Improving access to safe blood products through local production and technology transfer in blood establishments
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This project was developed by Dr Ana Padilla, Programme Manager, Blood Products and Related Biologicals, in the World Health Organization department of Essential Medicines and Health Products. The report was prepared by Dr Padilla with the collaboration of Dr Peter Page, Consultant, United States and Dr Thierry Burnouf, Human Protein Process Sciences, France.

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<td>API</td>
<td>active pharmaceutical ingredient</td>
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<td>BRN</td>
<td>Blood Regulators Network</td>
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<td>CAPA</td>
<td>corrective action preventive action</td>
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<td>CJD</td>
<td>Creutzfeldt-Jakob disease</td>
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<td>CMV</td>
<td>cytomegalovirus</td>
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<td>EBV</td>
<td>Epstein Barr virus</td>
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<td>EIS</td>
<td>electronic information system</td>
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<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>FFP</td>
<td>fresh frozen plasma</td>
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<td>F IX</td>
<td>factor IX (nine)</td>
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<td>F VIII</td>
<td>factor VIII (eight)</td>
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<td>GAP</td>
<td>Global Alliance for Progress</td>
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<td>GDP</td>
<td>gross domestic product</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HA</td>
<td>human albumin</td>
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<td>HAV</td>
<td>hepatitis A virus</td>
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<td>HBV</td>
<td>hepatitis B virus</td>
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<td>HCV</td>
<td>hepatitis C virus</td>
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<td>HEV</td>
<td>hepatitis E virus</td>
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<td>HGV</td>
<td>hepatitis G virus</td>
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<td>HIC</td>
<td>high-income countries</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>HSA</td>
<td>human serum albumin</td>
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<td>HTLV</td>
<td>human T-cell lymphotropic virus</td>
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<td>IBTO</td>
<td>Iran Blood Transfusion Organization</td>
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<td>ID</td>
<td>individual donation</td>
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<td>IG</td>
<td>immunoglobulin</td>
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<td>IM</td>
<td>intramuscular</td>
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<td>IRC</td>
<td>Indonesian Red Cross</td>
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<td>IT</td>
<td>information technology</td>
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<td>ITP</td>
<td>immune thrombocytopenic purpura</td>
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<td>IU</td>
<td>international unit</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<td>IVD</td>
<td>in vitro diagnostic devices or tests</td>
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<td>IVIG</td>
<td>IV immunoglobulin</td>
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<td>LMIC</td>
<td>low- and middle-income countries</td>
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<td>MCC</td>
<td>Medicines Control Council</td>
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<td>MIC</td>
<td>middle-income countries</td>
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<td>MoH</td>
<td>ministry of health</td>
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<td>MRB</td>
<td>Market Research Bureau</td>
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<td>NAT</td>
<td>nucleic acid techniques</td>
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<td>NBI</td>
<td>National BioProducts Institute</td>
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<td>NRA</td>
<td>national regulatory authority</td>
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<td>PCC</td>
<td>prothrombin complex concentrate</td>
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<td>PDMP</td>
<td>plasma-derived medicinal products</td>
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<td>PID</td>
<td>primary immune deficiency</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
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<td>R&amp;D</td>
<td>research and development</td>
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<td>SAHF</td>
<td>South African Haemophilia Foundation</td>
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<td>SANBS</td>
<td>South African National Blood Service</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<tr>
<td>TT</td>
<td>transfusion transmitted</td>
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<tr>
<td>TTI</td>
<td>transfusion-transmitted infection</td>
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<tr>
<td>TSE</td>
<td>transmissible spongiform encephalopathy</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>vCJD</td>
<td>variant Creutzfeldt-Jakob disease</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WNV</td>
<td>West Nile virus</td>
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Glossary

The definitions given below apply to the terms used in this report. They may have different meanings in other contexts.

**Albumin:** A plasma-derived medicinal product used for patients needing protein or volume replacement.

**Apheresis:** The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/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 collection:** A procedure whereby a single donation of blood is collected in a sterile receptacle containing anticoagulant and/or stabilizing solution, under conditions designed to minimize microbiological contamination, cellular damage and/or coagulation activation.

**Blood component:** A constituent of blood that can be prepared under such conditions that it can be used directly (or after further processing) for therapeutic applications. The main therapeutic blood components are red blood cell concentrates, platelet concentrates, plasma for transfusion, and cryoprecipitate.

**Blood establishment:** Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components when intended for transfusion or further industrial manufacturing. It encompasses the terms ‘blood bank’, ‘blood centre’, ‘blood service’ and ‘blood transfusion service’.

**Blood product:** Any therapeutic substance derived from human blood, including whole blood, blood components and plasma-derived medicinal products.

**Closed system:** A system developed for aseptic collection and separation of blood and blood components, manufactured under clean conditions, sealed to the external environment and sterilized by a validated and approved method.

**Cryoprecipitate:** A single-donor or small pool therapeutic plasma fraction obtained by thawing frozen plasma at 2–4°C and used to treat factor VIII, Von Willebrand factor, or fibrinogen deficiencies.

**Cryosupernatant:** A single-donor therapeutic plasma supernatant fraction obtained after removal of cryoprecipitate, used to treat deficiencies in vitamin K-dependent plasma factors (e.g. Factor IX). Also called cryo-poor plasma.
**Donor:** A person in defined good health conditions who voluntarily donates blood or blood components, including plasma for fractionation.

**Factor VIII:** Blood coagulation factor VIII, deficient in patients with haemophilia A. Also called ‘antihaemophilic factor’.

**Factor IX:** Blood coagulation factor IX, deficient in patients with haemophilia B.

**First time (tested) donor:** A donor whose blood or plasma is tested for the first time for infectious disease markers in a blood establishment.

**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 and/or chromatography), purification steps (typically ion-exchange or affinity chromatography) and one or more steps for the inactivation or removal of blood-borne infectious agents (most specifically viruses and, possibly, prions).

**Fractionator:** A company or an organization performing plasma fractionation to manufacture plasma-derived medicinal products.

**Good manufacturing practice (GMP):** 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. GMP is concerned with both production and quality control.

**Hepatitis A virus (HAV):** A non-enveloped, single-stranded RNA virus, causative agent of hepatitis A.

**Hepatitis B virus (HBV):** An enveloped, double-stranded DNA virus, causative agent of hepatitis B.

**Hepatitis C virus (HCV):** An enveloped, single-stranded RNA virus, causative agent of hepatitis C.

**Human immunodeficiency virus (HIV):** An enveloped, single-stranded RNA virus, causative agent of acquired immunodeficiency syndrome.

**Immunoglobulin:** Also known as ‘immune globulin’ or ‘gamma globulin’. 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 (e.g. rabies, tetanus, hepatitis B or Rh factor).
**Incidance:** The rate of newly-acquired infection identified over a specified time period in a defined population.

**Know-how:** A set of information in the form of unpatented inventions, formulae, designs, drawings, procedures and methods, together with accumulated skills and experience in the hands of a licensor firm’s professional personnel, which could assist a transferee/licensee of the object product in its manufacture and use and bring to it a competitive advantage. It can be further supported with privately maintained expert knowledge on the operation, maintenance, use/application of the object product and of its sale, usage or disposal.

**Look-back:** A procedure to be followed for recipients (or donors) when a donation from a high-risk donor that should have been excluded from processing is identified retrospectively.

**Manufacture:** All operational processes or steps – including purchase or selection of materials and products, production, quality control, release, storage and distribution of products and the related controls – used to produce a blood product. This also includes the donation process.

**National Regulatory Authority (NRA):** WHO terminology to refer to national medicines regulatory authorities. NRAs should promulgate and enforce medicines regulations.

**Nucleic acid amplification techniques (NAT):** A testing method to detect the presence of a targeted area of a defined microbial genome that uses amplification techniques such as polymerase chain reaction.

**Plasma:** The liquid portion remaining after separation of the cellular elements from blood, collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood.

**Plasma for fractionation:** Recovered (or apheresis) plasma used for the production of PDMP.

**Plasma for transfusion:** Plasma (from whole blood or apheresis) used for direct infusion into patients without prior fractionation step. It can be subjected to treatment to inactivate pathogens.

**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 and/or raw material for the manufacture of sub-intermediate or intermediate plasma fractions, constituents of the excipient and active substance(s), which are part of a medicinal product.

**Plasmapheresis:** Also known as apheresis and used for the collection of plasma (see above).
Plasma-derived medicinal products (PDMP): A range of medicinal products obtained by the fractionation process of human plasma. Also called plasma derivatives, plasma products, or fractionated plasma products.

Prevalence: The rate of infection identified, including both past and present infections, at a specified point in time in a defined population.

Prion: The infectious particle associated with transmissible spongiform encephalopathy (TSE). It is believed to consist only of protein and to contain no nucleic acid.

Recovered plasma: Plasma recovered from a whole blood donation and used for fractionation into PDMP.

Source plasma: Plasma obtained by apheresis for further fractionation into PDMP.

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 NRA.

Traceability: Ability to trace each individual unit of blood or blood component derived thereof from the donor to its final destination, whether this is a recipient, one or more batches of medicinal product or disposal. The term is used to describe forward tracing (donation to disposal) and reverse tracing (disposal to donation).

Viral inactivation: A process of enhancing viral safety in which a virus is intentionally ‘killed’.

Viral removal: A process of enhancing viral safety by removing or separating the virus from the protein(s) or plasma fraction of interest.

West Nile virus (WNV): An enveloped single-stranded RNA virus, causative agent of West Nile fever.

Window period: The time interval from when a person becomes infected with an agent and the time when a blood sample from that person first yields a positive result in a test for that agent (or corresponding antibodies). A blood donation during this period can transmit infection to the transfusion recipient. NAT shortens this period compared to serological testing.
Executive summary

This report presents an overview of activities undertaken by the World Health Organization (WHO) to assess the need to support local production of quality recovered plasma by blood establishments in low- and middle-income countries (LMIC), so that it can be used as an active pharmaceutical ingredient (API) and improve access to safe blood products. The report identifies needs and analyses the challenges and opportunities faced by LMIC to improve production standards in their blood establishments. Relevant findings have been obtained through scientific publications, visits to selected regions and countries, questionnaire-driven criteria and a workshop where major stakeholders gathered and discussed the current status and ways to move forward. This action is in line with the objectives of World Health Assembly resolution WHA63.12,\(^1\) which supports access to quality, safe blood products at the global level.

Blood products include not only blood and blood components produced as single-donor products for direct transfusion (i.e. red blood cells, platelets and plasma), but also, plasma-derived medicinal products (PDMP) (e.g. albumin, polyvalent and specific immunoglobulins, and blood coagulation factors, among others) that are manufactured from pools of thousands of plasma units at an industrial level. In high-income countries (HIC), the use of each unit of whole blood collected is optimized by separation into therapeutic blood components to support the concept of selective component therapy, based on the therapeutic needs of the patient. Plasma can be used directly for transfusion, or further manufactured into therapeutic plasma proteins, thereby serving the therapeutic needs of specific patients in an optimal fashion. Conversely, access to safe and essential blood products made from voluntary non-remunerated whole blood donations is a major challenge in LMIC, where local quality and safety standards in the production of blood products need to be strengthened in blood establishments and blood resources optimized.

Resolution WHA63.12, adopted in May 2010, addresses availability, quality and safety of blood products. It points out that a large percentage of human plasma, separated from whole blood, is discarded in most LMIC. This wastage occurs in large part because appropriate standards and technology to ensure required freezing and cold storage conditions, traceability of donors, testing to lower the residual viral risk, regulatory controls, quality systems and good manufacturing practices (GMP) are lacking. Deficient systems and documentation render the plasma unsuitable for production into fractionated medicinal products and lead to its destruction, which is not only unethical but also a waste of valuable human resources. There is a need therefore to build local capacity for production of plasma that is suitable for fractionation as an API in LMIC. Such a programme will enhance the quality and safety standards of the blood collection and provide the opportunity for access to needed plasma derivatives in LMIC.

\(^1\) See: http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-P2-en.pdf
A sufficient supply of safe blood products at the national level begins with and depends upon acceptable quality standards for blood collection. Improving production standards in blood establishments also dramatically enhances the safety and effectiveness of red cells and platelets, which are of key importance in primary health care. Improvement in quality standards, know-how and production processes in blood establishments therefore directly contribute to reducing the rate of transmission by transfusion of blood-borne infectious diseases. Furthermore, improving access to safe blood products in LMIC is key to accelerating progress on reducing childhood mortality, improving maternal health, treating trauma, and combating AIDS, malaria and other disorders requiring transfusion. A further public health benefit is an accurate identification of trends in prevalence and incidence of infectious disease markers among blood donors, which reflects the epidemiological status of the population as a whole.

This report examines the volume of plasma separated from whole blood that is currently wasted worldwide and identifies challenges and opportunities and the key steps needed to improve the situation. Evidence reveals that a substantial and increasing volume of recovered plasma potentially available in LMIC is currently wasted. This volume has been estimated, based on the global number of whole blood donations and volume of recovered plasma currently used for direct transfusion or for fractionation, to be close to 9.3 million litres each year. This corresponds to more than 40% of the world resources in recovered plasma, and represents a market value of about US$ 650 to US$ 1020 million (based on a price range of US$ 70 to US$ 110 per litre). This plasma could generate life-saving plasma derivatives with a market value of US$ 2.5 billion. The volume of wasted plasma is expected to increase as the volume of blood collected to meet the needs for red cells – the primary determinant of the amount of whole blood to be collected – is increasing and blood component therapy is developing strongly, supported by decades of clinical data from HICs. The challenge now is to support LMIC in improving the quality of the blood they collect, by increasing investment and knowledge in improving production standards and regulatory oversight in blood establishments, while emphasizing the impact that such a move will have on public health. Better quality blood products, through focused technology transfers that ensure GMP production of plasma, also mean a better chance of preventing transmission of infectious diseases and spread of emerging pathogens via blood in the world. To invest in improving local production standards in blood establishments of countries currently discarding large volumes of plasma is a means to improve access to essential PDMP as well as to invest in improving public health of the national and worldwide population.

