre, blood service and blood transfusion service.
Coagulation factors	Plasma protein components (such as factor VIII, factor IX, fibrinogen) that are involved in the clotting of blood; also termed clotting factors.
Concurrent plasma	Plasma collected during the same apheresis collection procedure as platelets (plateletpheresis).
Contract plasma fractionation	An arrangement in which domestic plasma is provided to a fractionator licensed in a foreign country and PDMPs are provided in return, according to predetermined terms for use within the country.
Cryoprecipitate	A single-donor or small pool therapeutic plasma fraction obtained by thawing frozen plasma at 2–4°C and used to treat deficiencies in factor VIII, factor XIII, von Willebrand factor, or fibrinogen.
Cryoprecipitate-poor plasma	A single-donor therapeutic plasma supernatant fraction obtained after removal of cryoprecipitate, used to treat deficiencies in vitamin K-dependent plasma factors (for example factor IX); also termed cryo-poor plasma or cryo-supernatant.
Fractionation	(Large-scale) process by which plasma is separated into individual protein fractions that are further purified for medicinal use (variously referred to as plasma derivatives, fractionated plasma products or plasma-derived medicinal products). The term fractionation is usually used to describe a sequence of processes, including plasma protein separation steps (typically precipitation or chromatography), purification steps (typically ion exchange or affinity chromatography), and one or more steps for the inactivation or removal of bloodborne infectious agents (most specifically viruses and, possibly, prions).
Fractionator	A company or an organization performing plasma fractionation to manufacture plasma-derived medicinal products.
Fresh frozen plasma	Plasma that is frozen within a specific time period, typically within 8 to 24 hours after collection, and stored in the frozen state until thawed for transfusion.

Global Benchmarking Tool	The Global Benchmarking Tool is the primary means by which the World Health Organization objectively evaluates regulatory systems, as mandated by World Health Assembly resolution WHA67.20 on regulatory system strengthening for medical products.
Good manufacturing practices	The part of quality assurance that ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required by the marketing authorization or product specification. Good manufacturing practices are concerned with both production and quality control.
Hyperimmune plasma	Plasma with a high titre of a specific antibody, administered to create passive immunity to the corresponding antigen.
Immunoglobulin	Also known as immune globulin or gamma globulin, immunoglobulin is used in the treatment of primary immunodeficiency, as well as a number of other conditions. Polyvalent immunoglobulin is prepared from a large number of donors. Hyperimmune or specific immunoglobulins are prepared from plasma containing high levels of antibody to a certain infectious agent or antigen (such as rabies, tetanus, hepatitis B or Rh factor).
Low- and middle-income countries (LMIC)	Resource-constrained countries with a gross national income per capita that is below a value determined each year by the World Bank.
National regulatory authority	WHO terminology to refer to national medicines regulatory authorities. National regulatory authorities should promulgate and enforce medicines regulations.
Nucleic acid amplification testing (NAT)	A testing method to detect the presence of a targeted nucleic acid area, for example of a defined viral or microbial genome, that uses amplification techniques such as polymerase chain reaction.
Plasma for fractionation	Recovered (or apheresis) plasma used for the production of PDMPs.
Plasma for transfusion	Plasma (from whole blood or apheresis) used for direct infusion into patients without a prior fractionation step. It can be subjected to treatment to inactivate pathogens.
Plasma-derived medicinal product (PDMP)	PDMPs include a range of medicinal products obtained by the fractionation process of human plasma. They are also termed plasma derivatives, plasma products, or fractionated plasma products.
Plasma master file	A document that provides all relevant detailed information on the characteristics of the entire human plasma used by a fractionator as starting material or raw material for the manufacture of subintermediate or intermediate plasma fractions, constituents of the excipient and active substances that are part of a medicinal product.
Plasmapheresis	A procedure for the collection of plasma (see "apheresis" above).

Pledge 25 Club	The Club 25 concept (also known as the Pledge 25 Club or Pledge 25), first launched in Zimbabwe in 1989, has proven to be a remarkably effective and relatively inexpensive way of targeting youth donors. In the original programme, students pledged to donate blood 25 times by the time they reached the age of 25; the commitment now varies depending on the country. For example, Club 25 members in Malawi (aged 16–25 years) pledge to donate blood at least 25 times in their lifetime; in South Africa, the pledge is to donate 20 times by the age of 25.
Quality assurance	A part of quality management focused on providing confidence that quality requirements will be met.
Quality management	The coordinated activities that direct and control an organization with regard to quality.
Recovered plasma	Plasma recovered from a whole blood donation and used for fractionation into PDMPs.
Repeat tested donor	A person whose blood or plasma has been tested previously for infectious disease markers in the blood system.
Source plasma	Plasma obtained by plasmapheresis intended for further fractionation into PDMPs.
Surplus plasma	Plasma prepared for clinical use that is not used for transfusion and that could be used to prepare PDMPs if of appropriate quality for fractionation.
Standard operating procedures	Domestic written instructions for the performance of a specific procedure in a standardized manner.
Technology transfer	Activities that involve a capacity-building component at the recipient site intended to enable the recipient to produce plasma for fractionation or plasma products. This is associated with training of the recipient in the use of the technology, procurement of technical support to the recipient, verification that the know-how is properly implemented, and approval of the plasma for fractionation or plasma products by the relevant national regulatory authority.
Toll plasma fractionation	An arrangement by which domestic plasma is processed by a fractionator licensed in a foreign country and PDMPs from this plasma are provided in return, according to predetermined contractual terms, for use within the country.
Transfusion-transmissible infection	An infection that is potentially capable of being transmitted by blood transfusion.

EXECUTIVE SUMMARY

This guidance has been prepared within the scope of the World Health Organization (WHO) Action Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood Products 2020–2023. It intends to provide a high-level overview of the actions recommended by WHO to increase access to plasma-derived medicinal products (PDMPs) in low- and middle-income countries (LMIC) through increased production of plasma suitable for further manufacturing.

Recognizing the importance of the provision of safe blood, blood components and plasma derivatives, the Fifty-eighth World Health Assembly, by resolution WHA58.13, supported "the full implementation of well-organized, nationally coordinated and sustainable blood programmes with appropriate regulatory systems", and stressed the role of voluntary non-remunerated blood donors from low-risk populations. The provision of blood, blood components and plasma derivatives from voluntary non-remunerated donors should be the aim of all countries.[1]

Supporting access to quality and safe PDMPs at global level further aligns with the objectives of World Health Assembly resolution WHA63.12 (2010) on availability, safety and quality of blood products, addressing a major unmet public health need that has steadily increased with expanded use of these medically important products.

Blood products include whole blood and blood components for direct transfusion in patients, namely cellular components (red blood cells and platelets), plasma and cryoprecipitate. However, blood products also include PDMPs, which are purified plasma protein concentrates that undergo pathogen reduction procedures, including dedicated virus inactivation and removal. PDMPs consist of a group of over thirty unique protein products (including albumin, polyvalent and specific immunoglobulins, and blood coagulation factors) that are typically manufactured in advanced economies from pools of thousands of plasma units by an industrial process called plasma fractionation. PDMPs are needed to selectively and safely treat specific conditions affecting many patients, including congenital or acquired deficiencies in coagulation factors, haemorrhagic and septic shock, immunological disorders, and viral or bacterial infections.

Several PDMPs are included in the WHO Model List of Essential Medicines, highlighting them as medications considered to be the most effective and safe to address the major needs in a health system. However, PDMPs are in shortage at global level, most severely affecting patients in LMIC. Inadequacy of PDMPs in those countries also results from an insufficient domestic supply of plasma of a quality suitable for non-domestic fractionation and from a lack of technical and financial capacity to implement a domestic plasma fractionation programme.

Therefore, governments in LMIC are strongly encouraged to correct deficiencies in the organization, financial support and regulatory oversight of their blood systems to permit production of quality-assured plasma and to consider the possibilities for foreign or domestic plasma fractionation to improve the availability of PDMPs. These actions concurrently would improve the availability, quality and safety of blood products for transfusion.

The need for red blood cells drives collection of whole blood, from which plasma can be separated as an independent product for transfusion. Plasma for transfusion can be repurposed for fractionation as "recovered plasma" when it is

[1] It is recognized that the global supply of PDMPs presently relies predominantly on plasma collected from compensated plasma donors in several high-income countries and may not be appropriate to implement in other settings. The countries that permit compensated plasma donation have implemented additional donor screening and donation testing strategies along with regulatory oversight to mitigate any potential increase in infectious risks that may be associated with compensation of donors and to monitor and safeguard the health of dedicated plasma donors. In addition, compensated plasma donation systems are managed in a way not to affect the well established system for collection of whole blood from voluntary non-remunerated donors and the infrastructure to supply blood components for transfusion to domestic patients.

not required for clinical use. Sadly, in LMIC, millions of litres of recovered plasma are discarded as waste because the technology, infrastructure and regulatory oversight to ensure its quality for fractionation are lacking. Plasma quality depends on compliance with good manufacturing practices (GMP) at all stages of its production, including selection of eligible donors, collection of whole blood or apheresis plasma, laboratory testing of donations for markers of transfusion-transmissible infections, use of validated reagents, devices and preparation procedures, proper labelling, and appropriate conditions and facilities for freezing, storage and transport of the plasma. Deficiencies in GMP compliance resulting in failure to utilize recovered plasma to make PDMPs constitute an unethical waste of valuable human resources. Conversely, use of plasma generated in excess of clinical need could be optimized by fractionation into purified and virally safe PDMPs, either by foreign manufacturers (through contract or toll fractionation) or by the establishment of a domestic fractionation facility, thereby contributing to superior treatment of patients. As clinical needs for PDMPs increase, additional plasma volume for fractionation could also be produced by automated plasma separation (apheresis), which can enable more frequent and larger plasma volume collections than is possible from donation of whole blood. However, this approach to plasma collection can be considered only if it does not divert donors from giving the whole blood that is required to cover essential patient needs for red blood cells.

This guidance is aligned with World Health Assembly resolutions and WHO documents. It is designed to provide a roadmap for policy-makers, national regulatory authorities, blood collection organizations, blood donors and their associations, clinicians and patients to prioritize actions to reduce wastage of plasma that could be fractionated to make the PDMPs that are urgently needed in LMIC. The document highlights the steps that can be taken to increase the production of quality and safe plasma from voluntary non-remunerated donors in LMIC and to enable its use in fractionation. The document explains the requirements that must be met and discusses the technical and economic challenges that must be overcome in meeting plasma quality standards. Models are provided for obtaining PDMPs through domestic or foreign fractionation of domestic plasma in an economically sound manner. LMIC are encouraged to examine prospectively which models can best fit their specific situation, considering the increasing volume of domestic plasma expected to be available over time and the domestic trends in clinical demand.

Investing in a well organized, stably financed and appropriately regulated national blood system capable of generating quality plasma suitable for fractionation is a crucial incremental step towards eventual sufficiency of PDMPs in LMIC. Implementing such a programme would enhance public health at all times and additionally promote resilience of the blood system in situations of crisis, including pandemics.

CHAPTER 1

BACKGROUND

1.1 Scope and objectives of the guidance

Plasma-derived medicinal products (PDMPs) are critical in the prevention and treatment of major morbidities associated with a wide range of inherited and acquired medical conditions and diseases (see Table 1). Human plasma, used as a source material to produce PDMPs, is recognized as a public good and of national interest. Ensuring a safe, secure, sufficient and ethically obtained supply of PDMPs is an important public health responsibility of every national government. Nevertheless, supplies of essential PDMPs are inadequate in many low- and middle-income countries. Increasing the collection within low- and middle-income countries (LMIC) of plasma suitable for fractionation and developing a better understanding of the plasma manufacturing processes, including related regulations, can contribute to national and regional sufficiency of PDMPs. This guidance identifies major barriers to utilization of domestic plasma for fractionation and suggests considerations and actions at national, regional and international levels that would assist countries in developing policies and strategies to increase the supply of PDMPs through fractionation of plasma collected in the national blood system. Therefore, the primary audience of this document is policy-makers, national regulatory authorities, blood collection organizations, blood donors and their associations, clinicians and patients in needs of plasma protein therapies in LMIC, and plasma collectors and fractionators.

This guidance provides a high-level perspective on steps that can be taken in LMIC to increase economical and sustainable access to PDMPs through increased generation and fractionation of recovered plasma that is separated from whole blood donations from voluntary non-remunerated blood donors. Additionally, the scope includes considerations for the implementation of programmes of plasmapheresis to generate source plasma intended for fractionation. Such programmes should only be undertaken in the context of national policies and effective regulations in support of domestic blood establishments, including through the recruitment of competent management and qualified personnel, implementation of a quality assurance system, technical infrastructure to allow separation of whole blood into its cellular components, plasma, cryoprecipitate, and cryoprecipitate-poor plasma, and training of physicians on appropriate clinical use of blood products, including preferred use of blood components instead of whole blood in most settings (for example, red blood cells to correct anaemia, cryoprecipitate to replace fibrinogen).

The guidance, as part of the World Health Organization (WHO) Action Framework to Advance Universal Access to Safe, Effective and Quality-Assured Blood Products 2020–2023 *(1)*, provides general guidance on how to increase the production of quality PDMPs in LMIC using domestic plasma resources. It (a) describes challenges, identifies major quality and technological gaps, and suggests stepwise actions at national and international levels to assist countries in developing policies and domestically appropriate strategies to increase supplies of PDMPs through an economically sound fractionation programme of plasma collected in the national blood system; (b) provides guidance on the regulatory oversight of a fractionation programme of domestically collected plasma; and (c) strengthens use of voluntary unpaid and repeated blood donations. Local transfusion medicine experts and professional societies should be directly engaged with the national situational assessment of the blood transfusion system, and closely involved in the decision-making process for capacity-building.

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

Human blood is the source of multiple therapeutic products, including blood components for transfusion (whole blood, red blood cells, platelets, plasma, cryoprecipitate and cryoprecipitate-poor plasma). Additionally, plasma is the source material for further manufacture of PDMPs that are produced at an industrial scale by fractionation of pools of plasma obtained from between several hundred to more than a thousand donors. The fractionation process allows separation of plasma into various protein fractions, each with a unique clinical value. Fractionating plasma into purified and virus-inactivated therapeutic protein products allows optimization of this highly valuable source material. Availability of certain PDMPs can more safely replace clinical use of fresh frozen plasma, cryoprecipitate and cryoprecipitate-poor plasma (to treat a variety of bleeding or immunological disorders) that can transmit infections when not subjected to proper pathogen removal and inactivation treatments, as is the case in the vast majority of LMIC *(2)*. To optimize the use of donated blood, nearly all blood collected in high-income countries is systematically separated into its cellular components and its plasma, which is stored frozen. This plasma is used either for direct transfusion or for fractionation. Plasma obtained from whole blood donations and used for fractionation is often called recovered plasma. Preferably, any surplus plasma that is not needed to cover the therapeutic needs in hospitals for direct transfusion is used for fractionation, provided the quality requirements of the fractionator are met. As the needs for PDMPs increase, the volume of recovered plasma generated at national or global level becomes insufficient, necessitating the collection of an additional volume of plasma by apheresis. Plasma for fractionation can also be generated by apheresis as a surplus by-product during preparation of a cellular product, such as platelet components (it is sometimes called concurrent plasma). Hyperimmune plasma with a high titre of specific antibodies – for instance, tetanus, rabies, Rho(D) or hepatitis B antibodies – is typically collected as source plasma *(3)*.

While in high-income countries essentially all the recovered plasma in excess of direct hospital needs is fractionated, this is not yet the case in LMIC, for reasons that are explained below. Progress towards improving availability of PDMPs in LMIC based on fractionation of domestic plasma must begin with correction of underlying deficiencies of the national blood systems.

1.3 PDMP therapies

Currently, about 30 distinct protein products can be isolated from human plasma *(3)*. Polyvalent immunoglobulins are needed to treat various immunological disorders, including primary and secondary immunodeficiencies, while high dose immunoglobulins have an immune modulating effect in neurological, haematological and dermatological (auto) immune diseases. Hyperimmune immunoglobulins with a high titre of a specific antibody have specific indications for the prevention or treatment of several infections, such as tetanus, measles and rabies, or for the prevention of haemolytic diseases of newborns *(4)*. Coagulation factor concentrates are infused to patients suffering from congenital or acquired deficiencies with products that contain single or multiple coagulation factors. Albumin is a physiological plasma expander that is administered in acute conditions to restore circulating blood volume and is also indicated for protein replacement in a number of liver diseases or used as replacement fluid in therapeutic plasma exchange. Several of these products have been identified as essential medicines by WHO *(4, 5)*. Table 1 lists the main plasma protein therapeutics and their respective clinical indications *(3)*.

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 1. Main PDMPs and their clinical indications continued

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)*.

1.4 Unmet needs for PDMPs

In 1975, the Twenty-eighth World Health Assembly, by its resolution WHA28.72, first established globally the principle of nationally supported, managed and coordinated blood systems as an essential part of the health system *(6)*. Subsequently, in 2005, the Fifty-eighth World Health Assembly, by its resolution WHA 58.13, recommended "the full implementation of well-organized, nationally coordinated and sustainable blood programmes with appropriate regulatory systems" and stressed the role of "voluntary, non-remunerated blood donors from low-risk populations" *(7)*. In 2010 the Sixty-third World Health Assembly, in resolution WHA63.12 on availability, safety and quality of blood products, expressed concerns about the unequal access globally to blood products, particularly PDMPs *(8)*. Patient organization surveys and market analyses indicate that the majority of patients in LMIC with clotting disorders, immunodeficiencies, autoimmune disorders, and other diseases treatable by PDMPs do not currently have adequate access to treatment *(9, 10)*. The WHO Model List of Essential Medicines identifies medications considered to be the most effective and safe to meet the major population needs in a health system. The listing of PDMPs on the WHO Model List of Essential Medicines is to encourage governments to recognize patients' needs, assess clinical demand, ensure that blood products are optimally used by clinicians, and ensure an adequate supply of those medicines at national level. Sufficient access to PDMPs can be achieved by importing commercial products or by producing plasma derivatives from domestically collected plasma, either through domestic fractionation or through specific supply agreements (such as contract fractionation) with a plasma fractionator *(9)*.

High-income countries are generally capable of ensuring an adequate supply of PDMPs, although even in these countries the treatment of some pathologies or clinical indications can suffer from product shortages or budget restrictions. By contrast, LMIC face critical chronic supply difficulties in PDMPs, even for those listed as essential medicines (immunoglobulins and coagulation factors). Due to insufficiency of products, most patients in LMIC with coagulation disorders, immunodeficiencies and autoimmune disorders do not receive adequate treatment. Besides, as a result of suboptimal manufacturing and lack of pathogen inactivation or removal steps, patients receive treatment with blood components (such as plasma, cryoprecipitate or cryoprecipitate-poor plasma) that may be deficient therapeutically and may expose them to bloodborne infections *(11, 12)*. A starting point in progress towards sufficiency

in PDMPs is national determination of the number of patients with obligate needs (for example, haemophilia A and B, primary immune deficiency) and acquired needs (for example, haemolytic disease of the newborn) for plasma protein products.

1.5 Wastage of recovered plasma

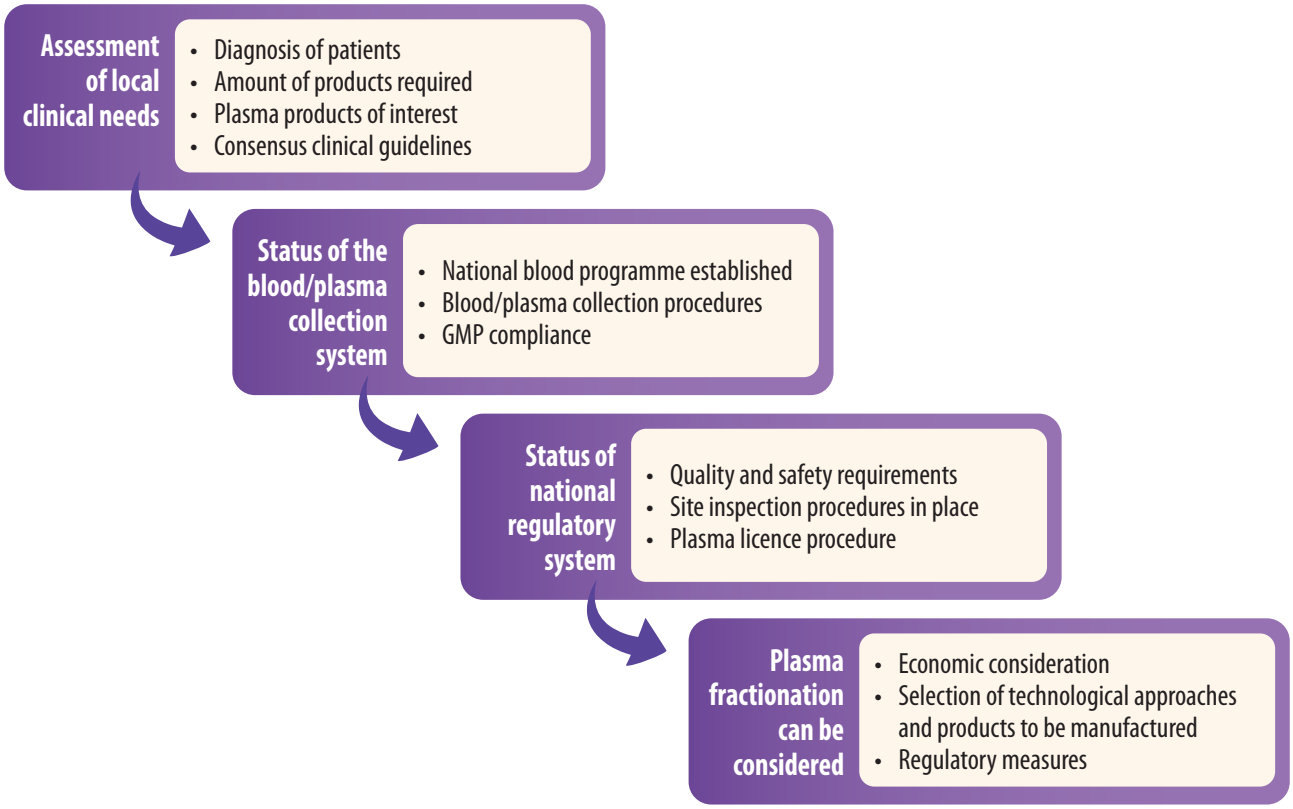
There is an urgent need in LMIC for a nationally coordinated approach to guarantee some measure of supply of PDMPs to facilitate patient access to these safe, effective and often lifesaving medicines. One obvious approach towards this objective is to facilitate the fractionation of recovered plasma generated in LMIC. If additional recovered plasma could be fractionated, these volumes of plasma would generate additional PDMPs crucial to meeting domestic needs *(9)*.

However, in most LMIC, millions of litres of plasma that could be recovered from whole blood are currently either not separated or are destroyed *(9)*. This practice is both medically wasteful and ethically questionable. The reasons for the non-production or destruction of recovered plasma are multiple. They include lack of a coordinated national blood transfusion system, with scattered small blood collection centres, absence or failures in good manufacturing practices (GMP) and good laboratory practices in blood collection, deficient testing or storage *(13)*, lack of production testing, insufficient infrastructure to permit plasma transportation and storage (for example, inadequate road access and unstable electricity), or lack of regulatory oversight, precluding the use of plasma as a source material for the production of PDMPs *(3)*. As the need for red blood cells separated from whole blood is steadily increasing in LMIC *(14)*, an increasing volume of plasma potentially usable for fractionation will be generated that will be discarded if no action is taken to improve national blood systems. A legal framework should also be in place to enable LMIC where this is currently not allowed to send plasma abroad for processing in return for vital plasma products.

1.6 Urgent need for capacity-building in LMIC

Supply of safe and essential PDMPs is a major ongoing challenge in LMIC. The supply and optimal clinical use of those products can be improved through concerted action. The four components of capacity-building are institutional development, financial resource development, human resource development and effective national society programmes. Capacity-building and competent leadership are needed to strengthen quality and safety standards in the production of blood components in blood establishments and to optimize blood resources. The model of centralization of blood donation testing and processing can be implemented in countries with fragmented blood systems. Appropriate blood collection, processing, testing, labelling and storage technologies, implemented in compliance with GMP and managed through quality systems and regulatory controls, should be in place to enable the supply of plasma suitable for manufacture into PDMPs *(9)*. Training of clinicians on use of blood components instead of whole blood can contribute to the availability of surplus plasma for fractionation. National blood regulatory authorities need to be strengthened to ensure an acceptable level of informed regulatory oversight *(9, 15, 16)*. In addition, acquisition of knowledge of plasma processing and pathogen clearance technologies, including methods of virus removal and inactivation, is needed to facilitate a gradual transition towards establishment of nationally appropriate programmes of plasma fractionation (in country or through external arrangements) that can meet the objectives and capacities of LMIC. Figure 1 summarizes the progressive areas of capacity-building and the main decision-making steps that can lead to fractionation of plasma, as explained in further detail in the subsequent chapters.

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



1.7 Optimal use of PDMPs

In addition to generating sufficient supplies of plasma for manufacture into PDMPs, an economically viable programme for provision of PDMPs needs to ensure that the usage of these medicines is based on sound medical practice and evidence. In recent years, historical indications for several products have been shown to have a weak evidence base, warranting more restricted use. For example, some uses of albumin and immunoglobulins have been reconsidered as they are outside well established clinical indications. In particular, several applications of immunoglobulins in primary and some secondary immunodeficiencies and neurological, dermatological and haematological conditions are being debated because the usage is not supported by compelling evidence-based data. However, clinical guidelines provide useful recommendations on the supported indications of immunoglobulins. Updated guidelines for administration of coagulation factor concentrates need to be followed to decrease the risks of development of inhibitors. The principle of patient-centredness is crucial to ensure the optimal use of PDMPs.

1.8 Concerted action in utilizing surplus protein products

In the current era of plasma therapeutics, immunoglobulin is the driver for plasma procurement in most medical systems in high-income countries. This in turn can result in the production of surplus amounts of other therapeutic proteins such as albumin. In countries that predominantly use recombinant factors, plasma-derived factors VIII and IX will also be generated surplus to demand. Such surplus protein products should be made available to relieve the medical systems of countries that lag behind in the manufacture and supply of these therapies. This can be achieved through regional cooperation and can be included in the assistance provided by some countries to the health systems of others.

CHAPTER 2

ENSURING AN ADEQUATE SUPPLY OF PLASMA-DERIVED MEDICINAL PRODUCTS

Provision of plasma suitable for fractionation depends on an organized system of blood and plasma collection and plasma preparation that ensures uniform compliance at national level with quality and safety standards under GMP and regulatory controls *(3, 13)*. Establishing and implementing such a system requires a high level of national commitment, supported by government involvement in policy formulation, development of legal frameworks and regulatory measures, and mobilization of financing to ensure a well organized, compliant and stable blood system.

A robust and well regulated national blood service operating in compliance with GMP, with effective vigilance systems for monitoring the safety of blood donations and of administered blood products, is key to building and strengthening national capacities and regional cooperation.

2.1 Barriers to supply of suitable plasma for fractionation

The source material for manufacture of PDMPs can be recovered plasma, which is plasma separated from whole blood donations, or source plasma, which is plasma intended for fractionation obtained by plasmapheresis. Plasma is a precious and strategic resource both for transfusion and for the manufacture of PDMPs. In the absence of an organized system, plasma separated from whole blood that is not used for transfusion (surplus plasma) is destroyed instead of used for fractionation. Major barriers to the provision of plasma for fractionation include failure to meet internationally recognized quality and safety standards for recovered plasma and an insufficient supply of domestic quality-assured, recovered plasma necessary to meet the needs of a (contract) fractionator located abroad or domestically. Absence of adequately resourced regulatory oversight, precluding assurance that appropriate standards are met at all stages of plasma production (donor selection, whole blood or apheresis plasma collection, laboratory testing, blood component preparation, plasma freezing, labelling, storage and transport), is another main barrier.

There are two main reasons that plasma may not be acceptable to a fractionator, namely insufficient quality and inadequate volume. First, non-compliance with GMP requirements is a basic concern. PDMPs are registered and authorized for marketing by competent regulatory authorities based on their efficacy, safety and quality parameters. As a condition of marketing authorization, PDMPs need to satisfy GMP requirements to ensure their safety, quality

and manufacturing consistency. Within this framework, registration of PDMPs entails scientific documentation of the quality of the starting material, which is the donated human plasma. Documentation of plasma quality consistent with GMP requires scientific data on all aspects of plasma collection and processing, including suitable design and layout for safe and efficient function, donor eligibility and safety measures in blood and plasma collection, testing donations for transfusion-transmissible infectious diseases, use of validated reagents, devices and procedures, timely collection and standardized freezing, appropriate plasma storage and transport facilities and conditions, periodic quality control testing, and bidirectional traceability between donations and end-products *(3, 17)*. These GMP requirements are to be confirmed by regulatory inspections. Even in LMIC where routine production of frozen plasma from whole blood is feasible in blood establishments, deficiencies in implementation of GMP remain major barriers to the availability of plasma acceptable to a fractionator.