To assemble evidence of the challenges and drivers of technology transfer and local production in blood establishments and the benefits that arise from this, WHO convened a stakeholders’ workshop in Geneva on 14–15 June 2012. Participants included representatives of National Regulatory Authorities (NRAs), blood collection organizations, patient organizations, national blood...
programmes, plasma fractionators, members of the WHO Blood Regulators Network (BRN), nongovernmental organizations, public health agencies and funding agencies. The steps proposed will have multiple benefits, at national, regional and global levels. They include strengthening local production capacities in blood establishments in countries currently discarding plasma, through transfers of technologies and know-how required, and building of technical capacity and expertise of NRAs in the whole blood area. The results of the information collated and the stakeholders’ views on the approaches taken in various countries are presented in this report.

The need to upgrade standards for local production of plasma for fractionation in blood establishments was unanimously and overwhelmingly endorsed. Cost-effectiveness analyses of investments needed were also considered. Cost benefits in production of plasma for fractionation and production of PDMP were highlighted, based on successful examples already in place in some LMIC. Prioritization of activities, development of metrics and milestones to assess progress, cooperation with other stakeholders, and financial support will all be key.
1. Introduction

*Improving access to safe blood products: a framework to improve public health*

The major objective of this initiative is to conserve human plasma that is currently discarded in many parts of the world and to improve access to essential medicines for people in low- and middle-income countries (LMIC). Recognition that human plasma is an active pharmaceutical ingredient (API) for preparing essential medicines and that many nations are unable to supply essential medicines prepared from plasma is critical to this objective. Recovering this plasma and transforming it into essential medicines would meet a major unmet health need. Two other objectives will be achieved if currently discarded plasma can be brought up to the world standard for fractionation into essential medicines: 1) Upgrading blood establishments to manufacture fractionation-grade plasma will also improve their capability to provide all blood components of higher quality and safety; and 2) Upgrading blood establishments to the status of good manufacturing practices (GMP) compliance in the collection of plasma will help avoid the ‘tainted blood’ tragedies of the 1980s that transpired when virus-contaminated blood was transfused and/or used as starting material for plasma products.

**Blood for transfusion and blood for manufacture**

Blood is a precious human resource that has been transfused for decades. However it has become increasingly important to separate the manufacturing aspect of blood preparation from the hospital transfusion service aspects of compatibility testing and infusion. Blood is a medicine. The blood donor, in addition to being a valued volunteer, is also the source of a ‘raw material’ (Figure 1).

*Figure 1. Manufacturing steps and blood transfusion process*
The process of manufacturing blood begins with screening and selection of the safest possible raw material (donation) and progresses through a variety of manufacturing steps that include separation, testing, labelling, shipping and storage. Each step, and indeed the entire process, must be carried out by personnel, in facilities, and according to operating procedures that meet current GMP.

When a tube of blood is spun in a centrifuge, the heavier red cells (also known as erythrocytes), which give blood its red colour, sediment to the bottom of the tube and the liquid portion of blood, the straw-yellow plasma, remains at the top (Figure 2). Other cells, such as white cells (or leukocytes) and platelets, are located at the interface of the red cells and plasma. Plasma represents about half of blood volume. Blood for transfusion is collected as ‘whole blood’ into a series of sterile, interconnected plastic bags. When whole blood is spun in a centrifuge, the red cells and plasma can be divided into separate components. Both components are suitable for transfusion. However in most parts of the world, more units of red cells than plasma are transfused and the unused plasma is rapidly frozen and sent to manufacturing plants where it is fractionated into biological medicines.

Figure 2. Separation of blood into blood cells and plasma by centrifugation
What is blood plasma?

Plasma is the liquid portion of blood. Of the usual 500 ml of blood collected from a donor, about 230 ml of plasma is generated into a separate plasma bag. This is often referred to as ‘fresh frozen plasma’ when it is frozen for transfusion purposes, and if it is sent to fractionation plants, it is referred to as ‘recovered plasma’ or ‘plasma for further manufacture’. Plasma may also be collected directly from donors by apheresis (‘source plasma’). Human blood plasma contains more than 1000 proteins and more than 250 of these have been well characterized. There are more than 100 licensed assays to identify these proteins and numerous international standards and reference preparations. More than 30 commercial preparations of blood protein concentrates are available as medicinal products; most are expensive and some are in short supply. New candidate therapeutics are identified almost every year. Several of these plasma protein concentrates have been identified as essential medicines by the World Health Organization (WHO). These include clotting factor concentrates to treat haemophilia and gamma globulin preparations to treat immunodeficiencies and several specific infectious exposures such as tetanus and rabies, or anti-Rho (D) for the prevention of the haemolytic disease in newborns (1).

Unmet needs

In LMIC economies, additional plasma for fractionation is needed to generate essential plasma-derived medicines (clotting factors and immunoglobulins). National and global sufficiency in plasma products can be achieved only by reducing wastage of non-transfused plasma. An estimated 21.6 million litres of plasma could be recovered from whole blood collections each year. Of this volume, an estimated 4.2 million units are transfused and an estimated 8.1 million units are sent for fractionation. This leaves an estimated 9.3 million litres that are discarded annually. The majority of patients in LMIC with clotting disorders, immunodeficiencies and autoimmune disorders do not currently have adequate access to treatment. Well documented data from the World Federation of Haemophilia indicate that patients with haemophilia in these countries are undertreated, many are untreated and many more are as yet undiagnosed. To some extent, definitive diagnoses are not even pursued because specific treatment is not available. The numbers of untreated or undertreated patients with immunodeficiencies do not currently have adequate access to treatment. Well documented data from the World Federation of Haemophilia indicate that patients with haemophilia in these countries are undertreated, many are untreated and many more are as yet undiagnosed. To some extent, definitive diagnoses are not even pursued because specific treatment is not available. The numbers of untreated or undertreated patients with immunodeficiencies and autoimmune disorders do not currently have adequate access to treatment. Well documented data from the World Federation of Haemophilia indicate that patients with haemophilia in these countries are undertreated, many are untreated and many more are as yet undiagnosed. To some extent, definitive diagnoses are not even pursued because specific treatment is not available. 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The unmet need in red blood cells for transfusion in LMIC will increase the number of whole blood donations, generating more plasma that could be used for fractionation, but which, under present conditions, would be discarded. WHO data (2) indicate that in many low-income economies, fewer than 5 units of blood are collected per 1000 inhabitants each year. Even in middle-income
countries (MIC), fewer than 10 units per 1000 inhabitants are collected. In high-income countries (HIC), the number is 30 units per thousand population. No one knows the ideal number of red cells per capita, but to satisfy the most essential need for red cells (for anaemia related to malaria, to prevent women in childbirth from fatal haemorrhage and for managing trauma) some 15 units per thousand inhabitants is estimated to be the basic number that needs to be collected. It is certain that the number of blood collections will rise in LMIC, mirroring increases in the developed world. In the United States, red cell collections increased 40% between 1994 and 2008, the last year for which complete data are available. Furthermore, the lack of appropriate technology means that in LMIC far more blood is transfused as whole blood than in HICs. If a higher proportion of the blood collected in LMIC were separated into components, millions of additional plasma units would be generated, which under current conditions are discarded. This is a human tragedy, an economic misfortune, and since these biological materials are often inadequately destroyed, an environmental calamity.

Conserving recovered blood plasma

If recovered plasma is to be conserved in LMIC, manufacturing practices and quality systems have to be improved along the entire manufacturing process, from the initial selection of the donor to the final shipment of the plasma to fractionators. A 2010 report by the WHO Secretariat recognized this:

“...a large percentage of the plasma collected in developing countries is categorized as waste material and destroyed. This wastage occurs because appropriate technology, regulatory controls, quality systems and good manufacturing practices are all lacking, thereby rendering the plasma unsuitable for conversion into fractionated medicinal products.

The facilitation of collaboration between developing and developed countries through appropriate regulatory standards and transfer of technology is a vital part of a global approach.”

Blood should be seen as a manufactured product. Implementation of GMP is critical and requires that blood establishments separate medical functions from manufacturing activities (e.g. plasma for fractionation). Current GMP addresses these activities (collection, testing, storage, processing, labelling and distribution) of the blood establishment. Testing of the finished product alone is not enough. Such testing does not address emerging infectious agents, variations in the existing agents (e.g. human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV, respectively)) that are not detected by current assays, and variations in quality of the proteins in the plasma. The process should be controlled from start to finish, as is required for the manufacture of other medicines.

**Why does WHO focus on recovered plasma?**

WHO does not collect, prepare or distribute plasma. The organization has a responsibility to assist countries to make best use of recovered plasma to generate essential medicines. Following the 1975 World Health Assembly resolution WHA28.72, which established the principle of nationally supported, managed and coordinated blood systems, a series of WHO initiatives (including the responsibility for developing standards for medicinal proteins and for in vitro diagnostic tests (IVD)) have been promulgated. These initiatives aim to improve public health through development of a safe donor pool and high quality blood establishments complying with GMP, increasing the supply of high quality plasma, increasing the supply of essential medicines derived from plasma, and assistance in the development of government bodies, such as inspectorates and regulatory agencies to improve blood quality. The latest resolution WHA63.12 on availability, safety and quality of blood products (2010), (3) tasks WHO to improve availability of safe blood products for patients, raise the quality standards in blood establishments, reduce the risk of transmission of infectious diseases, and enforce implementation of blood products regulations. WHO has produced technical documents that address plasma fractionation and implementation of GMP in blood establishments through the WHO Expert Committee on Biological Standardization and has established a Blood Regulators Network (BRN) to support the organization in enhancing NRAs in the blood area. WHO makes available guidelines and physical standards to improve biological products derived from blood. WHO is well positioned and should be adequately resourced to assist developing countries as they strive to make optimum use of recovered plasma and provide access to essential medicines. Furthermore, GMP-compliant blood facilities are ideally positioned to generate both products and data to further advance public health in these countries.

In summary, plasma product demand in the world is increasing and will expand significantly in the coming decades as will the need for related essential medicines. The availability of plasma protein therapeutics in developing countries is currently inadequate and much of the blood collected is either not processed to generate plasma, or the plasma generated is of such low quality as to make it unusable for fractionation and production of biological medicines. This plasma is currently discarded, a human tragedy and an economic calamity. LMIC will collect increasing volumes of whole blood and recovered plasma. Strengthening GMP should conserve discarded plasma, supply therapeutics and improve blood safety. Adequate treatment of haemophilia, immunodeficiencies, and an increasing number of diseases will require additional raw material (‘safe plasma’).
Lack of access to safe and effective plasma-derived medicinal products: economic and public health impact

The major conditions requiring treatment with PDMP are haemophilia A and B (FVIII and FIX deficiency, respectively) and the primary immunodeficiencies (PID). But other conditions also require PDMP, e.g. Von Willebrand disease, rare bleeding disorders, alpha 1-antitrypsin deficiency, Guillain Barré syndrome, immune thrombocytopenic purpura (ITP) and hereditary angioedema. Plasma-derived FVIII for haemophilia A, prothrombin complex concentrate (PCC) for haemophilia B and other factor deficiencies, and immunoglobulins (IG) for immunodeficiencies are on the WHO Model Lists of Essential Medicines (1).

It is estimated that there are 400 000 to 600 000 people with haemophilia worldwide, but only 162 781 have been diagnosed. The majority are not diagnosed due to the lack of availability of coagulation screens and factor assays, which are not difficult laboratory tests. To some extent, the incentive to diagnose these patients is reduced by the fact that treatment may not be available. Treatment consists of replacement of the missing clotting factor: FVIII or FIX. While recombinant FVIII and FIX have become available in developed countries, patient needs for FVIII and FIX are not being met in LMIC, where there is still a need for more PDMP. Recombinant clotting factors are being produced in increasing quantities, but for the foreseeable future, plasma-derived proteins remain a safe and largely more affordable alternative.

Treatment of haemophilia with factor concentrates is required as a minimum for life- or limb-threatening bleeding episodes and for surgery. While treatment with plasma or cryoprecipitate is also possible, safety cannot be assured. The optimum is prophylactic treatment to prevent joint damage, morbidity and mortality. If untreated, death often occurs in childhood. Lack of treatment also results in crippling arthropathy. Treatment with unsafe products risks HIV and hepatitis infection. Children who do not have access to treatment are generally unable to complete education due to frequent severe bleeding episodes, and this will constrain their ability to gain employment, raise and support a family and contribute fully to society. Whatever the level of treatment product availability in a country, use should be planned on a national basis.

For haemophilia A, 1 to 2 international units (IU) of FVIII per capita is needed for survival, 3 IU for functional independence (but still with joint damage), and up to 6 IU for maintenance of joint integrity. For PID 0.4 g/Kg IG monthly is a reasonable goal, with 1.0 g/Kg monthly being optimal. For haemophilia, there is great disparity in usage among countries, with HICs averaging 5 IU per capita, upper middle-income countries 1.4 IU per capita, and low-income countries only 0.02 IU per capita. Similarly there is great variation in IG usage, but, as yet, there is little data from developing countries.

Demand for plasma-derived FVIII has increased moderately (the increase constrained by availability of recombinant FVIII); demand for albumin has also increased moderately, but the demand for IG therapy has greatly increased
and is now the driver of plasma fractionation (as opposed to it being FVIII in the 1980s) in HICs. The great majority of plasma being fractionated comes from North America and Europe, less from Asia and very little from Latin America and Africa (4).