A second barrier to the suitability of plasma for fractionation from LMIC concerns the inability to generate an adequate volume of plasma. In a small size system, even if the plasma meets quality standards, fractionators may not be able to manage small lots of recovered plasma in their manufacturing schedule and may avoid or discontinue fractionation under contract. In some LMIC, inability to provide an adequate volume of plasma also results from organizational issues, such as a fragmented blood collection organization or the absence of a cold storage warehouse for storage of plasma. In a fragmented system, individual blood collection centres are typically unable to offer volumes of plasma sufficient for fractionation and for justifying the substantial efforts of GMP auditing by the fractionator and inspection by national and (possibly also) foreign regulators. Furthermore, in settings where quality management of the collection methods is not harmonized at a national level or among major blood establishments, small volumes of available plasma cannot be aggregated for use in fractionation. Another barrier to generation of adequate volumes of plasma for fractionation in LMIC is the high "up-front" cost of plasmapheresis, mainly related to the cost of plasmapheresis kits. The high cost of the plasmapheresis kits necessitates an initial investment that can only be recovered later when the corresponding products are received.

2.2 Requirement for a nationally organized, regulated and stably funded system

In order to increase the supplies of PDMPs through fractionation of domestic plasma, plasma needs to be generated within nationally or regionally coordinated systems that ensure compliance with international standards and possess the necessary infrastructure to collect, freeze, store and ship sufficient volumes of plasma to a fractionator. The preconditions for such systems include nationally organized and stably financed blood collection establishments, implementation of GMP at all stages of plasma generation, and a legally empowered regulatory authority capable of establishing and enforcing compliance with blood standards and GMP. Where these conditions are lacking, support from government is essential to ensure that an action plan to establish the national system is in place with clear milestones and dedicated key people working in coordination.

A first step in development of an effective national blood system is the creation of a national blood policy by the competent ministry, usually the ministry of health, consistent with guidelines promulgated by WHO or other internationally recognized organizations. Under such a policy, a model is defined and implemented for organization of the blood system and its integration within the larger public health system. The model will determine the number and location of establishments for blood collection, testing and processing into components, including plasma, and the logistics of product storage and distribution. A national programme for production of plasma for fractionation can promote or support centralization of critical functions (such as donation testing and component processing) in a limited number of blood establishments, thereby facilitating compliance with GMP and potentially increasing availability

of plasma suitable for fractionation. Roles and responsibilities are defined for governmental and nongovernmental components of the system, including the localized and centralized operators that collect and process blood donations and the related laboratory testing facilities. A mechanism is established for programme coordination and monitoring, and a legal framework is put in place for blood regulation. A body is set up under the ministry of health for policy- and decision-making related to blood safety and availability, with a provision for obtaining advisory inputs from stakeholders, including end users of PDMPS (that is, clinicians and patients). A national blood policy that includes directives on plasma donations is needed to set guidelines that ensure uniformity in the quality of plasma collected at multiple blood establishments.

In parallel with the establishment of the blood transfusion service and plasma collection service as a national blood system, an effective blood regulatory system is needed to put in place and enforce blood standards. Regulation provides assurance that blood components for transfusion consistently meet quality and safety standards. Likewise, regulation can ensure that the fractionator recovering plasma and source plasma consistently meets the necessary quality and safety requirements for manufacturing PDMPs. Effective blood regulation requires the legal establishment and implementation of a national regulatory authority as a competent authority for oversight of blood establishments and blood products. Furthermore, the national competent authority must be provided with the resources appropriate to conduct regular inspections of domestic blood collection centres and the eventual fractionator manufacturing PDMPs used in the country.

Developing a national blood programme requires a serious, sustainable commitment of resources, as defined in capital and operating budgets. Senior management has the responsibility of securing sufficient resources for the work to be undertaken. This entails developing a short-term and mid-term strategy, estimating budget requirements, and understanding the requirements of funding agencies and developing proposals accordingly. In most settings, a mixture of cost recovery plus external subsidy by governmental and other agencies will be needed to sustain the blood service. Development, execution and transparent reporting of costing are necessary to demonstrate to funders that spending is appropriately managed and will help strengthen the case for funding support.

2.3 Establishment and enforcement of standards

In manufacturing, quality means a state of being free from defects, deficiencies and significant variations from prespecified criteria. Quality requires strict and consistent commitment to established criteria prespecified in standards and regulations that achieve uniformity of a product within countries and regions in order to satisfy specific customer or user expectations. The need for strict adherence to standards reflects the biological nature of plasma and inherent risks to the quality and safety of PDMPs, which can be amplified by the pooling of thousands of units of plasma to make each product lot *(18)*. Effective regulation ensures that standards are defined and met at all stages of manufacture, from donor selection and qualification of the starting materials through manufacturing to distribution of the end-products. Full traceability from donations to end-products to points of care – and vice versa – enables action to be taken when (a) quality and safety issues are determined relevant to the donors and their previous donations; (b) patients experience adverse events attributable to the products; and (c) deviations in manufacture, storage and labelling necessitate product recalls.

WHO and various regulatory bodies *(19–22)* have set standards for plasma for fractionation to safeguard the quality, safety and consistency of fractionated PDMPs, to limit the wastage of recovered plasma, and to improve the supply of PDMPs. Guidelines published by WHO further contribute to the improvement of national blood collection systems and regulatory systems *(13)*. In compliance with GMP, key safety nets for the production of plasma for fractionation

include epidemiological surveillance of known and emerging pathogens that could affect blood product safety; donor screening with an approved questionnaire based on established criteria for donor eligibility; donation testing with licensed and approved in vitro diagnostic test kits and testing platforms according to validated test procedures and criteria for acceptance or rejection of donations based on the test results (such as repeated reactivity); and controlled plasma preparation (separation and freezing), storage and transportation according to validated and approved procedures. Periodic inspection of the establishments that supply plasma, both by national regulators and by foreign manufacturers that may receive the plasma, is essential to ensuring plasma quality and safety.

2.4 Regulatory authorization of blood and plasma collection, testing and processing

The regulatory oversight of blood and plasma collection and processing enables the fractionator to trust in the procedures established for guaranteeing plasma quality in accordance with internationally agreed standards. Provided that there is a fully competent authority, regulatory oversight provides assurance of compliance with standards. Independent assessment of blood-related regulatory functions and their implementation in the country can enhance trust in regulatory competence. WHO has included blood product regulation in its Global Benchmarking Tool for evaluation of national regulatory systems for blood and blood products *(23)*. The evaluation assesses the competencies and maturity of blood regulation at the national regulatory authority and identifies deficiencies as a basis for continuous improvement. In cases where blood regulation at the national regulatory authority is assessed as fully functioning (maturity level 3 or 4), other national regulatory authorities in the region may deem the assessment outcome as a sound basis for reliance on the decisions of that national regulatory authority. For example, a less mature national regulatory authority might accept the determination of a fully functioning authority in the same region that a specific donor screening test kit for HIV can be authorized for marketing, enabling acceptance of plasma by a fractionator. By combining plasma from countries whose national regulatory authorities have high maturity levels for blood regulation (or reach effective oversight through use of reliance), the combined plasma may be offered to the fractionator, with potentially more interest at the fractionator due to the combined higher volumes to be offered. Furthermore, based on maturity levels of the relevant blood regulators, national regulatory authorities in the country of fractionation may elect to rely on the oversight of blood and plasma in the sourcing countries and limit their own regulatory oversight of the plasma to a minimum.

Blood and plasma establishments that collect, test and process blood and plasma donations are authorized by national control agencies and are regularly inspected for evidence of compliance with requirements and standards, including applicable GMP *(4, 20)*. Regulatory licensing of blood and plasma establishments (or another formal regulatory mechanism of authorization) is fundamental to marketing authorization of PDMPs, since blood collection, testing and processing govern the quality and safety of the starting material for fractionation. Regulatory oversight aims to put in place an overall strategy and general logistics to ensure plasma quality, including through provision of information on plasma origin, quality and safety, and interaction between the manufacturer and the plasma supplier regarding contracts and notification systems *(24)*. Technical information on plasma origin includes identification of the supplying blood establishments and their audit record of GMP compliance, including recent inspection status, donor epidemiology, residual risk assessment, characteristics of donation, testing laboratories, donor selection and exclusion criteria, traceability, and look-back procedures. With regard to plasma quality and safety, information is provided on compliance with standards (such as those set by the European Pharmacopeia), plasma testing strategy (serology or nucleic acid amplification testing (NAT)), testing format (testing of individual donations, mini-pools and final plasma

pools), technical characteristics of blood bags, conditions of freezing, storage and transport, inventory hold and characteristics of the plasma pool *(20)*.

2.5 GMP audits by the fractionator

In addition to regular inspections by the national competent authority, the fractionator may perform GMP audits, which will benefit the blood establishment. Implementation of GMP in blood establishments increases the safety of all blood products and builds expertise within the establishment *(13)*. The written agreements and audits are an opportunity to develop a culture of quality, because they define the roles and responsibilities of the blood establishment and the fractionator. The manufacturers of PDMPs qualify the blood and plasma collection centres as suppliers of plasma. Audits are part of this qualification process and are performed according to written procedures. Audits of donation centres – which take place at a frequency of one to five years based on an assessed risk – are a regulatory requirement for fractionators and can help the fractionator to anticipate the impacts of regulatory changes. Acceptance criteria or critical parameters for determining the quality of plasma for fractionation, as applied by the fractionator, are as follows: selection of blood donors; collection time of the whole blood; centrifugation of whole blood; plasma processing; minimum volume of plasma (recommended 200 millilitres or a lesser volume as negotiated with the fractionator); basic requirements for ABO (blood group system) and transfusion-transmissible infectious disease testing of donations; temperature, kinetics and time of plasma freezing; physical–chemical composition of plasma including total protein and factor VIII level, conditions of storage and transport of plasma; traceability of plasma units and blood monitoring system (look-back management); and haemovigilance and pharmacovigilance *(3, 13)*. A robust change management system should be in place, because changes in the control process may have an impact on plasma quality and the critical operations of the PDMP manufacturer, and may necessitate that action be taken by the regulator.

2.6 Haemovigilance and pharmacovigilance

Haemovigilance is a set of surveillance procedures covering the entire transfusion chain from the donation and processing of blood and its components to their provision and transfusion to patients, and follow-up of the patients' well-being. Providers of recovered and source plasma for fractionation should participate actively in a haemovigilance programme. Haemovigilance includes the monitoring, reporting, investigation and analysis of adverse events and adverse reactions related to the donation, processing and transfusion of blood, and actions taken to prevent the occurrence or recurrence of any adverse reactions. Haemovigilance is properly regarded as an essential element of the quality system of all institutions that are involved in the collection, testing, processing, storage, distribution and clinical use of blood products *(25, 26)*. An effective haemovigilance system contributes to identifying and mitigating risks from blood donation and transfusion and ensuring the quality and safety of the products. Feedback of transfusion-related safety information to blood and plasma establishments contributes to monitoring the quality and safety of plasma that is provided for fractionation. Safety information on clinical use of PDMPs may also raise awareness of issues relevant to the plasma that was used in manufacture of the products. National commitment and oversight in this area consist of incorporation of haemovigilance within the national blood policy and plan; organization of a haemovigilance system with defined roles for the blood and plasma establishments, hospitals and care providers; and provision of mechanisms for reporting of adverse events and adverse reactions to a commission or governmental authority legally authorized and empowered to gather, analyse and respond in a timely manner to safety information. Hospital transfusion committees play a particularly critical role in a well functioning haemovigilance system. Nationally standardized processes, including terminology, definitions, report forms and reporting procedures, contribute to an effective and efficient system.

Similarly, as is the case for any medicinal product, a set of surveillance procedures, known as pharmacovigilance, should be established at organizational and national levels *(1)*. It should cover the entire chain from blood or plasma donation to the follow-up of patients after they receive PDMPs *(23)*, and should enable informed decisions to be taken to protect the health of the donors of plasma and recipients of PDMPs *(1)*. Pharmacovigilance is vital for PDMPs, which are complex molecules obtained using complex manufacturing processes for purification and pathogen safety that directly determine their safety, quality and efficacy profile *(27)*. A traceability system should be in place from the blood establishment to finished products and vice versa to protect the health of blood and plasma donors and PDMP recipients *(3)*.

CHAPTER 3

STRATEGIES TO OBTAIN PLASMA FOR FRACTIONATION

This chapter covers the following topics:

- surplus plasma separated from whole blood (recovered plasma) or collected by plasmapheresis;
- plasma intended or repurposed for fractionation collected by apheresis concurrently with a cellular product (concurrent plasma);
- plasma solely intended for fractionation collected by plasmapheresis (source plasma).

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. That recovered plasma is a critical starting material for the manufacture of PDMPs is not fully appreciated in many countries. Awareness of the value of plasma for manufacture of PDMPs and a commitment to avoid wastage of plasma that could be fractionated should be established by the competent health authority as part of the national blood policy. Additionally, supplying plasma to a fractionator can provide an economic return on the cost of investment in quality. Income from supplying plasma can enable blood establishments to achieve their mission of providing an adequate supply of safe blood products for transfusion through financing of critical operations, enhancing blood centre sustainability, and strengthening activities to promote community-based and repeated voluntary unpaid blood donation *(28, 29)*.

Changes in clinical practice in high-income countries due to patient blood management practices have reduced the need for red blood cell transfusions, with a reduction of the collection of whole blood units. The volume of recovered plasma suitable for fractionation stays relatively constant following a reduction of the clinical use of plasma for transfusion. The need for PDMPs worldwide continues to increase *(30)*. The current driver of the demand for plasma for fractionation is the clinical use of immunoglobulins. This use has increased continuously year after year, and it is anticipated that this growth will continue *(31)*. Therefore, it is important to optimize the quality and availability of recovered plasma *(28, 29)*. To obtain sufficient plasma for fractionation, LMIC additionally could develop, in a stepwise manner, plasma collection by plasmapheresis (or collection of other components by apheresis with production of plasma for fractionation as a secondary product). This programme could be started when the quality and safety of

whole blood donations is fully standardized in a system that meets internationally accepted norms, and when the clinical need for one or more PDMPs justifies expanded production of plasma for fractionation.

3.1 Recovered and concurrent plasma

Recovered plasma becomes available after the preparation of red blood cells from whole blood when the plasma that was generated is not needed for transfusion. Uncommonly, plasma usable for fractionation may also become available when plasma for transfusion that was generated by plasmapheresis is not needed clinically. Additionally, concurrent plasma arises as a by-product of the collection by apheresis of cellular components, especially platelets. The driver for recovered plasma is the demand for whole blood and components to supply the national transfusion need in hospitals for the treatment of anaemia in many different clinical settings. The steadily increasing collection of whole blood in LMIC with separation of components to cover the clinical need for red blood cell concentrates, has generated an increasing volume of recovered plasma that is currently wasted *(9, 31)*. Additionally, in many countries, failure to separate red blood cells from whole blood as a routine procedure constitutes a lost opportunity to generate volumes of recovered plasma that might be utilized for fractionation.