PID occurs in people born with failed immune systems, as a genetic defect that can vary in severity. There are over 250 different specific PIDs, with antibody deficiencies being the most common (65%); these require lifelong regular treatment with IG. There is usually a delay in diagnosis, with average age at diagnosis being seven. Over 75% do not have access to appropriate therapy. It is thought that a majority of the potentially 1.4 million people living with a PID require IG therapy. There are also a large number of patients who have acquired immunodeficiencies, such as patients who are treated for cancer and those who undergo bone marrow transplantation. A recombinant product is not an option for patients with primary PIDs or acquired immunodeficiencies since the broad spectrum of natural antibodies as found in plasma is required.

Without treatment, patients with PID have constant life-threatening or life-impairing infections with consequent long-term damage. If they survive, they have severe restrictions on activities and quality of life. Without treatment, health is assessed as good, or better than good, in only 16% of patients, but after diagnosis and treatment, it is good or better in 66%. 4

The ultimate objective of replacement therapy is to have a sufficient quantity of factor concentrate available to each person with haemophilia, or IG to each person with PID, to allow them to normalize their quality of life, achieve their potential with regard to education, employment and family, and take a full and active role in society.

The majority of patients with haemophilia or PID do not currently have adequate access to treatment, and the numbers of these patients being diagnosed are increasing. The future availability of longer-lasting recombinant FVIII/FIX should lower prices of current recombinant factors, which may depress demand and price for plasma derived FVIII/FIX in HICs and may limit production and plasma collection even more, a highly undesirable outcome for LMIC.

In conclusion, there is a need for increased global plasma fractionation into PDMP, enhanced regulatory capacity in developing countries to make the best use of recovered plasma, improved and optimized yields in plasma fractionation, and recognition that supply has become a safety concern, in addition to the more appreciated risks of HIV and hepatitis transmission. Plasma is a precious resource, and data indicate that demand will only grow, so safe plasma must not be discarded or wasted.

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4 Personal communication, Johan Prévot, International Patient Organisation for Primary Immunodeficiencies.
World Health Assembly resolution on availability, safety and quality of blood products

Resolution WHA63.12 on Availability, Safety and Quality of Blood Products (3) expresses concern about the unequal access globally to blood products, particularly PDMP, leaving many patients in need of transfusion and with severe congenital and acquired disorders without adequate treatment. The resolution also expresses concern that in developing countries, blood component separation technology and fractionation capacity are lacking, and that, because of insufficient regulatory controls and failure to implement appropriate practices in blood establishments, plasma from developing countries is often unacceptable for contract fractionation, with considerable wastage of plasma as a result.

To understand the importance of good practices and regulatory control, recent history is informative. The invention of technologies for blood transfusion and preparation of plasma derivatives were monumental achievements that dramatically improved prognosis and quality of life for patients with haemophilia and immunodeficiency disorders. There was little initial worry about potential risks because absence of treatment condemned these patients to disability or death. But the industrialized countries learned a painful lesson in the years following the early 1980s, when tens of thousands of patients were infected by blood products contaminated with HIV, HBV or HCV. This disastrous experience led to extensive efforts to improve practice and technology, and introduction of strict regulatory control. Certain viruses, particularly HIV, HBV and HCV, may initially elicit few or no symptoms, but persist in the body and circulate unnoticed in the bloodstream for a long time, before severe late stage illness such as AIDS, cirrhosis or cancer of the liver may develop. Infected individuals may feel well and fit for blood donation, even though they carry pathogens in their blood.

Therefore careful donor selection, including demographic screening, detailed interviews to disclose risk factors, and testing blood specimens for virus markers are crucial for blood product safety. Only meticulous screening of each donation reduces the risk of viral contamination of the starting material for plasma products. Virus reduction steps downstream during production are a further important contribution to safety, but they cannot replace meticulous donor screening. Furthermore, it is generally accepted that testing of final plasma products adds little to overall product safety. In order to ensure acceptable quality and safety of plasma for fractionation, it is of crucial importance to establish and maintain GMP throughout the entire production chain. This means a comprehensive well planned and controlled system covering blood donor criteria and testing to avoid blood donations contaminated with pathogens, particularly dangerous viruses, as well as manufacturing steps, preserving the integrity of labile proteins such as coagulation factors, e.g. maintenance of adequate cold chain during storage and shipment of plasma.
Crucial elements of plasma systems include adequate premises and equipment, appropriate training of staff, a functioning quality system and implementation of GMP at all stages of production (Figure 3). The specificity and sensitivity of IVD is intrinsically linked to the effectiveness of donor screening. Establishing, implementing and maintaining an adequate plasma system requires sustained efforts, commitment and substantial investments. Experience in industrialized countries has shown repeatedly that an adequate legal framework with government recognition and enforcement by stringent regulatory controls are of fundamental importance. Plasma will not be acceptable as starting material unless international standards of quality and safety are ensured by official control. Thus, any attempts to enhance the quality standards of plasma will be jeopardized if the system lacks regulatory stringency.

Resolution WHA63.12 (3) 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, and to update their national regulations accordingly. Member States are urged to establish quality systems, GMP for the production of PDMP and appropriate regulatory control, including the use of IVD to prevent transfusion-transmissible diseases with the highest sensitivity and specificity. In this context, resolution WHA63.12 calls on Member States to build human resource capacity through the provision of initial and continuing training of staff, and to enhance the quality of evaluation and regulatory actions in the area of blood products and associated medical devices, including IVDs. Resolution WHA63.12 requests that WHO guides Member States to meet internationally recognized standards in updating their legislation, national standards and regulations for effective control of the quality and safety of blood products and associated medical devices, including IVD. WHO is requested to advise and build capacity in Member States and to augment the support offered to Member States for developing and strengthening their NRAs and control laboratories. Further requests are to ensure sustainable development and provision of international biological reference materials5 (WHO International Standards) for use in the quality control and regulation of blood products.

and related IVD, and to develop, provide and disseminate guidance and technical support. There are already a number of important WHO guidance documents available, e.g. *WHO Recommendations for the production, control and regulation of human plasma for fractionation and WHO Guidelines on good manufacturing practices for blood establishments, assessment criteria for national blood regulatory systems.*

Nevertheless, further intensive and sustained efforts and financial resources will be needed in order to achieve the objectives of resolution WHA63.12. This will be a worthwhile investment, since reaching the goal of improving availability, safety and quality of blood products will be a major contribution to global public health.
2. Project objectives and activities

The aim of the current project was to analyse main challenges and opportunities and make recommendations to improving production of plasma as an API in LMIC and thereby increase access to safe blood products. It also aimed to identify main requirements to allow effective technology and know-how transfer into blood establishments for the local production of recovered plasma to be used as an API for the manufacture of PDMP.

Activities undertaken encompass an overview and analysis of the current landscape of quality standards for the production of recovered plasma in blood establishments and of the steps needed to implement successful transfer of technology programmes.

The ultimate goals are to:

a. reduce wastage of recovered plasma;
b. improve availability of safer blood components;
c. increase availability of plasma derivatives in LMIC; and
d. ensure a cost-effective approach through this process.

Activities

1. Conduct a survey of LMIC to determine amounts of plasma wasted and potentially available for fractionation.
2. Conduct an analysis of the main technological gaps that preclude the use of plasma from LMIC as an API for the production of PDMP.
3. Analyse the global trend of technology transfer and local production for plasma products in LMIC, with specific country examples.
4. Assess opportunities for and barriers to technology transfer and local production of plasma products.
5. Conduct a stakeholder workshop to identify opportunities and challenges faced by LMIC to secure access to safe blood products and to review technology transfer for local manufacturing capacity of plasma products.
6. Compile evidence and stakeholder opinion on technology transfer and local production.
7. Collate and synthesize all data into a summary report, generating points for consideration on the ways forward.

Methodology

Evidence was gathered and collated through a combination of available WHO information sources, a literature review and internet surveys, interviews with suppliers and recipients of technologies, and visits to selected countries based on questionnaire-driven criteria, to understand the technological gaps and define the main needs for technology transfer in production of plasma and
improved supply of plasma products. For all Member States, demographics in relation to blood collection based on population and donation rates were reviewed. On that basis, countries were identified in each region that would be able to provide at least 10 000 litres of plasma for fractionation annually. A high level questionnaire was then sent to selected countries to verify the volume of plasma that would actually be available for fractionation.

The purpose of the analysis was to describe drivers, barriers and trends, with the goal to provide an evidence-based reference for decision-making in future technology transfers regarding plasma products.

Three different questionnaires were developed, one each for:

- blood collection organizations in LMIC not producing plasma for fractionation;
- blood collection organizations in LMIC producing plasma for fractionation; and
- selected suppliers of technology for collection of plasma for fractionation and/or manufacture of plasma products.

Questions included reference to the current number of whole blood collections, volume of plasma not used for transfusion and discarded, quality assurance programmes in the blood establishment, viral marker rate in donors, examples of transfer of technologies to blood establishments, and perceived challenges.

A broad review of cases was undertaken and included both north–south and south–south cooperation and technology transfers conducted in the past two decades. Successful cases of technology transfer were identified and included in this report. This is thought to represent a comprehensive analysis of all the technology transfers to LMIC that have taken place over the past two decades. The reasons for potential failures in transfer of technology attempts were identified.

In addition, WHO organized a stakeholder workshop on 14–15 June 2012 to discuss the need to support local production of plasma API in blood establishments, in particular in countries with larger populations, and the experiences of transfers of technology and local manufacturing in LMIC.

Findings from the analysis of case studies of technology transfer from manufacturers were presented. During the workshop manufacturers, regulators, patient organizations and public sector agencies, as well as national blood programmes, were invited to present their experiences with, and views on, technology transfer for the production of blood products meeting internationally agreed standards.
3. Volumes of recovered plasma wasted in the world

An estimate was made of the volume of plasma wasted in the world that would be potentially available for fractionation. This calculation was based on an estimate of the total number of whole blood donations of about 92 million in 2008 worldwide (2). This number translates to a total volume of blood collected annually close to 39.1 million litres, based on a mean volume close to 425 ml of blood per donation. Assuming a conservative haematocrit of about 55%, this volume can yield, if separated into blood components, about 21.6 million litres of plasma each year. Market studies allow estimating that about 4.2 million litres are currently used for direct plasma transfusion and 8.1 million litres for fractionation (4).

The above estimates suggest that about 9.3 million litres of recovered plasma are wasted each year. It is a critical embarrassment to the world that such valuable voluntary-donated plasma resources are discarded while essential medicines that can be derived from plasma are in short supply. There is an ethical responsibility and financial value in using these donations effectively to produce essential plasma products. Such wasted plasma has a market value of US$ 650 to US$ 1020 million, based on the current cost of recovered plasma that ranges from US$ 70 to US$ 110 per litre. If the wasted plasma were of sufficient quality to comply with the standards for fractionation, this volume of plasma would result in about 1.4 billion IU of FVIII at a mean recovery of 150 IU/l (representing a mean minimal market value of US$ 400 million based on a conservative price of US$ 0.3/IU of FVIII). This quantity of FVIII would allow an additional 70 000 children with haemophilia A to be treated each year, based on an annual use of 20 000 IU shown in several on-going clinical studies done in LMIC to stop spontaneous haemorrhages and to introduce low-dose prophylaxis, a treatment that significantly reduces major joint impairments and musculoskeletal damages.

In addition, the same volume of plasma can generate an additional 2.3 billion IU of FIX at a mean recovery of 250 IU/l (representing a mean value of US$ 920 million calculated at a price of US$ 0.4/IU of FIX). This quantity, if made available, would permit the treatment of an additional 57 500 children with haemophilia B each year, assuming an annual consumption of 40 000 IU/year/patient, which is adopted for medium dose prophylaxis, and greatly reduces the risk of haemorrhages in patients and therefore hospitalization, musculoskeletal damages and disability. Alternatively, 3.2 billion IU of prothrombin complex concentrate (PCC) (US$ 970 million) at a mean recovery of 350 IU/l could be produced in place of FIX. This less pure concentrate would treat about 80 000 patients with FIX and/or other coagulation factor deficiencies if present in the concentrate.

In addition, the same volume of recovered plasma could be fractionated into 37 tons of IG at a mean recovery of 4 g/l representing a market value of US$ 1.5 billion. This quantity would be used to perform prophylactic therapy of about 105 000 primary immunodeficient adults treated at the established dose of 0.4 gram/kg body weight on a monthly basis. Finally, 230 tons of albumin,
with a market value of US$ 580 million calculated on a mean price of US$ 2.5 per gram and a recovery of 25 gram/l, could be produced. This quantity would cover the needs of a population of 1.16 billion inhabitants based on a consumption of 200 kg/million population. Plasma can be fractionated to yield other derivatives (e.g. fibrinogen, von Willebrand factor, antithrombin etc.) and, while not listed as essential medicines, these are important and widely used therapeutics that could meet the therapeutic needs of other categories of patients (Table 1).

**Table 1: Main plasma products and indications (5)**

<table>
<thead>
<tr>
<th>Products</th>
<th>Main indications</th>
</tr>
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<tbody>
<tr>
<td><strong>Albumin</strong></td>
<td></td>
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<tr>
<td>Human serum albumin</td>
<td>Protein/volume replacement</td>
</tr>
<tr>
<td><strong>Blood coagulation factors</strong></td>
<td></td>
</tr>
<tr>
<td>Factor VIII <strong>6</strong></td>
<td>Haemophilia A</td>
</tr>
<tr>
<td>Prothrombin complex (PCC/PPSB) <strong>7</strong></td>
<td>Complex liver diseases; warfarin or coumarin derivatives reversal <strong>6</strong></td>
</tr>
<tr>
<td>Factor IX</td>
<td>Haemophilia B</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Factor VII deficiency</td>
</tr>
<tr>
<td>Von Willebrand Factor</td>
<td>Von Willebrand factor deficiency</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Haemophilia C (FXI deficiency)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Fibrinogen deficiency</td>
</tr>
<tr>
<td>Factor XIII</td>
<td>Factor XIII deficiency</td>
</tr>
<tr>
<td>Activated PCC</td>
<td>Haemophilia with anti-FVIII (or FIX) inhibitors</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Antithrombin III deficiency</td>
</tr>
<tr>
<td>Alpha 1-antitrypsin</td>
<td>Congenital deficiency of alpha 1-antitrypsin with clinically demonstrable panacinar emphysema</td>
</tr>
<tr>
<td>C1-inhibitor</td>
<td>Hereditary angioedema</td>
</tr>
<tr>
<td><strong>Anticoagulants</strong></td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td>Protein C deficiency/(thrombosis)</td>
</tr>
<tr>
<td>Fibrin sealant (fibrin glue) <strong>9</strong></td>
<td>Topical haemostatic/healing/sealing agent (surgical adjunct)</td>
</tr>
</tbody>
</table>

**6** Some factor VIII concentrates containing von Willebrand factor are effective for the treatment of von Willebrand disease.

**7** Prothrombin complex contains factor II, factor VII, factor IX, and factor X. The content in factor VII may vary depending upon products.

**8** 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.

**9** Product obtained by mixing a concentrate rich in fibrinogen and a concentrate rich in thrombin.
Intramuscular immunoglobulins (IMIG)

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<tbody>
<tr>
<td>Normal (polyvalent)</td>
<td>Prevention of hepatitis A (also rubella, and other specific infections)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Prevention of hepatitis B</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Treatment or prevention of tetanus infection</td>
</tr>
<tr>
<td>anti-Rho(D)</td>
<td>Prevention of the haemolytic disease of newborns</td>
</tr>
<tr>
<td>Rabies</td>
<td>Prevention of rabies infection</td>
</tr>
<tr>
<td>Varicella/zoster</td>
<td>Prevention of chickenpox infection</td>
</tr>
</tbody>
</table>

Intravenous immunoglobulins (IVIG)

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<th></th>
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<tbody>
<tr>
<td>Normal (polyvalent)</td>
<td>Replacement therapy in immune deficiency states, immune modulation in immune disorders</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Prevention of HBV infection (e.g. liver transplant)</td>
</tr>
<tr>
<td>Rho (D)</td>
<td>Prevention of the haemolytic disease of newborns.</td>
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</tbody>
</table>

Even if not used initially to produce a large range of plasma products, the plasma currently wasted in LMIC could still serve the needs of many currently untreated patients with bleeding or immunological disorders. Replacement of plasma products by affordable recombinant products is unlikely in the near and mid-term future in LMIC.

There are four main reasons for the wastage of plasma in the world:

- First, in many LMIC where component therapy has not been introduced, whole blood is directly used for therapeutic applications, and under such situations plasma is not produced from whole blood. Extensive use of whole blood rather than components is neither optimum therapy nor a cost-effective practice.
- Second, in the absence of appropriate freezing or storage capacity, plasma separated as a by-product of red blood cells needs to be discarded.
- Third, plasma may be produced and frozen, but if the conditions used do not meet the requirements for fractionation (e.g. inadequate traceability, uncontrolled freezing and storage conditions), the plasma should be destroyed.
- Finally, there are a number of LMIC where non virally-inactivated plasma or cryoprecipitate are used for transfusion to treat bleeding disorders in situations where purified plasma derivatives would be a better and safer clinical alternative, should these products be available and affordable.
4. Options to secure production of safe blood components and improve access to plasma derivatives

Each unit of recovered plasma considered for use in the manufacture of plasma derivatives should meet pre-established quality and safety requirements (5). This is a prerequisite for any step towards the production of plasma as an API. Furthermore, every effort that is made to improve the quality and safety of plasma for fractionation has a positive impact on the quality and safety of blood components prepared for transfusion.

A national blood service that performs a component therapy programme, has the following options with regard to the recovered plasma:

1. Discard the plasma. This is a waste of a precious resource and is not desirable, but if the plasma does not meet the standards required for further processing it may be the only option. This involves additional handling for destruction and in many instances may generate an environmental hazard.

2. Separate the plasma into simple components, such as fresh frozen plasma, cryoprecipitate (or cryosupernatant), and the use of these to meet basic patient needs (6). This option does utilize this precious resource and can provide relatively inexpensive treatment. However, it may involve both safety compromises (e.g. due to risks of transmission of bloodborne pathogens) and treatment compromises (e.g. due to volume overload and intolerance) and cannot be considered to satisfy best plasma use objectives.

3. Supply the plasma to a fractionator, in exchange for plasma products of an equivalent value, or engage in a plasma contract fractionation programme or, when justified, in local production of plasma derivatives. This allows for fractionation of the plasma into purified and virally-inactivated products. Contract fractionation and local production are the best options to maximize the number of products from each litre of local plasma, and to treat the greatest number of indications under optimized safety criteria once the quality of the plasma is ensured.

To achieve such goals, several organizational challenges must be addressed. First, a legal framework and strong governmental support should be in place. An established legal framework supporting a national blood policy and a set of directives for processing blood donations support standards and guidelines and ensure homogeneous quality of plasma raw material at the national level. An NRA for blood products should be established to enhance the quality of evaluation and regulatory actions in the area of blood products and associated medical devices, including IVD. Strong political support is also needed for defining clear milestones, selecting dedicated key leaders working in coordination, and ensuring the commitment of well trained and skilled manpower.

There is an important know-how component associated with the production and control of plasma to facilitate access to safe plasma products. Such know-how
is well understood in countries with a mature blood collection organization and regulatory system. Avoiding wastage of plasma and facilitating its use as API for the production of PDMP require transfer of technology and know-how, targeting the introduction of GMP principles in blood establishments (7). Suppliers of equipment, as well as plasma fractionators or experts in other blood establishments with proven experience in production of plasma as an API for fractionation, may contribute effectively to providing such know-how.

Figure 4 shows the various stages involved in technology transfer for the production of blood and plasma-derived products. It encompasses technology transfer at the level of blood collection, blood components separation and industrial plasma fractionation. Furthermore, important technology transfers are required for safe production of plasma products, including those associated with fractionation plant design, validation and operation, as highlighted later in this report.

Regulatory requirements for the production of plasma for fractionation should also be identified and fulfilled. Blood establishments should be regularly inspected by the local NRA to ensure appropriate compliance, and the fractionator should perform regular internal quality audits. In addition, a set of specific documentation should be provided to enable the fractionator, when located in another country, to obtain plasma importation licences from the relevant authorities.
Figure 4. Technology transfer stages in the plasma product chain

- Epidemiological surveillance
- Donor candidates
- Information to donors
- Questionnaire
- Review of medical records and previous donations data
- Mini physical exam
- Donor interview
- Collection of blood or plasma
- Separation into blood components
- Freezing of plasma for fractionation
- Quality control of plasma for fractionation
- Storage of plasma for fractionation
- Shipment to fractionation
- Fractionation process
- Puriﬁcation and viral reduction treatments
- Aseptic ﬁlling +/- Freeze-drying
- Final plasma products

Plasma collection

Plasma fractionation
Plasma fractionation technology

Plasma fractionation is one of the most technically demanding industries in the entire biotechnology field, and includes both technical and regulatory aspects related to traceability, downstream protein production, viral reduction treatments, hygiene requirements and regulation.

Plasma fractionation technology was developed in the 1940s based on a process using cold ethanol precipitation to produce albumin and immunoglobulins (8, 9). Fractionation technology has since increased in complexity in order to allow the extraction of multiple proteins, including trace levels of labile coagulation factors, implementation of dedicated viral inactivation and removal procedures, and adherence to increasingly stringent GMP regulatory requirements (10–12). This has had significant impact on the process design and has forced the re-modelling of facilities to meet evolving requirements.

The following are elements of additional complexity in this industry:

- Each plasma unit contributing to a pool of plasma, and each respective plasma pool, are inherently different. In addition, plasma pools from different regions may have significantly different Ig content, as well as specific antibody content.
- Potential risks of contamination of the raw material by emerging infectious agents (known or unknown) require constant vigilance, surveillance and quick implementation of counter-measures, in coordination with regulatory authorities.
- Plasma fractionation requires specialized process know-how that encompasses protein purification steps, and viral inactivation and removal procedures.
- All process steps and quality control methods should be validated.

In addition, unique to the biotech industry, several PDMP are manufactured from the same, single plasma batch, using interconnected processes. Plasma products are fractionated following intricate manufacturing processes that are dependent on one another and are subject to dedicated viral reduction procedures that require strict process segregations (Figure 5). These elements underline the need for complex and specialized engineering, appropriate plant design, professional training of operators and competent validation methodologies, in order to avoid risks of cross and downstream contaminations.
Figure 5. Typical plasma fractionation schemes integrating chromatographic procedures with ethanol fractionation and viral reduction treatments.
Options for fractionation of recovered plasma

Two main options are available to countries considering the use of plasma as an API for the manufacture of PDMP: a) contract manufacturing; or b) local fractionation, through plasma fractionation technology transfer. Both options provide a means to improve the transfusion system and ensure the availability of safe blood products, and both pathways require, as a preliminary goal, the availability of quality plasma for fractionation (5, 6). Among other considerations, the choice between local fractionation and contract fractionation should take into account the high level of complexity of plasma fractionation technologies and of the regulatory oversight required. The two options can provide a country with an opportunity to find its own means to affordable and secured products.

Contract fractionation

If available plasma meets quality requirements for fractionation, and there are good prospects for sustained availability of plasma, there are good reasons to explore a prospective contract fractionation programme with an established fractionator. The substantial process know-how associated with this industry is a strong argument in favour of contract fractionation as an initial option. Other contract fractionation considerations include:

- Plasma represents approximately 30–40% of the cost of plasma products; this cost can be saved if local plasma is salvaged compared to imported plasma products.
- Contract fractionation provides a safe and reliable supply of life-saving products. The increased guarantee in the supply of essential PDMP reduces possible exposure to periodic market fluctuations that occur at global levels. Contract fractionation therefore provides a country with a level of control beyond that available from the purchase of commercial products.
- It can be performed from a relatively low plasma volume (e.g. from 10 000 to 30 000 litres). Volumes should not be very small, however, as fractionators will need to balance the cost of auditing centres and setting up the contract.
- The same high quality standard used by a contract fractionator (including the specifications of the plasma) will apply to the manufactured products issued from the country’s plasma, thereby guaranteeing product quality equivalence.
- It is a good educational tool to build knowledge on the specificities and technological and scientific requirements of plasma products, before possibly developing a domestic plant.
- Contract fractionation can have a real positive and direct impact on the quality of the blood collection system, and on public health in general, by upgrading transfusion safety and epidemiological surveillance (5, 7).
- Local production practices in blood establishments become exposed to the GMP requirements of highly regulated countries, a process that has been found to improve aspects as essential as:
  - donor selection criteria;
– blood donation testing;
– epidemiological surveillance;
– post-donation information systems;
– handling of blood during and after collection, and separation into components;
– plasma freezing, storage, and cold chain transportation.

• Contract fractionation allows for combined benefits of regulation by the local regulator as well as by the regulator of the contract fractionator. This offers a way for the local regulator to consider the safety issues of its own jurisdiction and ensure they are at the forefront of the regulations that drive production of API from plasma, and plasma fractionation.

There are some prerequisites to consider when evaluating the possibility of initiating a contract fractionation programme:

• Strong government commitment and active political support are of critical importance to the success of such programmes.
• The NRA of the plasma supplier should be involved from the time the programme is considered, as ensuring the quality of local plasma is a key factor in the quality and safety of the plasma products that will be ultimately produced and marketed in the country.
• A contract fractionation agreement is a proactive and prospective step that should follow well established contractual principles that clearly define the rights and obligations of both parties (i.e. the plasma supplier and plasma fractionator).
• Critical indicators for success include a guaranteed, consistent and sustainable volume of plasma supply that meets the quality requirements of the plasma fractionators, and of the respective NRAs of both the plasma supplier and fractionator.
• The number of products made should be matched to country needs for the optimal and efficient use of the plasma and the cost-effectiveness of the programme.
• The cost of fractionation will be influenced by the sophistication of the fractionation technologies used.
• A contract fractionation agreement is usually made with an established plasma fractionator that is often located in an adjacent country in the same region, or in another continent. Appropriate legal and technical means for plasma shipment and customs clearance must be in place.

Successful contract fractionation programmes, involving a plasma volume from 10 000 to about 200 000 litres of plasma per year, already exist between LMIC and industrially advanced countries (14–19). Contract fractionation agreements have also been developed between blood establishments and plasma fractionators located in LMIC (see case studies in Annex). Currently, a volume of 150 000 to 200 000 litres appears to be the maximum volume of foreign plasma that can be contract fractionated by a single fractionator. Experience from these countries indicates that, with an existing robust blood
collection system, a contract plasma fractionation programme takes two to four years to be established (including the time to further improve the quality of plasma API).

Contract fractionation of domestic plasma probably does not meet all national needs for major plasma-derived products, but does help to even out market price fluctuations, and potentially provides competition to imported plasma products from other manufacturers. Contract fractionation can continue as required and be followed, under certain conditions (i.e. plasma availability), by the construction of a local plasma fractionation plant through a transfer of plasma fractionation technologies.

Local fractionation

A successful contract plasma fractionation programme may serve as a ramp-up phase for local fractionation activities, which should only be undertaken after a careful assessment and feasibility study taking into account, in particular, the volume of available plasma. Strong government endorsement is an essential condition. Transferring a technology for the manufacture of plasma products represents a major endeavour that should be carefully planned. Discussions that took place during the preparation of the current report led to some degree of consensus that a minimum available plasma volume of around 300 000 litres per year should be considered prior to building a local, cost-effective facility, although it was also recognized that local situations may justify deviating from this estimate. For countries with a prospect of less than 300 000 litres of available plasma, establishing a cost-effective fractionation plant is challenging, but this could potentially be overcome by entering into agreements or alliances with neighbouring countries.

The complex technology transfers required to develop a domestic fractionation plant are discussed later in this report (Chapter 7). The high cost of building a GMP-compliant plasma fractionation facility should be carefully taken into consideration.