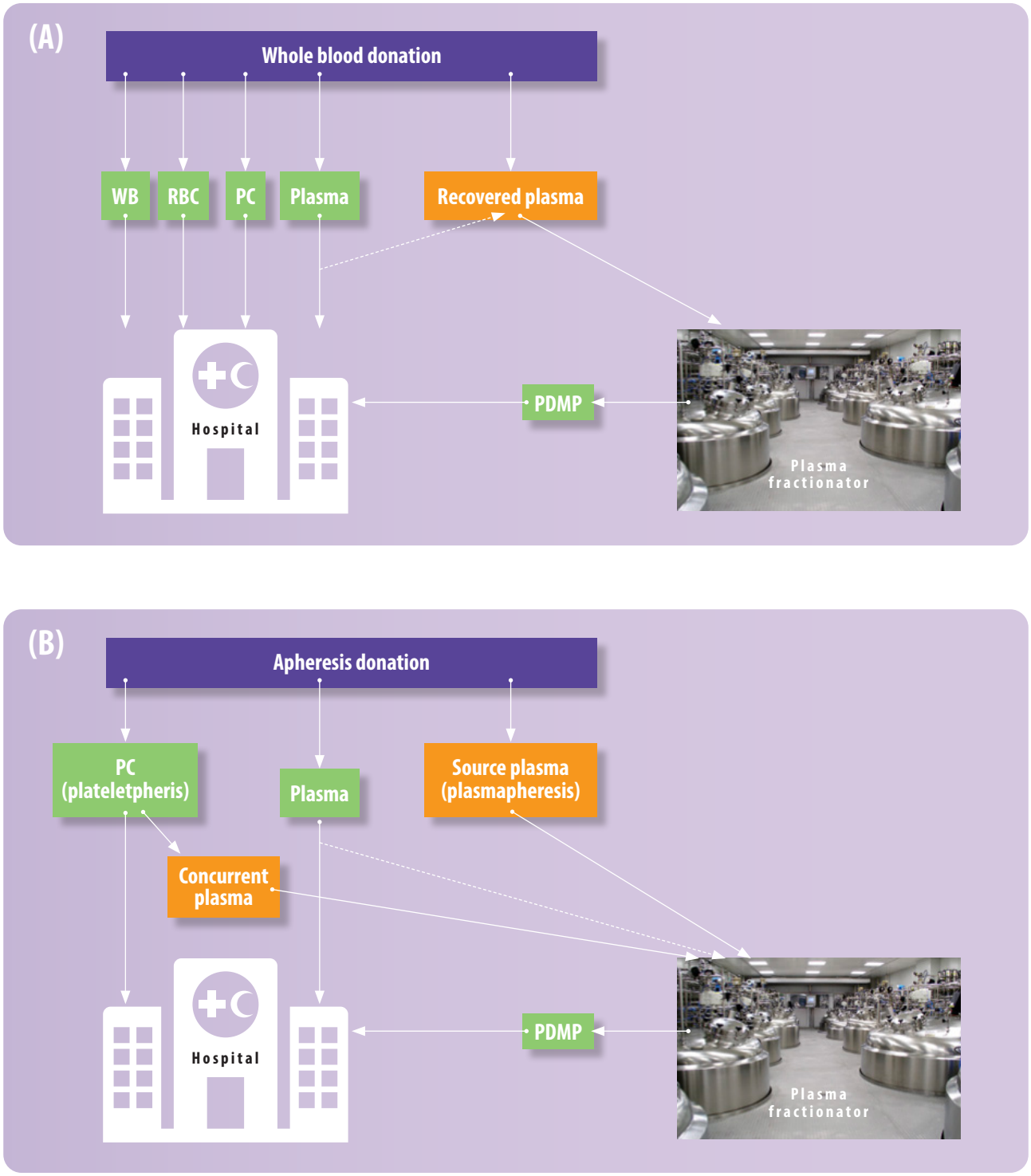
As explained in section 2.1, recovered plasma might be collected in sufficient quantities, but often cannot be used for fractionation due to several limiting factors:

- failure to meet internationally recognized standards for donor eligibility, laboratory testing and GMP in product processing to ensure that the quality of recovered plasma is acceptable for fractionation;
- poor cold chain and supply chain logistics to ensure that appropriate standards are met;
- absence of regulatory oversight to ensure that appropriate standards of GMP are met.

The volume of available recovered plasma is an important factor. Most contract fractionators are not able to process small lots of recovered plasma from low- and middle-income countriesLMIC in their manufacturing schedule, even when the recovered plasma is of approved quality. This situation typically arises in a fragmented blood service where donations are collected in low numbers at each of many non-coordinated blood establishments, and centralization of processing of blood components is not in effect. It is also difficult to ensure the quality of recovered plasma in a fragmented blood service where the collection establishments do not operate under uniform procedures.

As a result of these factors, large volumes of recovered plasma are unused and discarded. This is not acceptable from an ethical point of view. Not only would the use of recovered plasma increase the availability of PDMPs, it also would decrease the dependence on imported products *(9, 31)*. Production of recovered plasma that meets internationally recognized standards for fractionation aligns with a more general objective to ensure the GMP status of the blood establishment and subsequently the quality and safety of blood and blood components for transfusion. Increasing the availability of recovered plasma for fractionation therefore requires a stepwise approach to ensure the quality and safety of whole blood through appropriate donor selection, laboratory testing and processing in accordance with GMP *(3, 13)*. Use of plasmapheresis to prepare plasma for direct transfusion is infrequent in LMIC but can be a source of plasma for fractionation if not used clinically. Apheresis procedures to prepare platelet concentrates can generate concurrent plasma for fractionation when meeting quality requirements. Figure 2 summarizes the various approaches used to obtain blood components and plasma.

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



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

3.2 Source plasma

Source plasma is defined as plasma collected by plasmapheresis that is intended solely as starting material for further use in manufacturing PDMPs. To ensure the quality of source plasma and the protection of donors, 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. The first step is to implement a national blood policy that includes a programme on generation of plasma for fractionation along with effective regulatory oversight to ensure that blood collection and preparation of quality plasma meet internationally recognized standards of GMP and the requirements of a licensed fractionator.

Once the basic conditions for the availability of recovered plasma suitable for fractionation are met, the focus will turn to the volume of recovered plasma that can be made available. It is important to have a clear understanding of the clinical need for PDMPs to assess whether the volume of recovered plasma will be sufficient to meet the need. If that is insufficient, an assessment should be made as to whether it is feasible to start plasma collection with plasmapheresis technology without affecting the collection of whole blood to meet patient needs for red blood cells. Given the limitations of financial resources, equipment, and human resources in LMIC, strategic planning is needed to develop the most appropriate approach to plasma collection for the manufacture of PDMPs in compliance with domestic regulations.

The main task of national blood transfusion organizations is to provide safe and sufficient blood and blood components for transfusion, as needed by its population, entirely by means of voluntary and non-remunerated donation. Achieving this goal requires strong communication between the blood service and the general public under a clearly articulated national policy. Encouraging people at the same time to participate in regular plasma donation by plasmapheresis to support manufacture of commercial products can be challenging to cultural and ethical beliefs for voluntary and non-remunerated whole blood donation. For this reason, strengthening activities to promote donation of plasma through recognition of donors and engagement in activities that highlight their altruism should be done with the support of the plasma fractionation programme to emphasize the major medical importance of PDMPs similar to blood for transfusion. Also, many whole blood donors can be redirected to plasmapheresis if they are not eligible for whole blood donation, are of a blood group that is less frequently needed as a source of red blood cells, or have specific high-titre antibodies of interest for the production of hyperimmune immunoglobulins.

In cases where commercial operators become involved in the collection of source plasma, and are subject to appropriate regulations, there should be good communication with the local blood collection organizations. The goal would be to find the best way for a constructive coexistence that allows both blood and plasma collection to meet the clinical need of the country. Addressing this issue is especially important in LMIC that have not achieved self-sufficiency in blood for transfusion and have not yet achieved 100% voluntary non-remunerated donation. Fruitful coexistence of both systems will avoid competition between donation of source plasma versus whole blood. The national authority with responsibility for blood and plasma collection must be tasked with providing guidance to both sectors when it comes to donor recruitment and donor retention, and the potential impact of allowing remunerated plasma donations should be carefully considered.

A benefit of plasmapheresis technology is that red blood cells are returned to the donor during the procedure, and therefore a plasma donor can donate more frequently than a whole blood donor. More frequent donations also enable a profile to be maintained for closer monitoring of donor health. The allowed donation frequency is dependent on national regulations, which differ from country to country. One of the benefits of source plasma collection is that it results in larger volumes per donation, which makes it more attractive for contract or toll fractionation arrangements when a country does not have a national fractionation plant. A condition is that the source plasma generally must

meet the quality criteria that are set forth by the host country fractionator. Chapter 7 in this guidance focuses on that aspect. Also, close monitoring, for example of plasma protein levels, is required to protect the health of frequent plasmapheresis donors.

The use of recovered plasma is limited for the reasons previously mentioned. However, even when its use is optimized, recovered plasma as a sole source of plasma for fractionation will not eventually provide enough plasma to manufacture sufficient PDMPs to meet a growing demand for PDMPs in LMIC. Needs assessment for PDMPs should be a strategic and ongoing activity. In LMIC, plasmapheresis should not be excluded as an option, if economically feasible (see Chapter 8), conducted under regulatory oversight to protect donor health, and managed in a comprehensive programme that assures sufficient collection of blood for transfusion as a primary responsibility. With these controls in place it can and should be considered as a means of providing the quantities of plasma needed to manufacture the required volumes of PDMPs to meet the clinical need.

Source plasma is collected for the sole purpose of providing high-quality plasma for fractionation to make unique PDMPs. Consequently, the purpose and clinical value of source plasma differs from that of plasma for transfusion. For example, in LMIC, a significant number of people have high antibody titres against minor blood groups and a variety of infectious agents. Plasma from such donors, known as hyperimmune plasma, can serve as the starting material for the manufacture of critically needed hyperimmune globulins such as anti-Rho(D) and hepatitis B immunoglobulin. During past or recent pandemics, the efforts of many countries to provide experimental convalescent plasma therapy showed that access to source plasma collection facilities in special and emergency conditions can be helpful and even necessary. Also, the development of hyperimmune globulin against emerging infectious agents is heavily dependent on the availability of source plasma from donors who recovered from the disease.

CHAPTER 4

RECRUITMENT, RETENTION AND PROTECTION OF BLOOD AND PLASMA DONORS

4.1 Culturally sensitive promotion of blood and plasma donation and social marketing

Blood and plasma donor management is the first of many steps in the blood transfusion chain. It facilitates and supports all subsequent parts of the chain and helps to make the blood supply safer and more sustainable *(32)*.

The process of donor management involves several factors that should be taken into account to ensure that a donor population is healthy, stable, reliable and flexible. It needs to encompass ethnic diversities to assure availability of compatible red blood cells for transfusion and should be dimensioned to ensure an adequate supply of all needed blood components, including plasma for fractionation *(33)*. A high priority is the development and application of national and local strategies for donor recruitment and retention *(34, 35)*. Those strategies should aim systematically at maintaining a sufficient blood supply, taking into consideration the increasing demand for blood for transfusion due to medical advancements in LMIC and, in many countries, an ageing population, unmet needs for PDMPs, the impact of strict donor deferral criteria, and the limited shelf-life of blood products *(34, 36)*.

Promoting increased blood and plasma donation requires identifying the relevant behavioural and psychological characteristics of donors, that is, what motivates some individuals and not others to donate. Effective promotion of blood and plasma donation also involves understanding relevant aspects of donors' social networks and community, beyond focusing on appeals to altruism. Indeed, blood and plasma donation rates vary significantly by area, location and community. Different ethnic groups have different donation rates, and there are strong relationships between donation rates and age, gender, education, social class, occupation and religion *(33, 34, 36)*. Hence, interventions for donor recruitment and retention need to be socially and culturally focused and designed to overcome any discrimination. They should ensure that blood and plasma donation is seen as an inclusive process, encompassing not only individual-level factors but also the expression of socially determined commitments, including social reciprocity *(34, 37, 38)*. From this perspective, the decision to donate blood and plasma is sustained less by generic altruistic motives and more by donors' desire to enhance the status of their membership within their own social networks and to maintain the social relationships they trust. As a result, donors become motivated to act in the wider interest of the networks in which

these relationships have been formed. Consistent with this perspective, recognition of the social contribution of blood and plasma donors should be emphasized in media communications organized under the national blood programme.

Up-to-date principles of social marketing should be applied to recruitment and retention of blood and plasma donors if a secure and safe blood and plasma supply is to be ensured *(32)*, bearing in mind that donor recruitment is an area in constant evolution. Marketing of donor recruitment should be a socially oriented process that not only informs the population about blood and plasma needs but also changes attitudes and public orientation so that more members of the community will become donors. Social marketing is also a powerful tool to encourage donors to periodically repeat donating so that healthy, stable, consistent and flexible donor pools are created.

Social marketing in blood donation is not about selling or offering products but about selling a good feeling to donors and to the whole community. The ultimate goal is to create a solid and positive culture of voluntary non-remunerated blood donation as a normal part of a healthy lifestyle *(32)*. Therefore, it is fundamental for any well performing blood organization to establish a long-lasting relationship with donors and their social environment, since this can enhance consistency and flexibility of supply, cost-effectiveness and blood safety *(33, 34)*.

In several countries compensation for source plasma donation has enabled a high volume of plasma collection without affecting the level of collection of whole blood by blood establishments and the supply of red blood cells. Nevertheless, voluntary non-remunerated blood donation remains the foundation of a safe, adequate and sustainable blood supply for transfusion that also can support patient needs for therapies with PDMPs. Consideration should be given to the fact that in many countries in the world, millions of blood donors giving millions of blood and plasma donations per year are organized in not-for-profit, nationally recognized blood donor organizations and associations, coordinated at global level by the International Federation of Blood Donor Organizations (FIODS/IFBDO) *(39)*. These blood donor organizations and associations comply with rigorous ethical codes and strongly advocate voluntary non-remunerated blood donation, as recommended by WHO *(34)*. These blood donor organizations and associations make a significant contribution to their respective national and domestic blood establishments and organizations and health care systems. In collaboration with the relevant institutional bodies, they do this through promoting blood and plasma donation, alerting and educating donors on healthy lifestyles, and carrying out strategic plans and actions aimed at recruitment and retention of associated donors. So, where present, blood donor organizations and associations can represent a valuable resource for national blood systems, contributing to the establishment of appropriate social marketing policies within which they can play a strategic role in enhancing the efficiency, cost-effectiveness and sustainability of national and domestic blood systems *(40)*.