Using surplus plasma generated from the production of red blood cell concentrates may offer a significant economic advantage for developing countries. The use of recovered plasma for fractionation, and the revenues generated by new products from whole blood donations, provide additional resources that can serve to improve the blood collection infrastructure at a national level. Entry into the market of plasma products derived from domestic plasma should contribute to a lowering of plasma product prices through increased availability and competition (17, 20, 21). Added values of domestic fractionation include secured access to products at predictable and controlled prices, and reduction in the extent of dependency on monopoly markets. To achieve this goal, it is however important to understand the unique economics of plasma fractionation (22) as described below.
5. Economics of plasma fractionation

The high fixed costs of plasma fractionation drive an industry that is governed by economies of scale. Compliance standards are high and continually increasing; processes and products should be continually improved, developed and validated; and there are stringent regulatory requirements. Supporting a fractionation plant requires a large team of highly skilled and qualified professionals. A large proportion of these costs are incurred whether the plant produces any output or not. These fixed costs should be recovered steadily over the volume of outputs produced. If the output volume is small then those fixed costs are spread over a lower volume and the price of each unit of output will be substantially higher as a result. Conversely, if the production is very large those fixed costs are spread over a much greater volume and the price per unit required to cover those costs is significantly less. As a result, large plants are much more cost-effective than small plants and competitiveness is governed by economies of scale (Figure 6).

Figure 6: Impact of plant throughput on cost of plasma products

Globally, the fractionation industry has responded to this imperative through consolidation and expansion – the number of fractionation plants in HICs is falling while the total output of the industry is increasing, and hence the average size of plants is increasing. This means small plants can no longer be competitive in the developed world. It is difficult to give a clear indication as to the size a plant should be in order to operate effectively. In lower-cost environments and those where the plant may be supported by government or may not need to secure economic returns, small plants may be viable. In high-cost countries and situations where plants should satisfy the needs of private shareholders for economic returns, very large plants are required. As a very broad estimate, it is unlikely that a plant with a throughput of less than 300 000 litres per year can be cost effective.

Joint costs are also a key aspect of the economics of contract fractionation. As well as fixed costs, the contract fractionation industry involves joint costs. While some costs may be variable, they can also be shared across the various products (output) that are produced from each unit of plasma (input). The variable costs are largely driven by the volume of plasma input rather than by that of each product that is produced (Figure 7).
If only one product is manufactured from a unit of plasma (illustrated in red colour), all the costs of processing each unit of plasma need to be recovered through that single product. If, for example, three products (illustrated in red, green, and yellow colours) are recovered from each unit of plasma, the cost of processing will only be marginally higher but it could be shared across those three products, and as a result each could be manufactured for a significantly lower unit cost.

*Figure 7: Sharing of fixed and joint fractionation costs between products reduces unit costs*

Using available plasma to produce as many viable products as possible is a critical concept in optimizing the cost effectiveness of plasma fractionation.

**Product mix is a critical aspect of contract fractionation**

The demand for plasma products varies between countries, largely due to economic constraints, product reimbursement policies, under-diagnosis of specific conditions, or lack of sufficient supply. In relation to PDMP, demand in LMIC tends to focus mainly on albumin – there is low demand for IVIG and very little, if any demand of FVIII. In transition economies, demand is typically weighted more towards FVIII, as these countries have the resources and capacities to tackle haemophilia care. Albumin demand also remains strong in MICs, while demand for IVIG remains relatively low. In HICs demand is dominated by IVIG with usage growing strongly with relative wealth, and use of plasma-derived FVIII being replaced by use of recombinant FVIII.

For contract fractionation to be cost-effective it should also achieve a balanced product mix. Unfortunately, this ability to harness a range of markets to balance product output is not readily available to the user of contract fractionation services, so in general the only way to achieve this balance is by fractionating a volume of plasma in such a way that enables all three products to be produced and used within the country undertaking the contract fractionation. Product mix is thus a critical consideration and a special challenge in achieving cost-effective fractionation.

The needs of a typical LMIC that may be contemplating contract fractionation is illustrated in Figure 8.
Figure 8: Importance of a balanced product mix for cost effectiveness of contract plasma fractionation

If a country’s demand for the three major plasma products is converted into an equivalent quantity of plasma input, the issue of product imbalance can be seen more clearly. This ‘typical’ country appears to have demand for albumin that is equivalent to about 59,000 litres of plasma per year. It also has demand for IVIG and FVIII each equivalent to about 16,000 litres of plasma per year. If this country was to fractionate plasma, it could only be sure of using all three products if it were to fractionate 16,000 litres or less. Conversely, if it attempted to meet its demand for albumin, it may use only one product from as much as 43,000 litres per year. In such a situation, any country has three potential options:

• fractionate 16,000 litres and not meet its demand for albumin (i.e. have to purchase commercial albumin to meet the demand, and most likely not use all its available plasma);
• fractionate ~60,000 litres (if available) and meet all its demand for plasma products, but not use all the potential products, consequently failing to meet an important criterion for cost-effective fractionation; or
• fractionate ~60,000 litres (if available) and use this opportunity to improve treatment with increased access to IVIG and FVIII, achieve cost-effective fractionation and improve the health outcomes of the population.

The challenge is to find ways of achieving improved health outcomes and identify the resources to do so.
**Contract fractionation should be protected from fluctuating ‘spot’ prices**

As described, much of the costs of fractionation are incurred regardless of whether the products obtained from a given volume are required and/or sold. Commercial fractionators have an imperative to sell all the products they manufacture. They also have an imperative not to process more plasma than they can profitably use. To compound this, the industry has a very long lead time from collection of plasma right through to sale of product. In combination, these complexities and imperatives make supply planning a challenge and mean that from time-to-time fractionators may have product shortages or a strong need to market products before their remaining shelf-life is too short. Emerging markets are most likely to see these manifestations of a complex industry and from time-to-time experience both product shortages and instances of significantly lower prices.

A contract fractionation programme can protect countries from product shortages. However, a contract fractionation programme can be exposed to competition from temporarily low prices. On balance, for the majority of the time, a contract fractionation programme will provide a country with a reliable and affordable supply. But on occasions, prices of commercial imports may make the programme appear uncompetitive. Fractionation programmes should not be subject to reconsideration in light of such short-term events, they need to be focused on the long-term. To deliver the benefits of reliable supply they should also be protected from short-term market shocks. A contract fractionation programme requires a whole-of-government commitment.

**What contract fractionation volume is viable or cost effective?**

The viability of a contract fractionation programme is founded upon a combination of four factors: a) establishment cost; b) batch size; c) demand; and d) shelf-life.

As explained, fractionation programmes require effort and investment to establish, both on the part of the contract fractionator and the blood collection service. Contract fractionators need to recover establishment costs. If the plasma volume is large enough, then the establishment costs can, over time, be recovered through normal production. If the plasma volume is small, this is much less likely and the contract fractionator may need to charge separately for the costs of establishing the programme. As a consequence, small volume fractionation contracts may be costly to set up.

Fractionators typically manufacture in batches. Demand for plasma products in many countries can be low relative to these batch sizes. If the country requires only small volumes to be fractionated each year and that volume is equivalent to the size of the fractionator batches, only one batch of products will be scheduled and obtained each year. The shelf-life of plasma products varies but may be as short as three, or even two years. Thus if the plasma volume is low, contract fractionation can involve a complex balance of supply planning to avoid shortages, while also avoiding product expiration.
Despite these complexities and costs, relatively low annual fractionation volumes can be viable. For example, in Asia, there are contract fractionation programmes with volumes as low as about 12,000 litres per year in one country, and volumes between 20,000 and 30,000 litres per year in three other countries. These arrangements have all been in place for some time and have been viable and indeed successful.

In conclusion, a contract fractionation programme can be cost-effective, even if volumes are small, so long as the key requisites shown in Table 2 can be satisfied:

**Table 2: Key requisites of a contract fractionation programme**

<table>
<thead>
<tr>
<th>Requisite</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong and reliable government support</strong></td>
<td>A broad commitment to the programme is essential.</td>
</tr>
<tr>
<td><strong>Effective framework</strong></td>
<td>There should be a framework to deliver stable long-term access to plasma products, protected from sporadic market fluctuations.</td>
</tr>
<tr>
<td><strong>Product mix</strong></td>
<td>Fractionation should be balanced with demand and should strive to ensure the maximum production from each available litre of plasma.</td>
</tr>
<tr>
<td><strong>Realistic ambitions</strong></td>
<td>The drivers for contract fractionation should be secure and reliable product supply and improved health outcomes. The driver cannot be simply the pursuit of financial savings.</td>
</tr>
<tr>
<td><strong>Patience</strong></td>
<td>It is important to ensure all these requisites are met and in place prior to establishing the fractionation programme. The time required to achieve this should not be underestimated.</td>
</tr>
</tbody>
</table>
6. Points to consider in technology transfer for local production in LMIC

The study carried out to prepare this report identified main challenges and obstacles to technology and know-how transfer for local production of safe recovered plasma for fractionation and, when justified, plasma products. The relative feasibility and sustainability of plasma contract fractionation programmes and plasma fractionation facilities have also been evaluated based on concrete examples.

Technology transfer to facilitate access to safe blood and plasma products encompasses several steps. The first step involves technology transfer that aims at ensuring plasma meets the requirements for fractionation. This can be achieved by collaborating with a blood establishment that has experience in the production of plasma for fractionation, or directly with a plasma fractionator.

As highlighted in this report, implementation and enforcement of GMP for production of plasma for fractionation is a requirement in the manufacture of safe fractionated plasma products (5, 7, 10). Quality standard requirements for plasma for fractionation apply at a global, rather than national or regional, level. Collection and testing procedures should comply with the precise requirements defined by the fractionator and approved by the relevant regulatory authorities. Enforcement of these requirements in quality production of plasma for fractionation is ensured both through audits carried out by the fractionator and by inspections from relevant regulatory authorities.

Recent WHO guidelines provide updated recommendations on the production, control and regulation of plasma for fractionation (5). Technology transfers in the quality production of plasma for fractionation, especially when LMIC consider contract plasma fractionation agreements with countries with advanced regulatory infrastructures, allows for an educational process that benefits both blood establishments and regulatory authorities (19).

Main items that are often identified as relevant in transfer of technology for the production of plasma for fractionation are listed below:

- Implementation of standard operating procedures (SOP) at all stages of the collection process, with the establishment of a policy that guarantees compliance with approved procedures.
- Epidemiological control of the donor population leading to a formalized follow-up of the rate and trends in infectious markers in the donor population at the national level.
- Information system of blood donors, based on approved medical questionnaire within the scope of look-back requirements and follow up of donor medical history. This can lead to the creation of a national database of blood donors, the introduction of a common computerized system among blood establishments, and the harmonization of the barcode system among blood establishments at the national level.
- Introduction of a specialized training programme with appropriate evaluation of operator performance.
- Donor-screening procedures by the creation of suitable confidentiality suites for donor interviews at fixed collection centres and improvement of confidentiality in mobile collection units. This should include positive identification of donors (name, address, date of birth), proof of a permanent place of residence, telephone number, evidence of identity (e.g. identification card, passport, driving license).
- More precise selection criteria for donors, when relevant (e.g. tattoos, scarification, piercing).
- More rigorous validation of blood collection procedures and more careful control of the conditions for transportation of blood from mobile units to the processing centre, in particular avoidance of temperature fluctuations.
- Introduction of validation procedures, preventive maintenance, and monitoring of equipment used at all stages of the production process.
- Use of viral screening tests approved by the fractionator and its regulatory authority, and establishment of a quality control and release system for viral test kit lots at the national level.
- Reinforcement of the traceability system from donors-to-products and products-to-donors.
- Reinforcement of security systems in place for donations initially reactive for viral markers (e.g. quarantine zones, procedures, computer control).
- Formal validation of the plasma freezing procedure based on fractionator’s specifications and fractionated product range, together with control of homogeneity and consistency of freezer temperatures.

In addition, cold rooms should have sufficient capacity to comply with the plasma shipping volume required by the fractionator (this may imply building a centralized plasma storage facility for the whole country).

Case studies in the Annex provide supporting evidence for LMIC options to generate plasma that meets the requirements for plasma fractionation (23) and/or consider the concrete initiation of a contract plasma fractionation programme or, when carefully considered, the construction of a domestic plasma fractionation facility.

A contract-based plasma fractionation programme can bring substantial know-how to local manpower and develops valued expertise on the quality and regulatory requirements of plasma derivatives and their clinical use, as well as the plasma fractionation processes itself.

If justified, a further step can be initiated involving the transfer of technology and of know-how needed for the design, construction, qualification, validation and regulatory approval of a fractionation facility, together with obtaining the license(s) for the plasma products made in the domestic facility. Transferring technology for the manufacture of plasma products represents a major endeavour that should be carefully planned. It involves a complete set of know-how aimed at designing and building a facility, and at
transferring technologies of production for a range of at least three or four products (generally, albumin, IVIG, FVIII and FIX or PCC). Table 3 summarizes key organizational and technological requirements for building a local facility.

**Table 3 - Technology selection process for fractionation technology and stakeholders**

<table>
<thead>
<tr>
<th>Steps and parties involved</th>
<th>Objectives and roles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of technology by end-user</td>
<td>It should have been validated and proven for products of consistent quality and safety as evidenced by results of clinical studies, marketing authorizations and vigilance systems by NRA.</td>
</tr>
<tr>
<td>Technology supplier</td>
<td>Technical information and SOP package necessary to make the products under GMP, such as production files, technical information for the design of the facility, design and construction (or acquisition) of production equipment and utilities ('user requirements documents'), procedures for qualification and validation of the production processes, and marketing authorization dossiers, including pre-clinical and clinical data. Capacity to provide adequate training to local manpower, and to participate into the manufacture of the first validation batches prepared in the new facility, is also a key factor.</td>
</tr>
<tr>
<td>Selection of engineering company</td>
<td>Should be familiar with the technologies used by the selected plasma fractionator and with the updated GMP requirements for therapeutic biological products, in order to ensure that international requirements are met at optimal cost. May be responsible, in coordination with technology supplier(s) and technology recipient, for preparing basic and detailed designs, supervision of production of equipment, plant and equipment qualification and validation.</td>
</tr>
<tr>
<td>Equipment suppliers</td>
<td>Train operators in the use of equipment, in coordination with the technology supplier.</td>
</tr>
<tr>
<td>National Blood Product Committee</td>
<td>Oversee and endorse the selection process for the technology supplier.</td>
</tr>
</tbody>
</table>

Assessment of existing plasma fractionation technologies is a major step, including viral inactivation procedures (11) and potential suppliers of such technologies, as well as a determination of the targeted plant capacity based on local and regional needs.

Another element to consider in building a fractionation plant includes the choice of the plasma and product batch size, as this is a key factor to production costs. Currently, few fractionators have manufacturing plasma pool sizes below 2000 to 3000 litres, and end-products batch sizes below 3000 to 4000
litres. The final cost for a fractionation plant is highly dependent upon many different factors such as, for example, cost of know-how and/or license(s), engineering costs, training costs, quality of the design and the material and equipment used, the provision by the host country of highly qualified and experienced staff, local availability of engineering services required for the complex technologies involved in the fractionation process. It is regarded as unrealistic to expect to build, qualify, validate and start operating a plant of a capacity of 300 000 litres at a total cost lower than US$ 70 million. In most cases this is the initial cost for a plant producing four quality products, and may be significantly higher once the factors mentioned above have been fully considered.

Considering the sophistication of plasma fractionation technologies and fractionation plants, careful attention should be given to the selection of the engineering company. Invariably, a new facility resulting from transfer of technology cannot be a simple ‘copy and paste’ of an existing older facility if optimal design, benefit from technological development, and meeting evolving GMP requirements are to be achieved in the most meaningful and productive way. Many LMIC do not have local engineering companies with adequate expertise in the field of complex biological products. Most often, specialized manufacturing equipment is not commercially available and should be designed and built on demand in accordance with pharmaceutical regulations and the technology supplier’s specifications.

Training of operators in an existing fractionation facility is crucial to build a team of skilled and sufficient local manpower. Building a local facility implies independent and long-term operation of the plant by local staff. Full ownership of the technology and acquisition of the expertise and necessary skills to fulfil this objective are crucial. Local personnel should exhibit a high degree of competency, capability and motivation as well as a certain level of technological background.

This need for specific facility design and engineering, for dedicated process qualification and validation, implies that establishing new manufacturing sites for plasma products is both costly and time-consuming, and requires substantial expertise. Depending upon plant capacity and range of products, five to ten years may be required to design, build, install, qualify and validate a fractionation plant. The phases of such a project include identification of suitable land, conceptual and basic designs of the facility, definition of the specifications of the production equipment and utilities, detailed design, ordering of equipment, and the subsequent phases of qualification and validation.

When the decision is made to build a local plasma fractionation facility in partnership with an established plasma fractionator, planning must be realistic in relation to the resources required. In some cases, it may be advantageous to proceed in two steps by firstly, performing the basic fractionation process to generate intermediates, which can then be sent to the contract fractionator for further purification and/or viral inactivation processes; secondly, by
performing the complete production process for the whole product range. Ownership of a plant has the potential to convey complex technologies that can be transferable and utilized by the host country in other areas, such as chromatography or sterile biological manufacturing, or freeze-drying.

It should be noted that the option to establish a local fractionation facility, without a phase of previous contract fractionation arrangements, has been considered by some countries but presents major drawbacks and faces numerous risks of financial and technical failure. Indeed, although there is no public information available, it appears that several attempts to establish a domestic plasma fractionation facility in the past 15 years in LMIC, without a previous phase of contract fractionation, have been unsuccessful. By contrast, this report has identified ongoing projects on construction of a domestic plasma fractionation facility as a follow up of a contract fractionation phase.

The Annex illustrates the experience of stakeholders involved in technology transfer at several levels for the production of plasma for fractionation, contract fractionation, and local production of plasma products.
7. Need for regulation of blood and blood products

The importance of blood transfusion as a lifesaving and essential part of medical care is well recognized. Blood is used to treat bleeding and other causes of acute and chronic anaemia. In developing countries, blood transfusions are primarily needed to prevent death from malaria particularly in children aged under five; from obstetric bleeding during labour and delivery, a leading cause of death in the developing world; and also from trauma, particularly vehicle accidents. Collectively, these conditions drive the blood needs of the developing world.

As clinical practice evolves, the availability of blood permits many surgeries and sophisticated therapies such as cancer chemotherapy, organ transplantations or stem cell replacements. In country contexts, this is an evolution that happens in parallel with advancements in the human development index. Therefore, it is correct to say that the need for blood will increase with the overall stage of development of a country.

A benchmark concept has also been established that indicates a minimum blood donation rate of 15 collections per thousand population per year is needed to meet the most basic needs for transfusion. That is, to prevent deaths from haemorrhagic shock, and in the developing world, from malaria. This initial target sets a kind of ‘floor’ as to how much surplus plasma, separated from whole blood, will be generated as development in countries advances.

There is a long-standing debate regarding the use of whole blood or blood components. In the situation of haemorrhagic shock, blood is needed to correct anaemia, but also to replace blood volume and coagulation factors, including platelets. In countries where most blood transfusion is used to treat acute haemorrhage, it is rational to primarily use whole blood, especially fresh whole blood. However, as the national development stage and clinical practices evolve, selective use of blood components becomes more common and appropriate. For example in the treatment of malaria, it is mainly red blood cells that must be replaced, and therefore it is better to use the red cell component. Additionally, there would be an advantage to the separate use of platelets for other indications such as thrombocytopenic conditions, and plasma can be used selectively to treat coagulopathies. As the use of blood components made from whole blood increases, the possibility emerges that plasma generated in excess of the need for transfusion will become available in significant volumes. This ‘surplus plasma’ can be used to make PDMP. Therefore, the blood and blood component needs – driven by medical practice – will determine the amount of surplus plasma.

A number of PDMP have been identified as essential medicines in the WHO Model List of Essential Medicines (1). Once again, the use of and needs for these products will evolve as development in countries advances. PDMP already in the WHO Model List of Essential Medicines are needed to prevent or treat many specific infections such as rabies and tetanus, or to prevent fetal death from
Rh disease, to maintain health in primary immunodeficiencies and to treat immune-mediated thrombocytopenia. Similarly, blood coagulation factors are needed for management of heritable disorders of clotting factors and to treat coagulopathies, for example in trauma. Albumin, not included in the essential medicines list, is however a widely used plasma derivative to treat shock or as an adjunct in renal dialysis or cardiac bypass surgeries. These are the most important PDMP, most of them with limited access in developing countries. There are additional, much less common, blood protein deficiency disorders where replacement of inhibitor proteins prevents abnormal coagulation (e.g. antithrombin and protein C deficiencies), or slows lung destruction in hereditary emphysema (i.e. alpha 1-antitrypsin deficiency), and prevents and treats acute attacks of tissue oedema (C1 esterase inhibitor deficiency). This is a very brief summary of health benefits from the range of blood components and PDMP. However, even from such a cursory overview, it is clear that major attention should be given by governments in LMIC to avoid the large wastage of plasma estimated to occur.

Within this context, blood regulation is an essential and well documented mechanism that has proven to be effective in assuring the implementation and enforcement of national quality, safety and efficacy standards for the evaluation and control of blood products (24). As explained above, both blood components and PDMP are essential to individual health and quality of life. There are, however, inherent risks as well as variability in blood itself, which necessitate a comprehensive programme of blood standards and controls. The complexity of providing adequate and equitable access to safe blood products requires an organized regional or national blood system. This is a solid conclusion of experience in HICs. No country has succeeded in bringing forward an adequate and safe blood supply without a national organization and commitment. Within that system, a competent blood regulatory authority assures that appropriate reliable standards are met for the production of the blood products as well as the monitoring of quality and safety. These are both core elements; their implementation in LMIC has been and remains the greatest challenge.

In 1975, resolution WHA28.72 first established the principle of a nationally-supported, -managed and -coordinated blood system. Several subsequent resolutions have been directed at strengthening blood systems. Notably, in 2010, resolution WHA63.12 recognized the essential role of stringent regulatory control as vital to assuring quality and safety of blood products. This resolution urged Member States to update their national regulations and to ensure effective regulatory control in the area of quality and safety of blood products across the entire transfusion chain, typically characterized as ‘vein to vein’. Regulation thus operates at every step of the blood system, and traceability must be intact at every step in order to enable audits of the processes and interventions wherever needed.

The general blood safety strategy starts with a low-risk donor. Strategies to minimize infectious risks in donors include the use of volunteer non-remunerated donors to avoid incentives to donate, a medical interview to assess
risk factors, a limited physical examination to look for evidence of infections, donor education and science-based risk factor screening, all to avoid collection from 'unsuitable' donors. For example, a donor with a history of a positive test for HIV or hepatitis would be deferred. The virus safety of blood products relies on the determination of the infection status of a blood donor who might themselves not be aware of an infection. If undetected, an infectious pathogen could be transmitted to the recipient(s) of blood components. An important safety layer is the screening of each blood donation for markers of syphilis and virus infections, mainly HIV, HBV and HCV. Examples of other additional target pathogens that are important under epidemiological situations in different regions would be human T-cell lymphotropic virus (HTLV), West Nile virus (WNV), or Trypanosoma cruzi. Quarantine of collected blood is another quality element of the blood system, aiming to ensure reliability of the test result and the verification of the suitability of the donation before blood is released for use in transfusion. Quality processing should be assured at all levels and full traceability of production processes should be demonstrated.

The important role of the regulator is the establishment of blood standards, oversight of blood product manufacturing activities, and assurance that standards are met at all levels (24). Adherence to GMP, which is defined in guidance documents, is fundamental to ensuring that products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP is also an evolving science, which requires periodic re-examination to determine whether current best practices are met. Within the system, feedback procedures and capabilities should exist to correct deficiencies where found, and to disseminate relevant information. This will require the establishment of vigilance systems. Both haemovigilance and pharmacovigilance are analogous as mechanisms to observe, report and take actions to address adverse reactions in donors and in blood product recipients.

It is fundamental to recognize the importance of the selection and control of viral test kits in blood establishments due to their impact on blood products safety. Virus screening of blood donations started in the 1970s with the availability of hepatitis B virus surface antigen (HBsAg) assays, followed by anti-HIV and anti-HCV assays, all of them serological assays. More recently, a number of countries have introduced nucleic acid tests (NAT) as screening assays, in addition to serological assays. The NAT assays may further reduce the diagnostic window of serological assays in the early infection phase. Therefore, the additional benefit of NAT (i.e. NAT-only positives) is strongly dependent on the incidence (new infection rates) in donor populations and on the donation frequency of repeat donors. The probability of NAT-only positive results, indicative of recent infections, increases with higher donation frequencies among repeat donors. Conversely, the vast majority of infections in first time donors will be detected by serological assays as they are longer-standing infections. For HIV, HBV and HCV, cellular components and non-virus inactivated therapeutic plasma manufactured from screening-test positive, whole blood donations are highly likely to transmit infections to recipients. Therefore prevention of these virus transmissions by use of screening tests of appropriate quality is an essential element of blood safety.
Suitable donor screening assays are characterized by both high sensitivity and high specificity. Available assays with other characteristics may fulfill important tasks in other health-care settings (e.g. rapid tests in emergency situations and potential use by lay people) without being fully suitable for blood donor screening, because of limited sensitivity, specificity or other features. The differentiation between suitable and less suitable blood screening assays should be based on the actual state of the art of blood screening devices. The state of the art is defined by the most sensitive and most specific assays available on the market at a certain time. Because of steady improvements in test features, the state of the art qualification may increase over time, and defines test features at a certain time by comparative evaluation of all available test kits. In industrialized regions, regulatory requirements tend to reflect the actual state of the art, with regular updating of requirements, as far as possible.

Regional differences with respect to virus prevalence, virus incidence and viral genotype distribution should be reflected by region-specific regulatory requirements. For example, in some regions, higher attention should be given to the sensitive detection of regionally prevalent viral genotypes rather than those more prevalent in other parts of the world. This specific focus may be defined by regulatory authorities or by expert users of IVDs. Data on the clinical or so-called ‘diagnostic evaluation’ already performed by the IVD manufacturer are a potential source of information for this estimation. These data may be assessed by experts in the diagnostic field to assure suitability of test kit features with respect to the actual use of a given test. This assessment may be complemented by laboratory investigations focusing on the most relevant aspects, such as analytical sensitivity of tests. More advanced regulatory authorities will set up quality specifications for the tests to be considered as blood safety related IVD. WHO supports this kind of laboratory investigation by global provision of WHO International Standards (biological reference preparations that can be used for test calibration and/or limit of detection determination), and of WHO International Reference Panels, which contain the most prevalent viral genotypes.

Assuring the quality and safety of PDMP requires control measures at all levels, i.e. blood collection based on donor selection, donor testing for markers of infectious diseases, and quality standards for plasma pooling and processing. Many safeguards are also needed in the fractionation process, such as validated bacterial and fungal sterilization and viral clearance. Final container testing is required to assure product purity, potency and microbial sterility of each batch. However, such end-product testing does not assure all elements of quality and safety. The need for defined conditions of shipping and storage should also not be overlooked, including temperature controls and careful attention to expiration dating, which depends on the type of product and its formulation characteristics (e.g. liquid, lyophilized, residual moisture if lyophilized, stability information under refrigerated and/or room temperatures).