4.2 Sensitization and education of blood and plasma donors on the specific value of plasma and its products

Human plasma should be recognized as a critical national, regional and global resource. In a recent study of 105 low- and middle-income countries LMIC it was found that the median number of WHO listed blood products of human origin found on the national lists of essential medicines was 4 (range 0–10). Immunoglobulins were most frequently included (73%), overall inclusion of plasma-derived products was around 50%, and blood and blood components, which were added to the WHO listing in 2013, were the least selected products (15%) *(41)*. This shows that while policy-makers in LMIC are aware of the public health need for immunoglobulins, there is much lower recognition of whole blood and blood components as essential medicines. This is the background against which raising the awareness and enhancing the education of blood donors on the value of plasma and its derived products should be implemented. Similarly, the

awareness of policy-makers should be enhanced on the role of human plasma both for clinical use and particularly as a raw material for the fractionation and manufacture of PDMPs.

Sensitization and education of blood donors on the importance of plasma components for transfusion and of plasma as a raw material for fractionation, and on the clinical value of PDMPs, should focus on their crucial role in the prophylaxis and treatment of patients with bleeding disorders, immune deficiencies, autoimmune and inflammatory diseases, and a variety of congenital deficiency disorders. In this context, the continued importance in LMIC of fresh frozen plasma, cryoprecipitate and cryoprecipitate-poor plasma as alternative therapies in the absence of specific lifesaving PDMPs (for example, factor IX, factor VIII and fibrinogen) should be emphasized. In low- and middle-income countries, the intensity of interventions, including social marketing to promote blood and plasma donation, should be commensurate with the state of development of the blood system, taking into account gaps that may exist in GMP compliance of the blood services.

An important element of raising awareness of the value of plasma for fractionation is the delivery of an appropriate sequence of health-related and socially relevant messages. These may focus on key factors such as:

- the importance of donated plasma as the essential resource that enables patients to be treated with PDMPs;
- the unethical wastage of valuable plasma that could be manufactured into PDMPs;
- the heavy dependence of patients needing PDMPs in LMIC on imported products;
- pursuing self-sufficiency for the most important PDMPs as a national goal;
- the current reality that plasma for fractionation is an economically important raw material that is at risk of supply interruption because most of it is produced in a very limited number of countries in the world;
- the strategic goal of increasing the supply of domestic plasma to increase the availability of the most important PDMPs.

Hence plasma should be considered a strategic resource comparable to other natural materials deemed important for national or regional independence and security of supply *(30)*. Additionally, immunoglobulins made from domestic plasma are likely to have an antibody composition directed against domestic pathogens that is more suitable to treat immunodeficient patients than those made from non-domestic plasma. Promoting blood and plasma donation is therefore a national responsibility. Notably, World Blood Donor Day is observed annually on 14 June, representing a special opportunity to build a culture of voluntary blood donation at global level. This event is aimed at celebrating and thanking blood donors and highlighting the lifesaving role they play in the health care systems of their communities. It also has the goal of raising awareness of the need for sufficient supplies of safe blood, and how this vital need can be accomplished only if many more people throughout the world make a commitment to regular voluntary non-remunerated blood donation *(7)*. Since World Blood Donor Day provides a springboard for longer-term donor education programmes and blood donation campaigns throughout the year, it could serve concurrently to raise awareness in all countries of the importance of plasma as a strategic resource. Likewise, the same messages could be made part of educational programmes and operational plans run by international organizations, such as the Pledge 25 Club.

The progression of blood collection from whole blood to whole blood plus plasma (through plasmapheresis) is a path towards increased production of plasma for fractionation. It should be the result of a national self-sufficiency

programme that focuses first on optimizing production of recovered plasma that meets quality standards appropriate for fractionation. Raising awareness of the value of plasma for fractionation is intrinsically challenging. The introduction of plasmapheresis together with whole blood collection, especially in a not-for-profit environment, is a step forward. It requires significant additional investment in terms of specific promotion, social marketing interventions involving donor education and motivation, and a strong focus on donor retention. Despite these challenges, it can bring remarkable advantages in terms of donor flexibility and availability to provide different types of donation.

To successfully introduce plasmapheresis, there should be effective communication on the importance of source plasma donation and, where necessary, on how it can beneficially complement whole blood donation, alongside existing initiatives for the promotion of whole blood donation. Adequate information should be provided to both potential and repeat donors on the essential characteristics of plasmapheresis, including its safety, frequency and duration of donation, and its accessibility in terms of donor eligibility criteria. Targeting specific donor populations for plasmapheresis programmes may help to focus information and education campaigns on potential source plasma donors who are most likely to take part and who meet donor selection criteria *(42)*.

In conclusion, any country deciding to introduce fractionation of domestic plasma should be aware that significant investments are required in donor management. Successful blood and plasma donor recruitment and retention will depend on effective and efficient socially oriented initiatives, with messages focused on donor education and sensitization.

4.3 Protection of donors' health and rights

Protecting the health of blood and plasma donors is a primary responsibility of any national blood system, together with ensuring a safe blood supply and protecting blood recipients *(43)*. All feasible steps should be taken to protect donor health and safety, and appropriate safeguards should be in place to ensure that the products derived from donations are used appropriately and equitably for recipients *(44)*. Protecting donor health is also an imperative for ensuring a continued supply of blood, and even more so of plasma for manufacture. As with monitoring of transfusion safety, donor vigilance should be undertaken as a basic part of a nationally organized haemovigilance system to detect, document, report and take follow-up action to prevent adverse reactions in donors. The safety of the PDMP, and in some respects its quality, is dependent on the health of the donor, which is therefore linked to the safety and efficacy of the product in the patient. Importantly, when frequent plasmapheresis is introduced, it is necessary to monitor, in particular, donors' levels of serum proteins, especially immunoglobulins *(45)*, to ensure that safety requirements established by the national regulatory authority are observed. Moreover, protein depletion is more likely to occur in donors living in LMIC, where nutritional conditions can be suboptimal. Wherever possible, monitoring should adopt a personalized approach to collection volume and frequency, which will ensure that donor immunoglobulin G (IgG) levels are regularly monitored and the collection volume and frequency tailored to the individual donor's physical ability to replace removed IgG *(46)*.

Protecting the rights of blood donors is part of the fundamental ethical principles underpinning any well established national blood organization. The rights and responsibilities of donors and patients are of equal importance, and the health, safety and well-being of donors should not be compromised in order to meet the needs of patients. At the same time, donors' eligibility to donate should not be unnecessarily restricted. The acceptance criteria should not be conditioned arbitrarily by gender, race, nationality, religion, sexual orientation or social class, thus excluding any kind of non-evidence-based discrimination *(43, 44)*.

The fundamental rights of blood and plasma donors should be fully respected by all the professionals serving in blood organizations, in accordance with the four basic principles of biomedical ethics (autonomy, beneficence, non-maleficence and justice), as well as with the general principle of dignity *(44)*. Donors should be informed of their rights, starting from education programmes and campaigns aimed at donor recruitment and retention. Protecting donors' rights can be promoted by blood donor nongovernmental organizations, which have already been established in some LMIC and also internationally.

Donors' rights include:

- freedom from coercion to donate;
- the right to clear and appropriate information, including the purpose of donor selection;
- the right to withdraw from blood or plasma donation at any time during the procedure for any reason, including doubts as to their suitability as blood or plasma donors, without any need to explain this decision;
- the right to confidentiality and privacy throughout the whole donation process;
- the right to give informed consent to the donation after provision of adequate information, including information on possible commercialization of the products derived from the donation and whether the donation might be used for research, quality control or any other purpose;
- the right to be informed in case any clinical or laboratory data related to the selection and donation may be relevant to their health.

For further information on this topic, see the WHO B*lood donor counselling implementation guidelines (43)* and the International Society of Blood Transfusion *Code of ethics relating to transfusion medicine (44)*.

CHAPTER 5

STANDARDS AND QUALITY MANAGEMENT IN BLOOD ESTABLISHMENTS

The quality of plasma is dependent on careful donor selection, as well as appropriate collection, testing, processing, storage and transport of the products. The quality of plasma for manufacturing influences the range, quality and safety of PDMPs. If a blood establishment wishes to supply recovered plasma for the manufacture of PDMPs or to implement the collection of source plasma by means of plasmapheresis, compliance with international standards is necessary. The safety and quality of plasma for fractionation should be ensured by implementation of standards at the blood establishment where plasma is prepared. The importance of establishing reliable quality assurance systems for the whole chain of blood collection, processing and distribution of blood components in blood establishments was emphasized by the Sixty-third World Health Assembly in resolution WHA63.12 on the availability, safety and quality of blood products *(8)*. In that resolution, quality assurance is seen as a necessary measure contributing to increased global availability of plasma that meets internationally recognized standards. Fractionators should only use plasma for fractionation from blood establishments that are subject to inspection and approved by a national regulatory authority in order to ensure that they comply with the required standards.

WHO has published appropriate recommendations and standards, including epidemiological monitoring in blood donors, that can be used as a reference *(3, 13, 23, 33)*. Specific criteria may be added by the plasma fractionator as part of the contractual agreement in order to ensure appropriate quality of plasma for the specific manufacturing processes.

5.1 Standards for donor selection

The assessment of blood donor suitability and deferral, where appropriate, aims to exclude donations from individuals at risk of transfusion-transmissible infection, particularly from those with recently acquired infection that may not be detected by routine screening tests, or with an infection for which no effective blood screening test is available. Blood and blood components should be obtained from healthy voluntary non-remunerated donors who are carefully selected using a systematic and validated process consisting of review of the donor's health assessment, social behaviour history (through the donor questionnaire) and a medical examination. A list of permanent or temporary deferral criteria used for potential donors should be clearly defined *(33)*. National regulatory authorities are pivotal in establishing a harmonized framework for donor acceptance and deferral criteria, appropriate to the country in which

plasma is collected. Such donor selection standards should be national requirements that are applied nationwide. Within the scope of their role of establishing and implementing effective national regulations, national regulatory authorities should enforce such criteria.

The donor questionnaire is the key tool in donor selection for assessing donor health and safety and for reducing the risk of transmission of significant bloodborne infections, including emerging infections for which no suitable screening tests are available. A standardized donor questionnaire incorporating selection criteria is now widely accepted as being necessary for uniformity and consistency in approach and for ease of implementation in assessing donor suitability. It should be updated as appropriate based on risk-based decision-making. Using a questionnaire ensures that the same information is collected systematically about each donor on each occasion of donation. A standard questionnaire that elicits a prospective donor's demographic, medical and infectious disease risk history should be used throughout the country and therefore directed by national regulatory authorities. The questionnaire should be simple, unambiguous, culturally acceptable, easy to complete and available in domestic languages where appropriate. Donor selection staff should be trained to recognize donors having difficulty in understanding any questions, for example due to low literacy levels, and to explain the questions and facilitate the process for donors to provide accurate responses. An example of a blood donor questionnaire is included as Annex 2 of the WHO *Guidelines on assessing donor suitability for blood donation (33)*.

The donor questionnaire is followed by a one-to-one confidential interview between the donor and a donor selection staff member, during which the completed questionnaire should be reviewed prior to donation, so that an assessment can be made of the donor's general health, medical history and any transfusion-transmissible infection risks. It also provides an opportunity to check whether the donor has understood the questions and has answered them correctly and truthfully. Donor identity must be confirmed at critical steps prior to donation.

Whenever possible, the medical history should be further elaborated by a donor selection staff member, particularly for new donors. Similarly, relevant travel information may be elicited. When there is a proven risk of transfusion transmission of a medically significant infection, but no appropriate screening assays are available, donor selection criteria should be developed to identify and defer potentially infected donors for an appropriate period of time, as per WHO recommendations *(3)*. Confidential records should be kept of donations and deferrals so that the donor's individual history can be reviewed for any issues of current concern.

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

Laboratory testing should be performed in an environment of good laboratory practice, characterized by a well established quality management system and regular quality assessment checks. The extent and modalities of blood donation testing are different amongst blood establishments in different countries and regions, depending on economic, epidemiological and risk-based decision-making factors.

Blood establishments should assess the potential risks of infection present in the donor population and should establish a strategy to address these risks either in the donor selection criteria or by testing the donors, aimed at minimizing the risk of transmission of infection from donors to recipients. The selection criteria and testing strategy should be based on the prevalence, incidence and epidemiology of transfusion-transmissible infections, as well as up-to-date information on known and emerging infections. Donors may have been exposed to HIV, hepatitis B, hepatitis C, human T-cell lymphotropic virus types I and II (HTLV-I/II) or syphilis via several different routes. These primarily include sexual

contact and percutaneous exposure through high-risk sexual behaviours, unsafe blood transfusion, illicit drug injection practices, cosmetic treatments and rituals. Some transfusion-transmissible infections also may be acquired through geographically based environmental exposures (for example, malaria, Chagas disease, West Nile virus, babesiosis, Zika virus), medical procedures (for example, hepatitis C from contaminated injections and endoscopies), or foodborne exposures (for example, hepatitis E, variant Creutzfeldt–Jakob disease). The testing strategy may be different if plasma is collected for transfusion or solely for further industrial manufacturing.

Coordination and cooperation among key national institutions, agencies and major stakeholders, such as blood services, public health institutions, hospitals, regulatory agencies and professional bodies, is essential for the recognition and control of known and emerging transfusion-transmissible infections. This includes knowledge of disease prevalence, incidence and epidemiology; active surveillance of emerging infections and potential new endemic areas; implementation of appropriate donor selection criteria; quality-assured screening of all donations; validation of virus inactivation or removal steps during manufacturing; and systematic surveillance of transfusion-transmissible infection in transfusion recipients.

Each unit of blood or plasma needs to be tested for transfusion-transmissible infections. National regulatory authorities are pivotal in establishing a harmonized framework for donation testing, appropriate to the relevant infectious risks, and the epidemiological data for disease prevalence in the country in which plasma is collected. Such testing standards should be national requirements and should be implemented within the scope of an effective national regulatory system.

WHO recommends that, at a minimum, screening of all blood donations for transfusion should be mandatory for the following infections and using the following serologic markers *(47)*:

- HIV-1 and HIV-2: screening for a combination of HIV antigen and antibodies;
- hepatitis B: screening for hepatitis B surface antigen (HBsAg);
- hepatitis C: screening for either a combination of HCV antigen-antibody or HCV antibodies;
- syphilis (*Treponema pallidum*): screening for related antibodies.

In some WHO regions, additional testing of whole blood donations for serological markers, for example for Chagas disease, HTLV-I/II or *Trypanosoma cruzi*, is required.