Donated plasma, the raw material for manufacture of PDMP, is also the active pharmaceutical ingredient (API) of such products. Consequently, the quality
and safety of the starting plasma is key to the quality and safety of the PDMP obtained through fractionation. This situation reflects the inherent complexity and risks of plasma as a biological source material. For example, the entire fractionation pool can be contaminated and become infectious from one contaminated collection entering into thousands of units in the plasma pool. Additionally, at the other end of the process, hundreds if not thousands of patients can receive the products made from one batch from one plasma pool. There is, therefore, a potential for many patients to become infected from a contaminated product made from a single batch. This is the tragedy that was experienced with HIV and hepatitis infections before effective controls were put in place. Moreover, even if contaminated plasma pools can be identified, withdrawal from the market of potentially infectious products made from contaminated plasma pools may result in widespread product shortages. Thus, it is essential to avoid contamination of plasma pools by unsuitable collections and in order to prevent adverse health outcomes among patients, especially those with obligate needs, to avoid wastage of precious plasma resources and the products themselves, as well as to prevent product shortages due to withdrawals. In brief, these and other inherent risks drive the absolute need for quality standards to be applied to plasma for fractionation. Standards to assure the quality and safety of surplus plasma as an API serve concurrently to assure the quality and safety of all the blood components for transfusion, because these standards come into play at the level of each donation.

In addition to the safety characteristics of the donor, based on the epidemiology of infectious diseases, many operational parameters affect the quality of the plasma for fractionation in terms of preserving the integrity of constituent proteins. These include the method of plasma separation, the specific anticoagulant used, time of separation of the plasma from cells, the time and temperature from collection to freezing, the cellular content of plasma itself, the rate of freezing and final temperature, and the temperature during transport and storage. Control of temperature is especially important when the plasma may travel a great distance, particularly in warmer climates. Additionally, a system of recalls is needed to prevent the use of plasma units in the instance of quality defects.

Plasma fractionators specify the preparation conditions and quality standards for the plasma that they will accept for fractionation. However, there is an absolute need to ensure that those specifications have been and are continuously being met. This is where regulatory action plays a fundamental role, in particular to provide enforcement and oversight of GMPs in blood collection and processing, and quality validation and control of blood safety-related IVDs including donor screening tests for infectious diseases.

The motivation for regulation of blood and blood products arises from recognition of several key insights. Foremost, it should be accepted that blood is a national resource. This is because the blood that is collected from the population is the predominant source to make the products that are needed by the same population. This very particular condition of blood as a national resource – and which links the health of donors to that of recipients – implies
an ethical responsibility greater than in most other areas of medicine, and therefore that governments should establish its appropriate regulation at the national level. Also for this reason, the legal and regulatory frameworks must assure protection of the donors, and especially of repeat donors. Donors should be assured that their gift of blood will be put to good use, and that the process of blood donation is safe. Legal measures to bar the commercialization of blood collection contribute to protection of donors by preventing exploitation and at the same time promote safety assurance of the products.

Safety of blood for transfusion is paramount, requiring standards for donor selection, infectious disease testing and quality in blood processing. However, assuring equitable access to safe transfusion – both as sensible public health practice and as a social good – further requires a national blood policy with commitment of adequate resources. In the absence of a national blood policy and blood system, such equity is hard to achieve. Instead, disparities between the advantaged and the disadvantaged in the population tend to govern access to and safety of blood. Thus, assuring safe and adequate blood for transfusion requires an integrated public health strategy, including oversight through active regulation.

In sum, regulatory oversight is a necessary safeguard to ensure that blood collectors, plasma fractionators and care providers have control over the entire production processes, monitoring the quality and safety of the product/s and taking appropriate action if quality is compromised or if adverse events occur. Unsafe or inadequate blood supplies are costly both in economic and human terms. Evidence from around the world indicates that such failings arise from the lack of a coordinated system operating under a national blood policy.

How can regulation be made effective? The first insight is that it requires a comprehensive national approach established in law. Regulation assures that blood standards are met, but it depends on empowerment through a legislative framework. Health legislation for a national blood system should include government support; more specifically, resource commitment and allocation of responsibilities for different parts of the system. The government entities accountable and responsible for delivering blood products and services should be clearly specified. Secondly, a legal framework is needed for establishing and maintaining the coordinated network of blood services. Laws against commercialization of blood collection, for example, are needed to prevent exploitation of donors. Protecting recipients requires assuring quality, safety and accessibility of blood for transfusion. Toward this end, legislation is needed to empower a national regulatory authority (NRA) to carry out the job of setting and enforcing blood-related standards.

WHO has developed a tool on assessment criteria for national blood regulatory systems (25) to assist capacity building of national regulatory authorities for blood and blood products, as part of the regulation of medicines. The
tool serves to define best practices, and has value both for developed and developing countries, so that they can benchmark the functionality and sufficiency of their blood regulators, to identify both any gaps and areas for future development.

The assessment criteria for national blood regulatory systems identify the essential control functions that are needed to assure effective quality and safety of blood, blood products and related substances. The latter include the medicines and the medical devices such as IVD that are necessary in order to operate the system. The document also identifies a set of indicators for these functions in order for users to assess performance of the blood regulatory system against these necessary and recommended criteria. Twelve core functions have been identified that should be carried out by the national blood regulatory system. The word ‘system’ has been chosen to describe national blood regulation, recognizing that in many countries the necessary set of functions may not be carried out by a single governmental entity. Regardless of their structure, the relevant authorities collectively must deliver regulatory oversight consistent with internationally agreed best practices. Benchmarking authorities and functions against internationally agreed best practices is a basis to determine whether the regulatory system works.

As described in the WHO tool, the core functions of the national regulatory system are considered to be the following: licensing and registration of blood establishments (the blood collectors/the plasma collectors); licensing and registration of the manufacturers and distributors of the plasma derivatives; approval of blood and blood components; approval of PDMP; oversight of all the associated substances (e.g. anticoagulants, additive solutions, collection containers, IVDs including donor haemoglobin tests and haemoglobin scales, donor tests for infectious diseases, and transfusion compatibility tests); access to a laboratory that is independent of manufacturers in order to verify that the results being produced by the manufacturer are true and accurate; and all elements of quality management. Control of clinical trials becomes an essential feature based on the stage of development when beginning to approve nationally manufactured products. Similarly, when the regulator is undertaking independent approval of products that are made either outside or within the country (i.e. no longer accepting licensing from other countries), the regulator will need the capacity to evaluate the quality of the data that are produced to demonstrate product quality and safety. The ability to perform inspections is another essential function that is linked with enforcement powers. A fundamental concept is the insufficiency of an authority to merely make inspections and report findings; regulatory authorities must exercise effective oversight through legal empowerment of enforcement tools. Additionally, vigilance systems should be in place for monitoring adverse events either of blood donation or receipt of blood products. This function depends on ensuring record-keeping and traceability by the manufacturers – of all the regulated products including blood components, plasma derivatives and related medicines and medical devices. Lastly, as the system advances, the regulator should be part of the international environment of standard-setting.
and of communication, particularly about adverse effects related to products that might be distributed across borders.

In summary, PDMP and blood components should be regulated as biological medicines and therefore subject to government-based regulation. Based on their nature as biological medicines, the ultimate quality and safety of these products cannot be assured by end-point testing. Instead, quality processes and controls are needed at all stages of blood product manufacturing. Governments have a unique ethical responsibility to protect blood donors against exploitation and to assure equitable access to safe transfusions.

Blood and blood products safety requires a comprehensive national policy and strategy that start with government commitment. Principal elements of safety include selection of low-risk donors, testing for the major bloodborne diseases and implementation of GMP at all stages of blood collection and processing.

Plasma suitability for fractionation depends on meeting quality standards for blood collection and component manufacturing. Therefore, national and global sufficiency in plasma products can only be achieved by upgrading the quality production standards in blood establishments and reducing wastage of non-transfused plasma.

Blood regulation within a legal framework is therefore an essential element of any blood system to assure that appropriate quality standards are met.
8. Discussion summary

Based on the information presented, and the discussion during the stakeholders’ workshop, it was unanimously agreed that local production of plasma as an API in blood establishments improves access to safe blood products. There is a double benefit of using plasma as an API for manufacture of PDMP, which not only improves access to needed plasma derivatives but also enhances the safety of all blood components. In addition, the effect on blood components will improve sustainability and in time may provide a new source of revenue for the blood establishment.

A number of factors should be taken into consideration:

1. A centralized blood system is a key element of an efficient and safe blood collection programme, and is helpful in optimizing allocation of blood products to patients in need. The blood system is a primary element of a public health programme, and blood regulation through a NRA is the only way to ensure that quality standards of blood establishments and blood products are maintained. The national blood regulatory system should be in line with international standards, especially when local plasma is fractionated in another country and PDMP are then returned.

2. LMIC can only secure the supply of blood-derived products in a more affordable and sustainable way by using blood plasma collected in their own blood establishments and from their own population. Having local plasma used in production of immunoglobulin is also important with respect to its effectiveness in providing protection against local infections.

3. Substantial volumes of plasma are estimated to be discarded in many countries with no access to PDMP. A gap analysis and identification of investments required is needed. In many settings, improving the infrastructure would involve acquiring blast freezers and strengthening the cold chain. The residual risk in plasma remains to be determined and testing strategies devised to reduce the risk is essential. A strong GMP environment is also critical, including information technology requirements, traceability, validation and expertise in both blood establishments and NRAs. Prioritization of tasks required is needed in line with determination of cost benefits.

4. Cost sharing of production processes improves financial sustainability in blood establishments. As fixed costs increase with imposition of higher standards, sustainability improves as more products and revenues are found. These fixed costs include facilities, freezers, production and testing equipment, as well as information systems. Production of red blood cells, platelets, plasma for transfusion and recovered plasma acceptable as an API for fractionation into various PDMP, has the potential to generate more revenue for the blood establishment, making the programme sustainable, and spreading the fixed costs over a wider array of blood products. Over time, this should result in improved cost efficiency and cost recovery. These advantages are not available if whole blood is the only product generated.
An analysis of the opportunities and main barriers to local production of quality, safe recovered plasma as an API in blood establishments was presented to the stakeholders' workshop, including collated information and selected case studies (see Annex). The suitability and feasibility of local production of plasma as an API for fractionation, and the related transfers of technology and know-how that would be required in countries discarding relevant volumes of plasma, were discussed. Three different steps were outlined:

The first step is to improve the quality of available plasma such that it becomes suitable as an API. While there are already generally relevant criteria, some aspects (e.g. testing) may vary depending on the epidemiology of the country and even upon the particular fractionator. WHO can help to facilitate efforts to improve the quality of the plasma. In some countries this may also require initial external funding to improve the blood establishment infrastructure, as well as the expert help, not currently available in some LMIC. A strong quality system and GMP culture in blood establishments are essential. The time and resources to achieve this should not be underestimated, and will depend on the current status of the country’s blood establishment operations. This is one level of transfer of technology, the initial step.

Building on the experience in South Africa, a model of a fractionator and national blood service working together in an epidemiologically challenging environment, an objective analysis was performed regarding the potential for transfer of technology to enable fractionation of plasma from two other countries in the Sub-Saharan region, those being Uganda and Zimbabwe (see Annex for case studies).

In Asia, Indonesia was identified as a large country with support and interest from the government for the regulatory authority and the blood providers to improve and secure the blood supply. About 50 000 litres of plasma that are currently being discarded were considered potentially usable for fractionation from a few of the larger local centres. This could later be expanded to the other centres and impact the entire country.

The next, or perhaps intermediate step, would be for the country to work with an existing plasma fractionator to ensure that the quality of the local plasma meets the fractionator’s specific requirements, such that contract fractionation can be organized. The larger number of PDMP fractionated, the more cost-effective the process will be. The minimum annual volume of plasma required may vary with different fractionators, but cost effectiveness will improve with larger volumes. The fractionator may pay the country for recovered plasma and/or may return certain finished plasma derivatives to the country for local use. In either event, this provides a new revenue stream for the blood establishment that can be used to further improve its operations. When derivatives are returned to the country, it has been demonstrated that this is at a substantially lower cost compared to importing finished products, when available, as exemplified in Argentina, Brazil, Iran and South Africa (see Annex).
A subsequent step might be for the country to consider developing a local fractionation facility, but due to the tremendous complexity and expense, this should be entertained with an established fractionator as a partner to guide in the process. Fractionators with such expertise and willingness to share technology already exist. The greater the volume fractionated annually, the more cost-effective the plant will be. Small countries should therefore consider collaborating on a regional basis to increase the volume of plasma to be fractionated in a planned plant. The number of different PDMP produced should be optimized to at least three. Establishing a new fractionation plant involves the most complex level of transfer of technology. The time required to complete this should not be underestimated, as it may take at least five years before operations are fully in place.

Examples and information included in this report demonstrate that technology and know-how transfers to facilitate the use of local plasma resources in order to improve access to safe PDMP are feasible, having a beneficial impact on access to safe plasma products, increasing product supply sources and improving health status. A systematic evaluation of requirements, drivers and barriers could help facilitate successful technology and know-how transfers for manufacture of plasma as an API, leading to improved local or regional access to safe plasma products.

Government support and regulation of blood establishments and fractionators are essential throughout this process, and must be assured from the start. While there are elements in common, regulations that may already be in place that are pertinent to traditional pharmaceutical manufacture, are not sufficient, since raw material derives from individual human blood donors, and the screening tests on donations need to be of high sensitivity and specificity, and appropriate to national epidemiology. These regulations should be consistent with international standards as the recovered plasma and the resulting derivatives may cross international borders, going to and from the fractionator.

Along with government support, this sequence of events should prove cost effective over a reasonable period of time, in addition to improving public health in several important ways.

**What we have learned**

It has been estimated that 9.3 million litres of human plasma are wasted in the world each year. Such plasma, when meeting GMP requirements, could be used to treat over 200,000 patients with bleeding disorders and primary immunodeficiency if fractionated.