For these serologic markers, usually proficient laboratory-based enzyme immune assays (such as enzyme-linked immunosorbent assay, or ELISA) are in place; however, there are still situations where more simple point-of-care tests or rapid tests have to be used, for example in cases of urgency or lack of infrastructure. These testing platforms, however, are generally not acceptable for plasma fractionation where testing requirements are driven by the fractionation company based on international standards or regulations, for example international pharmacopoeia monographs that should be considered. Some of the tests that are mandatory for components for direct transfusion are not mandatory for plasma for fractionation. For example, individual donations are not tested for antibodies related to syphilis. However, some additional testing may be required during the plasma fractionation process (for example, testing of samples taken from the first homogenized pool).

In contrast, to further improve transfusion safety, blood establishments in many developed countries have introduced NAT-based screening to limit the risk posed by infection in the serologic diagnostic window phase and some phases

of chronic infection, such as occult hepatitis B infections. However, even these highly sensitive NAT-based systems are characterized by a residual window phase, though much shorter compared to serologic assays.

Testing strategies implemented by blood establishments differ not only between economic regions but also sometimes within the same economic region; the respective decisions are often based on specific virus epidemiologies and different risk acceptance attitudes. WHO provides guidance on estimation of the residual risk based on data on virus infections in the blood donor population and comparing different testing scenarios *(48)*. In order to facilitate cooperation, a national or regional standardized testing strategy should be agreed upon and implemented to ensure that all blood establishments comply with uniform good manufacturing practices and processes. Standardized screening and safety measures should be in place to reduce the risks arising from the establishment of multiple testing standards within an organization or country. The acute viremic infection phase of further transfusion-transmissible infections, such as West Nile fever, hepatitis E virus or Zika virus, is exclusively covered by NAT. This testing has been introduced for some of these markers by several high-income countries, based on epidemiological and health care considerations, and in the absence of licensed pathogen reduction treatment of blood components intended for transfusion. Serologic or NAT-based screening is also implemented in some high-income countries to prevent transmission of malaria, Chagas disease and babesiosis.

The outcomes of the laboratory screening of donations remain the final decision point for the release of blood components for clinical use or for further manufacturing. However, even with the high-quality assays and systems now available, the screening process cannot be considered to be totally effective, because an infection in donated blood may not be detected due to the collection of the donation during the window period of infection, or failure of assay sensitivity or other error. There are some emerging infections for which screening is not available or effective. A donor may be infected by an infectious agent for which donations are not routinely screened; in such cases, the donor selection process may be able to identify and defer the infected donor based on their medical examination, travel history or other perceived risk.

Plasma used for fractionation is usually tested for HIV, hepatitis B virus and hepatitis C virus by NAT. In resource-constrained settings, the testing can be done by the plasma fractionator. Based on risk analysis and where appropriate for cost-saving purposes, mini-pools of plasma are often tested. In the case of a positive result, the mini-pool is resolved to identify the causative plasma unit. If NAT for recovered plasma has been introduced as a routine test in the blood transfusion system, the parallel virus safety of labile blood components may be assured. In other testing scenarios, reporting or look-back procedures may be considered in the case of positive results. In Europe, for specific products made by fractionation, regulatory requirements are in place for plasma to be further tested by NAT for human parvovirus B19 and hepatitis A virus, which are considered less important for single unit components for transfusion than for large pool size products.

There should be a system for notifying and counselling the donor if the test is confirmed as positive. It is recommended that national algorithms be developed and used to enable consistent resolution of discordant, indeterminate or unconfirmed results.

5.3 Good manufacturing practices (GMP) and quality management

Quality management is a wide-ranging concept under the general principles of GMP. It covers all matters that individually or collectively influence the quality of blood and blood components, thereby ensuring their safety, efficacy and consistency. It is the sum total of the organized arrangements made with the objective of ensuring that blood components are of the quality required for their intended use *(13)*.

For the manufacture of PDMPs, GMP becomes even more important and more complex due to the biological nature of the products and their starting material. The implementation of GMP in blood establishments aims to:

- introduce the application of quality assurance principles in all steps involved in the selection of donors and in the collection, preparation, testing, storage and distribution of blood components;
- support the systematic application of donor selection criteria for each donation;
- reduce errors and technical problems in collection, preparation, testing, storage and distribution;
- contribute to the release of products that comply with safety and quality requirements;
- ensure adequate documentation and full traceability for each donation and product, enabling continuous improvement in donor selection, collection, preparation and testing of starting materials;
- facilitate regional cooperation networks in order to reach compliance at the required level.

Blood establishments should therefore establish and maintain quality systems, based on the principles of GMP, for all activities that determine the quality and safety of the products.

Some blood establishments have implemented a quality management system that has been successfully certified under ISO 9001, which sets out the criteria for a quality management system, while others have achieved certification to ISO 15189, a laboratory quality management system standard specifically for diagnostic testing laboratories. These certifications are often erroneously thought to be equivalent to compliance with GMP; although valuable, neither standard is intended to apply to the manufacture of PDMPs. A quality management system according to ISO 9001 is mainly focused on quality assurance elements of a service and is client oriented, whereas in GMP these elements are adapted to the situation of producing a pharmaceutical product. The ISO system, however, lacks those aspects of GMP that ensure that quality is built into the product, and GMP is therefore the well recognized international standard that should be fulfilled during manufacture of a therapeutic product. A blood establishment that is certified according to ISO does not automatically fulfil the principles of GMP. Compliance with GMP is critical for manufacturers to meet stringent quality and safety requirements. This key difference between the GMP and ISO standards is poorly understood, and blood establishments are often reluctant to discontinue their ISO certification, resulting in confusion over how to integrate GMP into the blood establishment's ISO systems, and continuation of the costs of ISO certification, which are not inconsiderable.

WHO has developed specific guidelines on good manufacturing practices for blood establishments *(13)*. In these guidelines, WHO defines the relevant aspects of quality system requirements for blood establishments, including those aspects of GMP that are applicable and necessary for the preparation of blood components for transfusion or for further manufacture of PDMPs.

The quality system should be designed to ensure the quality and safety of prepared blood and blood components, and to ensure donor and staff safety and customer service *(13)*. A compliant GMP system requires suitable organization and qualified personnel, adequate facilities and suitable equipment, a system of documentation with approved procedures and appropriate records ensuring traceability, validated and robust production processes, correct materials, and suitable transport and distribution.

5.3.1 Suitable organization and trained personnel

The organization should have an adequate number of personnel with the necessary qualifications, training and experience. A competent management is needed, with the ultimate responsibility of determining and providing adequate and appropriate resources (personnel, financing, materials, facilities and equipment) to implement and maintain the quality management system and continually improve its suitability and effectiveness through participation in management review. A responsible person should be designated to ensure that any unit of plasma is collected and prepared in compliance with existing standards. Personnel directly involved in the donor selection, collection, testing, processing, storage and distribution of blood components should be given initial and continuous training.

5.3.2 Suitable facility and equipment

Premises, including mobile sites if applicable, should be located, constructed, adapted and maintained to suit the activities to be carried out. The workflow should be designed and arranged to enable work to proceed in a logical sequence, resulting in a predictable flow of staff, donors and products, thus minimizing the risk of errors. The construction should allow for effective cleaning and maintenance in order to minimize the risk of contamination.

A separate donor area should be set aside for personal interviews. Laboratory testing should take place in a dedicated laboratory area separated from the donation area and with access restricted to authorized personnel. The storage area should provide secure and safe storage of plasma, and provisions should be in place in the event of equipment or power failure in the storage facility.

All equipment should be qualified and used in accordance with validated procedures. The extent of qualification depends on the critical nature and complexity of the equipment and its impact on the quality of the products. For some equipment, installation qualification and calibration may be sufficient. Equipment that is more complex may need a more thorough approach to qualification and validation to include the instruments, the associated operations and the software involved. The qualification and maintenance should contribute to preventing unexpected problems that might have an impact on the quality or availability of the products.

5.3.3 System of documentation and traceability

Proper documentation is essential to the quality system. Appropriate and up-to-date procedures and well maintained records ensure that work is performed in a standardized and uniform manner and that all steps are traceable. Written instructions should include all applicable methods and procedures, should be accessible to all authorized personnel,

and should be strictly followed. A document control system should define the establishment, review, revision history and archiving of documents.

The documentation should set out specifications, procedures and records covering each activity in the blood establishment and plasma collection centre. Records provide evidence of various actions taken to demonstrate compliance with instructions, such as activities, events, investigations, and, in the case of processed blood and blood components, a history of each unit (including its distribution). Records include the raw data that are used to generate other records. For electronic records, instructions should define which data are to be used as raw data. All data on which quality decisions are based should be defined as raw data. Records should demonstrate compliance with good documentation practice.

Despite the pooling of thousands of plasma donations in the manufacture of PDMPs, it is necessary to ensure full traceability between individual blood and plasma units collected and the final plasma products manufactured. This is important to enable any quality and safety problems, in particular problems related to infection risks, to be traced back to individual blood or plasma donations, and to allow relevant measures to be taken to protect the donors as well as the patients who received the blood components or the PDMPs. The system to ensure traceability of components and critical materials should be enforced through accurate donor, donation, product and laboratory sample identification procedures; diligent maintenance of records; and use of an appropriate labelling system.

5.3.4 Validation of operating procedures and quality monitoring

All critical processes in the manufacture of blood and blood components should be validated before implementation according to a predefined protocol of tests and acceptance criteria. Critical processes include donor selection and determination of suitability, component preparation, donor testing for infectious diseases, ABO blood typing and antibody screening where applicable (for example, for red cell concentrates), labelling, storage and distribution.

The collection of plasma by using a qualified sterile blood bag system should minimize the risk of microbial contamination. Microbial control should be maintained through aseptic collection procedures using such a closed system.

A system should be in place to prevent a plasma unit from being released before all mandatory requirements have been fulfilled. Before release, each plasma unit should be kept administratively and physically segregated from released plasma units. The system should clearly distinguish between released and non-released plasma units.

Regular quality monitoring and quality control activities should be performed to demonstrate that the in-process parameters and finished components comply with the approved specifications. There should be written procedures for testing materials and blood components at different stages of processing, describing the methods and equipment to be used. The tests performed should be recorded and undergo a regular review and trend analysis.

CHAPTER 6

COUNTRY BILATERAL AND REGIONAL COOPERATION

A pragmatic way for a blood transfusion system to deal with the 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. This can overcome or at least delay the initial capital investment needed for domestic fractionation and can give the country, or countries that are collaborating economically in a specific region, time to prepare for its own fractionation site. Implementation of the requirements for quality of the plasma accepted for fractionation under a contract may serve as knowledge and technology transfer to less experienced blood transfusion services *(31)*.

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). It is necessary to resolve or advance promptly all the legal and administrative aspects involved in the signing of the agreement. Typically, products obtained from such contracts are factor VIII concentrate, immunoglobulin, albumin, prothrombin complex concentrate and factor IX concentrate *(31, 49)*.

A national process roadmap for the supply of plasma should be developed and followed. First, the country needs to identify the quantity of the recovered plasma that is currently not produced (for lack of component separation from whole blood) or is being discarded. It should also check the regulatory status and oversight of plasma that is produced and ascertain whether this might be recognized by other parties (foreign national regulatory authority, fractionator). Regulatory benchmarking of the national blood regulation using internationally accepted tools – such as the WHO Global Benchmarking Tool *(23)* – can assist in gaining recognition. In any case, the national regulatory authority of the plasma home country will need to agree on the process for export of plasma to an external fractionator – for example, a regional contractor. Pooling of plasma from multiple countries within a region may be considered as a means to increase the cost-effectiveness of the fractionation, in agreement with the authorities of the countries and the fractionator. A risk assessment to determine the residual risk for HIV, hepatitis B and hepatitis C, and potentially further relevant transfusion-transmissible infections, is needed in each participating country. Harmonized testing standards and best practices should be implemented to ensure comparable blood safety at country and subregional levels. If the residual risks are similar among the countries supplying plasma for pooling, then pooling may be considered.

At the next stage, countries intending to supply plasma will contact possible fractionators and supply them with the relevant information (including the residual risk assessment for transfusion-transmissible infection). It is recommended that the plasma fractionator undertake a paper audit and analysis of the information supplied. If the analysis is favourable, the plasma fractionator will conduct a physical audit and provide a gap analysis and may offer support to develop plans to close the gaps.

A shopping basket of requirements should be drawn up, including equip¬ment requirements. The plasma-supplying country will therefore need to undertake a cost–benefit analysis and decide how to proceed. After an implementation plan is drawn up and rolled out, the fractionator should perform a follow-up audit. It is highly recommended that a dedicated project management team be formed to improve the likelihood of success. Once the fractionator is comfortable with the outcome of the audit, it will seek regulatory approval from the authority in its home country on acceptance of the plasma. Depending on the regulatory benchmarking outcome in the plasma home country, the national regulatory authority responsible for the plasma fractionation activities may either rely on the regulatory assessment outcome or may decide to perform an inspection of the blood transfusion system in the source country to confirm compliance with international requirements. Once approval to accept the plasma is granted by the regulatory authority of the fractionator's home country, a contract should be signed between the fractionator and the blood transfusion system of the supplying country and a delivery schedule agreed. The requirements for regulatory approval of PDMPs manufactured from the plasma should be discussed with the national regulatory authority of the plasma home country. Regulatory approval of PDMPs in other regions should be sought and possibly applied. Reliance based on benchmarking assessment outcomes might be a pragmatic way forward, especially in resource-limited settings. The distribution of PDMPs via the blood transfusion system or appointed pharmaceutical supply chain will also be agreed.

A number of business considerations should be taken into account in determining the cost of compliance with the plasma specifications of the fractionator, including the availability of funding for infrastructure development; the 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); and the cost–benefit ratio of the entire process. In addition, compliance with the requirements for the registration of the products by the different national registration authorities involved must be met.

Fractionators will require information on risks related to certain transfusion-transmissible viruses and the ability of the manufacturing process to remove or inactivate these agents. In general, fractionators will require NAT-based screening for HIV, hepatitis B, and hepatitis C to qualify plasma for fractionation. NAT-based screening of donations reduces the risk of contamination of the plasma pool for fractionation and avoids rejection of pools that might test positive for viral RNA/DNA. Discussion is needed on whether the fractionator rather than the blood transfusion system might perform NAT screening, and whether mini-pool testing of donations would be acceptable. The impact of different testing algorithms on blood safety has been addressed in a WHO guideline *(48)*. It should be noted that introduction of NAT of individual blood donations and improving infrastructure alone may not be sufficient to obtain approval to process all available plasma from any given country. Other factors – such as the robustness of the product quality, cold chain and information technology systems to be determined according the requirements of the authorities and fractionator – will also need to be taken into account. A full assessment is necessary for a fair evaluation, including epidemiological surveillance data.

CHAPTER 7

PRODUCTION OF PLASMA FOR FRACTIONATION

Provided that plasma quality is ensured and that volumes of plasma suitable for fractionation are generated, availability of PDMPs in LMIC can be improved by domestic manufacturing using locally donated plasma or by providing the plasma for fractionation to existing non-domestic plasma fractionators (contract fractionation or toll fractionation).

7.1 Quality agreement between the blood establishment and the plasma fractionator

A contractual agreement will be signed between the blood establishment and the fractionator *(3, 9, 49)* with the objective of ensuring compliance with quality and safety requirements of plasma as a starting material suitable for use in the production of PDMPs. An underlying goal may be to reduce the volume of plasma that is currently discarded and ensure its use for fractionation in a licensed facility and through licensed production methods. Under a toll fractionation programme, not only is the plasma provided as starting material to the fractionator, but the contractual agreement also contains provisions that the manufactured PDMP using this plasma is going to be returned to the country of plasma origin, thereby providing safe products to patients in need in LMIC. A toll fractionation programme is an option if sufficient domestic plasma of assured quality is available, but no suitable fractionation plant is available within the country.

In such agreements, all critical areas regarded as important in relation to plasma as starting material for the manufacture of safe and efficacious PDMPs should be covered. Indeed, quality standards pertaining to the quality of plasma for fractionation in place at the blood establishment have, as for the fractionation process itself, an influence on PDMP quality and safety. It is a requirement that quality standards be agreed between the blood establishment and the fractionator. The national regulatory authority involved in supervising plasma fractionation should perform regular inspections aiming to verify that such a contract is in place, that it complies with the regulations in force, and that it is properly and rigorously implemented in practice by both parties *(3, 9, 49)*.

The *WHO recommendations for the production, control and regulation of human plasma for fractionation (3)* specify the areas that should be part of a quality agreement between a blood establishment and a fractionator. Table 2 summarizes areas of particular relevance in formulating a quality agreement. Other WHO documents provide additional information *(9, 49)*.

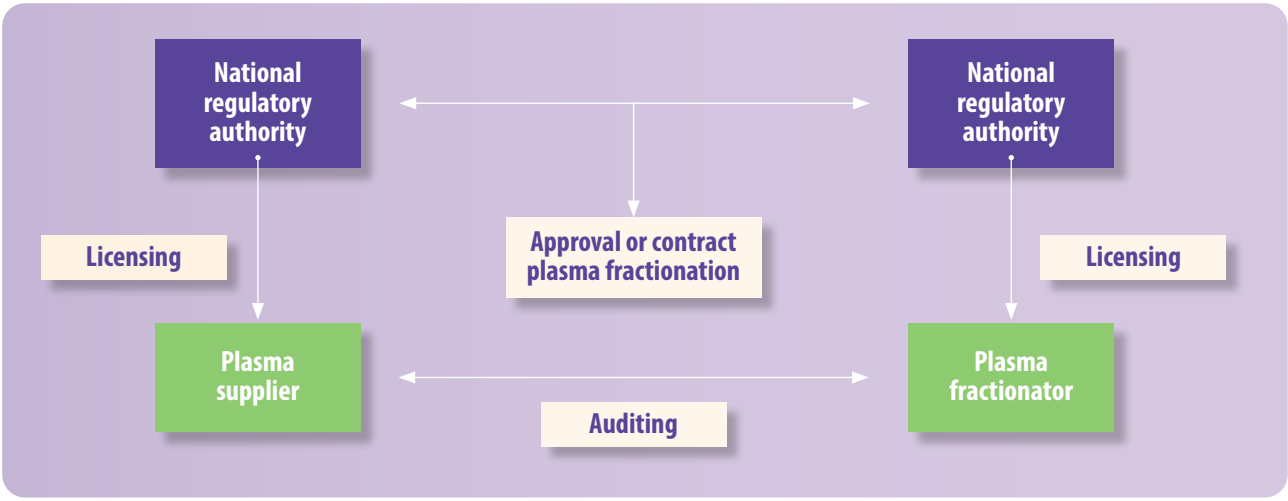
Table 2. Areas of particular relevance for a quality agreement between a blood establishment and a fractionator

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)*.

In parallel to this agreement, the regulatory authorities of the countries involved should collaborate in the supervision of the plasma fractionation agreement *(49)*. Figure 3 summarizes the process.

Fig. 3. Parties involved in a plasma fractionation agreement



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

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 to adverse events and adverse reactions in product recipients depend on the existence of bidirectional traceability of the entire chain. Likewise, individual donations need to be traceable to final products. In this way, subsequently learned information about a plasma donation that would have caused it to be deemed unsuitable for fractionation can enable actions against final products (such as recall) when necessary. Blood establishments and fractionators therefore need to establish and implement mechanisms to ensure that any important information related to the plasma unit that could have an impact on the quality or safety of the plasma unit is reported.

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, in-process quality controls, quality assurance, batch release, storage and shipment conditions, donor records and testing records of the involved batch that needs to be recalled. The process for addressing such a situation needs to be described in the contract to ensure that the essential information for a case report is available *(50)*.

7.3 Stepwise approach for improving the supply of PDMPs

The development of a system that results in an increase in the supply of plasma for fractionation to a contract fractionator or a domestic fractionator will not be the same for each country. Multiple factors need to be taken into consideration, as outlined in Chapters 2–6 and as further described below. It is assumed that:

- each country knows the clinical need for blood components and PDMPs;
- each country has quality systems in place that have been validated to provide a safety track record of the plasma that is accepted by a fractionator.

Once it is known what the national needs are for blood components for transfusion, a determination is needed of how much recovered plasma can be made available for fractionation. If this is insufficient to produce the PDMPs to meet the clinical need in the country, the country will depend on the import of PDMPs, while at the same time it needs to consider options to increase the volume of recovered plasma. Reorganization and centralization to reduce system fragmentation may help to achieve the objective of higher availability of recovered plasma, provided that clinical needs for plasma are met and that blood components are prepared in a quality-assured system *(51)*.

Recognizing that it takes time and a significant investment of financial resources to reach a volume of quality-assured domestic plasma sufficient for industrial fractionation, and that the cost and global shortage of some PDMPs may prohibit their import, alternative intermediate strategies aiming at domestic production of pathogen-reduced plasma fractions can be considered. Such strategies should seek to provide patients with safer treatment options than non-pathogen-reduced plasma components (such as plasma, cryoprecipitate and cryoprecipitate-poor plasma). Those strategies should also avoid the wastage of an increasing amount of quality plasma that does not yet meet the volume requirements for fractionation. Technologies are available that enable the preparation of pathogen-reduced plasma, pathogen-reduced cryoprecipitate and immunoglobulin concentrates from small-sized plasma pools. In particular, pending the availability and affordability of relevant PDMPs in LMIC, the treatment of cryoprecipitate by established virus inactivation technologies can dramatically increase the clinical safety of locally produced cryoprecipitate, providing a safe and effective alternative therapeutic product for patients with haemophilia A, von Willebrand disease and fibrinogen depletion or dysfunction *(12, 52)*. The implementation of these technologies should follow a comprehensive assessment of the existing domestic need for these products and the feasibility of providing them in a quality-assured system and at an appropriate scale *(12)*.

If blood and blood component demand for transfusion is fully satisfied and preparation of the maximum volume of recovered plasma is achieved, the country should next determine whether plasma collection programmes through plasmapheresis can be developed to further reduce dependency on imports of PDMPs. Once volumes of quality plasma sufficient for fractionation are generated reliably, a contract for fractionation can be negotiated with a foreign fractionator, including specification of the volumes of plasma that will be supplied. Over time, a country may wish to consider whether to continue with contract fractionation, or to build a national fractionation plant *(9)*. The latter option would require substantial financial and human resources, and careful consideration needs to be given to its feasibility. More details are provided in Chapter 8 on the economics of such an operation.

Table 3 illustrates the stepwise approach required in improving the supply of PDMPs at national level.

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

CHAPTER 8

ECONOMICS OF PLASMA COLLECTION AND DOMESTIC MANUFACTURE OF PDMPs

When national initiatives are developed on the domestic supply of plasma for the manufacture and domestic distribution of PDMPs, the ambitions and objectives for sufficient supply often override an understanding of the factors involved in ensuring long-term economic viability of a plasma fractionation programme. These factors include resources, facilities, materials, skilled personnel, management, production technologies, capacity, production plans, balanced product portfolio, marketing and sales. An assessment should be made of the cost drivers, investments, return on investments and (even in a not-for-profit setting) revenues needed for continuity and sustainability. For compliance with GMP for plasma collection, manufacture and distribution of PDMPs, significant financing is needed. Manufacture and supply of PDMPs must take account not only of regulations regarding plasma sourcing, manufacture, efficacy, safety, storage and distribution, but also of such factors as economies of scale, registration, licensing, price setting, marketing, sales, and competition with other PDMP suppliers. Since the economics of fractionation is governed – due to the cost of plasma and the high complexity of the technology – by the extent to which the plasma can be processed into the greatest number of saleable products, adherence to business plans and financial oversight is paramount if operations are to be carried out efficiently and profitably.

8.1 Good manufacturing processes

Plasma for fractionation should be produced in compliance with the GMP principles described in Chapter 5 and WHO recommendations *(3)*. All these GMP activities incur costs. Some blood transfusion organizations consider GMP only as an expense, questioning whether the costs of implementing GMP will be a benefit for the organization or not. Implementation of GMP improves the quality of work but also reduces the high costs of failure caused by incidents, rework, recalls and complaints. These high costs of failure should be recognized. By addressing control measures and taking preventive actions, the costs of failure will decrease. Reaching the balance point of financial equilibrium between quality costs and prevention should be the goal of this process.

8.2 Cost considerations in plasma collection

The investment necessary to design, build, validate, license, accredit and operate a technologically appropriate network that provides quality-assured plasma for fractionation should not be underestimated. The minimal quality standards that constitute GMP should be adhered to by all providers of plasma and should include both recovered plasma and source plasma. The cost of generating recovered plasma is relatively low because it is a surplus by-product of the preparation of blood components that generate revenues. As such, the cost of production of recovered plasma is allocated over a range of components (typically red blood cells, platelets, plasma and cryoprecipitate). However, additional costs may be incurred to establish quality-controlled transport and storage of recovered plasma for use in fractionation.

If a country considers developing a programme for collection of source plasma, it should be realized that the ultimate goal should be to obtain the plasma at a cost in line with the average market price of plasma for fractionation. The organization should have the following objectives that contribute to minimizing costs of plasma collection. The size of the area and region from which donors can be recruited determines the maximum size of the collection centre. Donor data management should be efficient and, when possible, appointments should be made electronically by the centre or donor. To create a bond between the donor and the collection centre, investments should be made to ensure minimal lead times and provide entertainment during waiting and donation periods. The efficiency of personnel will increase with the size of the facility. The size of the collection facility is an important consideration. Based on the potential for donor recruitment, an optimal size can be calculated.

During the collection process, registration and the response to medical questions should be done by the donors themselves. The examination of the donor should entail only a brief conversation with the medical assistant or physician, during which only inconsistent or unclear responses to questions on the standardized donor form need to be addressed. Laboratory tests performed post-donation must include those that are legally required. The costs of the apheresis procedure can be reduced by having the beds ordered in such a way that a cluster of beds can be controlled by one or two qualified assistants. The collection should aim for standardization through the collection of one product, obtained with one type of apheresis machine to optimize operating and maintenance costs. Through this approach, activities, materials, and layout can be standardized, and deviations successfully managed and minimized.

The production processes, including freezing, storage, transportation and the required quality checks, should be supported by use of information and communication technologies. This will include both complete support through a custom-made information system and automated communication with all support machines for the reporting and sharing of critical parameters of the examination, collection and subsequent processes.

8.3 Cost consideration in domestic plasma manufacturing and associated risks

Risks are associated with the initiation of domestic fractionation, as it is a highly specialized manufacturing activity linked in particular to the multiplicity of the PDMPs manufactured, the complexity of the purification scheme of each product, and the integration of dedicated virus reduction treatments within the process of production *(18)*. Such manufacturing complexity requires very careful engineering studies for the design of the facility, the selection of the production and utilities equipment, and the flow of products, human resources for production, and waste, among others. It is also vital to ensure the permanent availability of skilled expertise at all levels to guarantee ongoing safety and appropriate oversight.

The unique economics of fractionation requires that as many products are harvested from each industrial pool of plasma as is technically feasible and reflective of clinical needs. The establishment of a facility for plasma fractionation requires a capital investment that is often underestimated. The costs of building a pharmaceutical plant that complies with pharmaceutical and biotechnological requirements are high, and the production processes require continuous development in technology and products, ensuring validation requirements are met, and adaptation to an evolving clinical demand. Compliance with regulatory requirements is a continuous process that requires regular investment.

In general, these costs can be divided into fixed costs and variable costs. Fixed costs apply to the fractionation plant, the equipment, the different sections with upstream and downstream processes, laboratories, storage and transport facilities, and highly skilled and qualified personnel. Because of the high fixed costs, economy of scale is an important element to consider. Large plants that fractionate high volumes of plasma are more cost-effective than small plants, because the fixed costs are spread over a larger volume of plasma and the higher number of units and products being sold. In LMIC, a domestic fractionator should therefore consider an appropriate plant size, taking into account available budget, cost–benefit ratio, clinical demand, and management of the plant to optimize its efficiency. Variable costs are based on the volume of plasma fractionated and the source materials for production. A number of PDMPs (such as albumin, clotting factor concentrates and immunoglobulin products) can be fractionated out of plasma, and some joint costs (donor recruitment, collection costs, testing, initial fractionation steps) can be shared across the various products. The revenue stream is dependent on how many proteins can be manufactured at a given yield and sold from the maximum volume of plasma fractionated. The greater the yield and the variety of products, the more the fixed, variable and joint costs can be shared across the different products, making the cost per unit significantly lower.

Based on global epidemiological data, the number of patients requiring treatment with PDMPs can be calculated per country. In LMIC, this number of patients and the clinical demand for the PDMPs varies between countries due to underdiagnosis, variable availability of trained physicians, lack of sufficient supply, and distinct product reimbursement policies. To ensure that domestic plasma manufacturing is cost-effective, the types of required PDMPs and the volume of present and future clinical need should be estimated as accurately as possible and be included in the business plans for the operation. Fractionation of plasma to meet a high demand for one product might create a surplus of other products for which there is no demand. This will create an imbalance between production and sales, and the fractionation will not be cost-effective. Because of the sharing of variable and joint costs, a three-product portfolio (currently immunoglobulins, albumin, and a coagulation factor) is advised for LMIC, with typically smaller volumes of plasma processed, as the minimum possible for a viable operation. An imbalance in demand for various plasma products could be countered in various ways: fractionating a lower volume of plasma and not meeting the clinical need for a single product; improving the treatment of patients depending on PDMPs with better access to clinically needed products; or collaborating with other countries in the region to rationalize supply of surplus or deficient products. Competition is always present and may lead to lower prices of PDMPs.

8.4 Additional financial considerations for domestic fractionation projects

LMIC planning for domestic fractionation projects need also to consider the following financial aspects.

Investment. The major fixed cost will be investment in a production facility, through the whole process of construction to completion and validation. The costs involved will include land investment, equipment procurement (including logistics and import tax), design and construction costs, technology transfer and training costs, quality approval and validation compliance costs, and other contingencies.

Operation. Variable costs will become a consideration when commercial operation starts, and the factory commences production. The variable costs will include certain elements of human resources, raw materials (including plasma and other chemicals and disposable materials for production), and mainstream production costs that vary with production capacity and final target volume. Volume of production also impacts utility costs (water, electricity, fuel and waste management). Those laboratory costs that are related to quality control and assurance in all production steps are also considered as variable costs. When PDMP lots are released, costs incurred will include warehouse costs, maintaining standard procedures for storage, and shipping and distribution to end customers. Management costs include marketing, logistics, insurance, safety measures, and responsibility for environmental management and social concerns. Post-marketing surveillance activities, including pharmacovigilance, clinical examination, dealing with complaints and compensation, and customer care, are considered as variable costs since they increase with the volume of production and product use. In the case of transferred technology, the royalty fee will be as agreed in the contract, and the owner should consider the costs involved in research and development to drive improvements in quality of products and processes.

Maintenance. Regular maintenance costs, including repair and replacement of equipment (especially critical spare parts), may be allocated in the annual budget as a variable cost, or reimbursed from the income derived from product sales. After two to three years of operation the factory has to plan for a major shutdown period for renovation, repair and replacement of crucial equipment, or even expansion of production capacity through further investment.

8.5 Contract manufacturing

It is generally considered less risky to initiate the development of fractionation of domestic plasma by contract or toll fractionation. Such a system involves fractionation of domestic plasma by a foreign fractionator into products that are used in the country that supplied the plasma. Through toll manufacturing, all products manufactured from the supplied domestic plasma return to the country from which the plasma originates. This is not always the case with a contract manufacturing agreement, and different arrangements for the products manufactured can be made. For example, plasma can be provided in exchange for products from the fractionator. When aiming for domestic fractionation, the contract or toll fractionator could preferably be selected with a view to future technology transfer of the fractionation technology. Contract or toll fractionation in a regulated environment demands significant quality of the imported or exported plasma (see Chapter 5). Successful collaboration with a contract or toll manufacturer requires sustainability, continuity, establishment of sufficient capacity to fractionate the extra plasma, ensuring quality of plasma, putting in place extra safety measures if needed, and aligning volume of plasma with normal production volumes. It has been calculated that around 45% of the overall product cost of plasma fractionation is the cost of plasma. In addition, the costs incurred for the plasma fractionation process are charged by the fractionator to the plasma supplier. The toll fractionation profit margins for the fractionator are not easily calculated and depend on the type of contract and the range of products required. The charges vary considerably and may include strategic considerations linked to overall market access by the fractionator in the client's country, as well as immediate revenue through the toll activity *(49)*.

In summary, to ensure long-term success, engaging in a plasma fractionation programme should be done with full consideration given to the economic aspects, and should take place in a gradual, stepwise manner.

CHAPTER 9

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

As highlighted in this guidance, ensuring an adequate supply of PDMPs from locally collected plasma, either through fractionation abroad or through domestic industrial-scale fractionation, is a long-term and challenging process for many LMIC. Pending advancement to 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

It is recognized that the optimal treatment of patients with congenital and some acquired bleeding disorders involves the administration of specific clotting factor concentrates (plasma-derived or recombinant) *(53)*. Likewise, patients with immune deficiency disorders are best treated with industrially fractionated concentrates of immune globulins. However, access to these products in most LMIC is severely limited, even though these preparations are on the WHO Model List of Essential Medicines *(4)*. In the absence of clotting factor concentrates, replacement therapy for haemophilia A, von Willebrand disease and fibrinogen deficiency or dysfunction in many LMIC depends largely on the use of non-virus-inactivated cryoprecipitate produced domestically *(11, 54)*, while therapy of haemophilia B depends on the transfusion of plasma that is not virus inactivated. Most immunodeficient patients in LMIC receive no specific treatment for lack of access to any immunoglobulin concentrates *(55)*.

It is therefore an immediate priority to correct the supply problems existing in the treatment of bleeding disorders and immunodeficiency in LMIC. Additionally, it is vital to address the safety issues that accompany the currently limited treatment options available in those countries. Use of products that are made from poorly tested, non-virus-inactivated donations exposes many patients to a significant risk of acquiring transfusion-transmitted infections (HIV, hepatitis B, hepatitis C, and emerging infections such as West Nile virus, Zika virus or dengue) *(2, 11, 12)*. These issues can be addressed by implementation of efficient virus inactivation technologies that have been developed for plasma (as a therapeutic product or as a source for cryoprecipitate), cryoprecipitate itself *(12, 45, 53)*, and small-scale preparations of immunoglobulin concentrates *(56)*.

The availability of plasma, cryoprecipitate, cryoprecipitate-poor plasma and immunoglobulins subjected to established virus inactivation technologies preserving product efficacy can dramatically increase the clinical safety of locally produced plasma and plasma components. This strategy can provide improved therapy for a wide range of patients with bleeding disorders (haemophilia A, von Willebrand disease and fibrinogen depletion or dysfunction, haemophilia B) or immunodeficiency until clotting factor concentrates and immunoglobulins are available. The implementation of these technologies should follow a comprehensive assessment of the current domestic need for these products and the feasibility of providing them in a quality-assured system and on an appropriate scale *(2)*. Consequently, supplies of safer plasma, plasma components and immunoglobulins should be produced locally pending the availability of PDMPs generated by fractionation of domestic plasma *(57)*.

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

Preparation of virus-inactivated plasma, cryoprecipitate, cryoprecipitate-poor plasma and immune globulins depends first on separation of plasma from whole blood. After a careful assessment of the clinical needs in plasma for transfusion and plasma components at the domestic level, the government should take steps to ensure that sufficient infrastructural, financial and human resources are made available to the local blood establishments to promote plasma production. This financial support can assist blood establishments to purchase and operate the needed equipment for blood separation and storage of blood components and to initiate a progressive improvement in the supply, safety and quality of plasma and plasma components, including introduction of virus inactivation and removal methods and small-scale concentration of immune globulins. Such an action can be initiated in the most advanced blood establishments in the country and can then expand as needed to others based on the know-how existing domestically. In addition, recovered plasma that fails to meet freezing and storage standards for the production of coagulation factors can be used to produce stable proteins such as immunoglobulins and albumin *(3)*.

9.2.1 Transfer and implementation of validated virus inactivation technologies

Photochemical inactivation and solvent/detergent technologies are available that enable the preparation of pathogen-reduced single-unit plasma from whole blood or obtained by apheresis procedures *(58)*. Cryoprecipitate and cryoprecipitate-poor plasma can be prepared from such pathogen-reduced plasma following the standard procedures for cryoprecipitate production and isolation of the cryoprecipitate-poor supernatant plasma *(58)*. In addition, technologies are also available for the dedicated virus inactivation treatment of small-sized cryoprecipitate pools by solvent/detergent *(45, 53, 59)*, and of immunoglobulin concentrates from small-sized plasma pools by caprylic acid purification *(56, 60)*. The decision on the size of the pool should result from a risk assessment analysis taking into account all measures contributing to virus safety, including screening of donors, range and sensitivity of individual donation and pool virus testing, and the robustness of the virus reduction procedures to inactivate or remove viruses. Use of transferred virus inactivation technology should serve as an intermediate stage to ensure some access to treatment until PDMPs made from domestic plasma are available in sufficient quantities *(12, 29)*.

9.2.2 Stepwise measures to be taken

The following stepwise measures for blood establishments in LMIC are recommended, with the objective of progressively improving the availability of plasma and plasma components meeting the standards for optimally safe transfusion in patients in need of plasma-derived therapies.

- Ensure that the establishments involved in the collection, testing and processing of blood donations comply with internationally recognized GMP. In particular, put in place a blood donor screening and collection procedure, donation testing infrastructure, system of selection and validation of in vitro diagnostic tests and platforms, and traceability system in each participating blood establishment to guarantee that internationally recognized quality and safety requirements for blood donation are satisfied.

- Increase and improve the separation of whole blood into its components to generate an increasing volume of plasma that should be frozen (fresh frozen plasma) and stored following relevant local and international guidelines, under operational conditions to preserve its native quality, including the content in coagulation factors.

- Increase and improve the processing of individual fresh frozen plasma by applying rigorous thawing, centrifugation, freezing and storage procedures that enable preparation of single-donor native cryoprecipitate and single-donor native cryoprecipitate-poor plasma under conditions preserving the functional activity of coagulation factors, such as factor VIII, Von Willebrand factor, fibrinogen, and factor IX.

- Consistent with maintaining an adequate inventory of plasma components, consider introducing a quarantine period of three to six months for plasma, cryoprecipitate and cryoprecipitate-poor plasma so that regular repeat blood donors can undergo, when eligible for a subsequent donation, a new set of testing for viral markers. If the results for the viral markers are non-reactive, the plasma, cryoprecipitate, or cryoprecipitate-poor plasma produced from the previous donation can then be released for transfusion. If the donor does not return by the end of the quarantine period, the units should not be transfused, but can be repurposed for additional manufacturing into final products by methods that include virus inactivation (for example, fractionation or small-scale production of immunoglobulins). Although quarantine is hardly possible in LMIC with a low proportion of repeat tested donors, such a system, when fully operational, contributes to avoiding the risks of transfusing plasma or plasma components from donations that were collected previously in a window period of viral infection.

- When a quarantine is not technically feasible, consider a holding period of two weeks during which the blood establishments should store the plasma or plasma components. The objective of such a holding period is the retrieval of plasma or plasma components in instances where post-donation information would disqualify the donor.

- Consider the transfer of validated virus inactivation technologies of plasma, cryoprecipitate, and cryoprecipitate-poor plasma, and small pool size manufacturing methods of virus-inactivated plasma components such as cryoprecipitate and immunoglobulins in settings where commercial concentrates are unavailable or unaffordable.

- Consider the implementation of small facilities and of equipment for virus inactivation treatments of plasma, cryoprecipitate and cryoprecipitate-poor plasma.

- Expand the number of blood establishments able to prepare virus-inactivated plasma, cryoprecipitate, cryoprecipitate-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.

Balancing the pros and cons of the different models of plasma fractionation with the advantages and disadvantages of local preparation of safe blood products using virus inactivation technologies in existing blood establishments is a crucial exercise to perform after developing a national situational assessment. The best option needs to be realistic and sustainable in the present and future environment.

CHAPTER 10

CONCLUSION

There is tremendous wastage of plasma generated in LMIC that could be used to manufacture urgently needed PDMPs if standards for plasma quality were met. This guidance advocates and provides a roadmap for actions that can be taken to reduce this wastage of plasma in order to increase supplies of PDMPs in LMIC. The primary audience of the guidance consists of national regulatory authorities, blood collection organizations, blood donors and their associations, clinicians and patients. The main points communicated in the guidance are the following.

- Human plasma is a strategic resource that can be processed into over 30 unique therapeutic proteins used to treat various haematological and immunological disorders and specific infectious diseases.
- The WHO Model List of Essential Medicines includes several PDMPs (for example, normal immunoglobulins, coagulation factors VIII and IX, and anti-D immunoglobulin).
- PDMPs are produced by a complex industrial process called plasma fractionation, which requires large volumes of plasma that meet strict criteria for quality and safety.
- Plasma fractionation involves protein purification and dedicated virus inactivation and removal technologies. Many high-income countries have domestic access to these technologies or purchase PDMPs from abroad.
- The supply of PDMPs in LMIC is profoundly deficient relative to patient needs, reflecting both global shortages and the costs of PDMPs, and resulting in increased mortality, morbidity and higher health care expenses.
- To increase access to PDMPs through fractionation of domestically produced plasma, LMIC should first reinforce domestic infrastructures to collect blood or plasma from voluntary non-remunerated donors and to ensure its quality and safety through implementation of good manufacturing practices and effective regulatory oversight.
- While it is a prerequisite for the fractionation of domestic plasma, the implementation of good manufacturing practices in blood establishments will also enhance the quality and safety of blood components for transfusion, thereby improving patient care and lowering the risk of transfusion-transmitted infectious diseases.

- Improvement in the infrastructure and quality practices of blood collection requires local competent leadership and human resources, as well as initial financial support, but eventually will improve the effectiveness of the national blood service and ensure its sustainability.

- National regulatory authorities are a key stakeholder in ensuring the quality and safety of collected blood and plasma.

- Any programme to improve the volume and quality of collected blood and plasma needs to receive the support of domestic blood donor organizations.

- LMIC are strongly encouraged to monitor the clinical needs for blood and blood products at country level, and to promote proper education of clinicians on the evidence-based clinical indications for use of blood products.

- When such an assessment is made, stepwise measures should be taken to ensure a continuous increase in the volume of quality plasma suitable for fractionation.

- An intermediate option pending sufficiency of PDMPs reached through purchasing and fractionation of domestic plasma is the domestic manufacture of pathogen-reduced plasma or plasma fractions, such as cryoprecipitate and immunoglobulins, using validated methods. This approach should follow a comprehensive assessment of the existing needs for these products and of the feasibility of providing them in a quality-assured system and on an appropriate scale.

- Within a region, it is possible for multiple countries to combine their available volumes of plasma for fractionation if plasma quality standards are met in each country and mutual recognition of this practice is established among the relevant regulatory authorities.

- When the necessary volume of plasma meeting requirements for fractionation is reached, several options can be considered for production of PDMPs.

- One option is the implementation of a contract or toll plasma fractionation programme, whereby domestic plasma is fractionated abroad by a fractionator licensed in a foreign country and products are provided in return, according to predetermined terms.

- Another option is the construction of a domestic plasma fractionation facility, which should be operated under well defined conditions to ensure the quality and safety of the manufactured PDMPs. Careful planning is needed to ensure cost-effectiveness of this operation.

- Such capacity-building requires competent local leaders in transfusion medicine who should be closely associated with the decision-making process.

- A number of WHO guidelines, recommendations, and reports, including those referred to in this guidance, are already available to assist LMICs in improving access to PDMPs.

In conclusion, in the interest of public health, LMIC are encouraged to take gradual measures to increase access to vitally needed PDMPs by enabling fractionation of domestic plasma. This requires (a) recognition that plasma is a national resource that ethically and pragmatically should not be wasted; (b) taking concrete steps to improve and ensure the quality and safety of plasma both for transfusion and further manufacturing; and (c) establishing a contract with a foreign fractionator or developing a domestic fractionation facility.

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