Implementation and upgrading of production standards for recovered plasma in blood establishments can lead to an upgrade in such establishments overall, and provide a real benefit to public health. This public health benefit includes provision of better epidemiological data for the population, as well as a reduction in transmission of infectious diseases by blood transfusion (e.g. HIV and hepatitis) by virtue of red cells, platelets and plasma transfused directly as components.
The key elements in GMP during production of plasma as an API that could be implemented within a reasonable period of time include: introduction of information technology and traceability systems, equipment validation, calibration and maintenance, corrective actions in case of defect, selection and qualification of in vitro diagnostic tests, cold chain for plasma, quality systems, and GMP expertise development for blood establishments and NRAs.

Implementation and enforcement of GMP in blood establishments is a requirement for reliable production and traceability of plasma for fractionation. The public health benefit includes the availability of a local API for the manufacture of plasma derivatives contributing to universal coverage. Close collaboration and coordination between the NRA of the plasma fractionator, and the NRA of the plasma supplier, is needed.

Contract fractionation programmes in large countries, such as Brazil and Iran, with government commitment, have allowed cost reductions of up to 40% compared to similar imported PDMP (see Annex). In addition, products made from local plasma may induce a lower price for derivatives imported from abroad, due to competition within the internal market.

Apart from utilizing otherwise wasted plasma, improving the safety of components for transfusion, and making PDMP available, contract or local fractionation can provide security by protecting the country from worldwide shortages and wide price fluctuations in commercially available derivatives from other countries. If a country aims to have local fractionation capability, consideration should be given first to plasma contract fractionation as a transitional step. Expertise should be sought in this regard for transfer of knowledge and technology. Regional collaboration may be preferable to ensure that a sufficient volume of plasma is reliably available to make a fractionation facility viable.

Ways forward

Further refinement is needed in estimations of the volume of plasma potentially wasted and/or discarded in selected countries and regions, and in assessing how much could be brought to fractionation quality within a reasonable number of years. While there are clearly substantial unmet patient needs for PDMP, better data should be sought regarding the identification and diagnosis of local patients treatable by plasma derivatives, in order to determine the projected need for plasma derivatives in a given country. This could be achieved through collaboration with patient organizations.

Development of an ‘aide-memoire’ as a decisional framework document was requested, that describes a typical roadmap to help countries plan and achieve the steps needed for plasma to become an API, and to decide whether or not local plasma sources are ready for fractionation. More specifically, such a roadmap should guide countries through the contract or local fractionation decision-making process, and provide specific related criteria. Guidelines regarding contract fractionation or local fractionation need to be developed.
to help Member States with evaluation of potential challenges and technical options since an early stage of the decision-making process (e.g. tools for cost-effectiveness analysis, technical agreements with fractionators, choice of fractionation and viral inactivation technologies etc.). Acceptable standards and requirements for plasma for fractionation are already considered in published WHO guidelines (5,7). Information regarding the required timelines for initiating contract fractionation and to develop local fractionation capabilities should also be emphasized.

A suggestion was made to convene a working group of plasma contract fractionation procurers to share experiences and guidance. With implementation of plasma fractionation technology, expertise is built in the country that would help in other areas of bio-manufacture, e.g. logistics, cold chain, sterile manufacture.

Furthering regulation specific to blood products was considered of utmost importance with an overwhelming and unanimous agreement from stakeholders for WHO to support Member States and coordinate the phase two activities in this project. Varying degrees of assistance may be needed in different regions for building technical capacity in blood establishments and NRAs. The technical capacity of NRAs will need to be strengthened in order to define the appropriate requirements in support of quality, safety and efficacy of locally made products prior to the time of switching to contract or local manufacture.

Building technical and regulatory capacity in blood establishments and NRAs, by way of GMP training workshops and mock inspections, introducing a ‘production culture’ in blood establishments was identified as a major need. Educational activities on the regulatory and technical requirements of plasma fractionation are priority steps. The precise selection of viral test kits should take into account several scientifically-based considerations including: the sensitivity and specificity of the tests (including local tests) (1); local epidemiological situations (e.g. viral genotypes); donor characteristics (e.g. first time versus repeat donors); evolution of testing technologies; and, understanding the risks and knowing the limitations of the assays used. The international standards and reference preparations established by WHO will be of help in this regard, as requested in resolution WHA63.12 on availability, safety and quality of blood products (3).

Information should be shared with blood establishments and NRAs with respect to the selection of technologies and to facilitate assessment of opportunities for fractionation of plasma. Support to regional initiatives for organizing a network of local regulatory authorities was recommended. A recommendation was also made to promote the inclusion of blood and red blood cells in the WHO Model List of Essential Medicines (1,26,27).
9. Conclusions

To summarize, the main conclusions drawn from discussions at the stakeholders’ workshop and analysis of information are as follows:

a. There is currently a major wastage of plasma in LMIC.

b. Local production of recovered plasma as an API in blood establishments of LMIC will improve access to essential medicines and to safer blood products.

c. The means to produce plasma as an API are well understood and mastered in HICs and can be transferred to LMIC. Know-how is readily available and WHO can help coordinate these efforts with the collaboration of relevant stakeholders. One or two pilot LMIC should be selected to serve as models for this project.

d. There is a clear public health need for affordable essential blood derived medicines in LMIC. In many LMIC plasma derivatives are frequently not available. Insufficient treatment in the whole range of blood products leads to increased mortality and morbidity and increased health care expenses for the country.

e. The lack of recovered plasma meeting required quality standards in LMIC is a major impediment to its use for fractionation as an API and for the manufacture of essential PDMP.

f. Improving the quality of recovered plasma from local donations concomitantly increases the safety and efficacy of the other blood components being transfused, thus reducing mortality and morbidity among many patients by reducing the risk of transfusion-transmitted infectious diseases.

g. Transfer of technology and know-how to improve the quality of plasma produced by blood establishments in LMIC is feasible. It will require some initial financial support for infrastructure improvements in some LMIC.

h. Local production of higher quality plasma can improve the cost effectiveness of the local blood establishment and ensure its sustainability.

i. Developing a relationship with an established plasma fractionator, for contract fractionation as well as subsequently – if justified – for establishing a local fractionation facility, has been shown to be a feasible approach under certain conditions.

j. Supporting the local production of quality plasma from voluntary non-remunerated blood donors is the only pragmatic way to improve the supply of life-saving blood derived medicines in LMIC.

k. Building technical and regulatory capacity and facilitating transfer of technology for the production of plasma as an API for fractionation in LMIC are fundamental elements, upon which a second phase of the project will need to focus.
While the examples presented in the stakeholders’ workshop involved countries already aware of the benefits of this project, information must also be disseminated to those countries not yet aware of the advantages of fully utilizing their plasma supplies, particularly those with the potential for large volumes of plasma that could achieve the quality needed be an API for plasma derivatives. It was considered that a successful pilot project with proof of concept would be effective in convincing other countries to pursue this approach.

The project would benefit patient organizations, clinicians, manufacturers, blood establishments, NRAs, and ultimately national, regional and global public health. It has the measurable parameters of increasing transfusion safety and decreasing plasma wastage, both of which will improve public health. With regard to financial support, the project described in this report has a clear entry point, and a clear exit point, i.e. when the available plasma has been successfully processed by a fractionator. Subsequently, with continued government and regulatory oversight, the project should be sustainable.
References


Annex: Case studies

A. Production of recovered plasma for fractionation

A.1 Production of blood components for transfusion and plasma for fractionation in developing countries. Analysis of costs versus benefits based on information from South Africa, Uganda and Zimbabwe.

Blood establishments in LMIC mainly collect whole blood, but there are significant differences among countries as to the proportion of whole blood units separated into blood components. Collection and use of whole blood may seem to be the most cost effective in some settings, but the country then has no access to platelets and PMDPs. Most value can be derived from a unit of whole blood by producing red cells, platelets and plasma for direct transfusion or plasma for fractionation. However, maximizing component production and usage depends on the infrastructure of a given blood establishment, as significant collection, transport, production, testing and staffing are required to ensure quality.

Producing quality plasma that can be used as an API for fractionation requires a regulatory framework responsible for setting standards (in particular, if the plasma will cross international borders), which should apply to blood component separation, cold chain (including prompt blast freezing, essential to preserve clotting factor activity), blood processing and storage, donation testing (serology and NAT depending on epidemiology), and a validated quality assurance system.

The South African National Blood Service (SANBS), responsible for virtually all the blood donations in the country, collects 800,000 units of whole blood annually (an increase of 100,000 in the past five years); 83% of donations are from repeat donors; 98% of blood collected is separated into components, and 96% of the separated plasma is frozen within 24 hours. Individual donation NAT was added to serological testing in 2005, in order to reduce the window period (WP) for infectious diseases and increase blood safety. The number of processing centres was reduced, and all donor testing was consolidated to two testing laboratories. With these improvements in quality, 153,000 litres of plasma have been provided for fractionation, providing 13% of SANBS annual revenue.

Quality-assured serological testing is the most powerful factor in reducing risks of transfusion-transmitted infection (TTI) and is mandatory. In countries with a high prevalence of infectious diseases, implementation of individual donation NAT can further increase safety. This would add a cost to each unit of blood (approximately US$ 20), but increases safety, reduces the chance of litigation, improves donor confidence and thereby increases the blood supply – it also improves confidence in the blood supply, increasing usage and ultimately benefitting patients.

Prior to SANBS implementing NAT in 2005, there were two confirmed HIV TTIs per year. In the subsequent six years, there has been none reported. During this
period at least 96 HIV positive donations were detected with NAT that would have been missed previously with serological testing alone. For hepatitis B virus (HBV), the corresponding figure is 206 HBV positive units only detected with NAT. Considering that each donation can be separated into two or three components, the number of TTIs prevented is even larger.

The benefits to South Africa are substantial in that many HIV and HBV TTIs are prevented annually; and 153 000 litres of plasma are fractionated into PDMP, such that the needs of the country for plasma derivatives are essentially met.

An approach to strengthening the blood establishments to produce quality, low-risk products involves performing a gap analysis, assessing the investments required, and analysing the costs versus benefits. For Zimbabwe, 98% of all blood donations are separated into blood components; about 15 000 litres of usable plasma are discarded annually; the prevalence of confirmed HIV-positive donations is 0.7%, and 0.88% for HBV. Using the same approach as South Africa, the residual risk for window-period transmission of HIV in Zimbabwe is 1 in 14 000 and for HBV is 1 in 10 000. In South Africa, prior to 2005 the risk for HIV TTI was 1 in 38 000 and now, with NAT-tested donations, it is 1 in 100 000. It is unlikely that any fractionator would accept plasma with the current levels of residual risk for HIV and HBV. With the implementation of NAT in individual donations, it is estimated that an additional six HIV-positive and 15–20 HBV-positive donations would be identified, thereby preventing about 10–12 HIV transmissions and 30 HBV transmissions annually. Currently, there are five processing centres, which can be reduced to three in order to optimize use of equipment, particularly blast freezers that will need to be acquired. New storage refrigerators and freezers will also be needed. Automated equipment is already in place for blood component production. Based on a preliminary evaluation, the initial capital costs are projected to be US$ 500 000 (US$ 1.36/donation), with US$ 863 000 (US$ 11.40/donation) annual operating costs for the first two years. After implementation and acceptance of plasma for fractionation, revenue for the plasma was calculated as US$ 975 000 per year, with savings from not discarding plasma of US$ 165 000, and avoided costs of litigation for HIV and HBV transmissions could be US$ 128 000. Additional revenue from plasma derivatives provided in the country is not included here. The total costs for the first year would be about US$ 2 000 000, with cost recovery anticipated during subsequent years.

A similar case study was done for Uganda. Currently, about 40% of all donations are separated into blood components; about 42 000 litres of usable plasma are discarded annually. The estimated prevalence of confirmed HIV positives is 0.75%, and for HBV it is 1.5%. The residual risk for window period transmission of HIV is 1 in 13 500, and for HBV is 1 in 6000. With the implementation of NAT in individual donations, it is estimated that an additional 16 HIV-positive and 60 HBV-positive donations would be identified, thereby preventing about 25–30 HIV, and 100 HBV, transmissions per year. There are seven processing centres, which could potentially be reduced to three. Automated equipment for component production, and blast freezers would need to be acquired. The initial capital costs would be US$ 606 000 (US$ 0.60/donation), and annual
operating costs would be US$ 2,561,000 (US$ 12.63/donation), with resultant revenue from plasma of US$ 2,470,000, and potential savings of US$ 390,000 in litigation avoided and US$ 35,000 in plasma not destroyed. Again, revenues from newly available plasma derivatives are not included. The total costs for the first year would be about US$ 4,000,000.

In summary, the above information indicates that it is cost effective to improve infrastructure and testing so that plasma can be supplied for fractionation, and PDMP can then be made available in the country. Other benefits include safer red cell and platelet products (many HIV- and HBV-positive transmissions prevented), and improved confidence in the blood supply.

A.2 Indonesia: Gap analysis in blood establishments

Currently, blood services in the country are provided by 212 Indonesian Red Cross (IRC) blood establishments. Recently, in an effort to increase access to blood, the government established another 202 blood establishments in government hospitals, in areas where there are no IRC centres.

In 2011, just over 2 million units of whole blood were collected, resulting in a donation rate of 8 per 1,000 population, with most of it collected by IRC blood establishments. This donated blood comes from first-time donors (40%) and repeat donors (60%). Moreover, in order to increase efficiency of blood usage, 64% of this blood was processed into components. However, more efforts are still needed to increase blood donations nationally as currently only 70% of needs are met. Most blood donations are serologically tested by enzyme-linked immunosorbent assay (ELISA), some are by rapid testing, and a few by NAT.

Among the 212 IRC blood establishments, the biggest centres are located in Java island and comprise approximately 40% of the national blood supply. Blood components are produced from 80 to 90% of these units, but this results in discarding approximately 68,000 litres of recovered plasma per year. Indonesia expects this excess plasma can be fractionated to produce human albumin and IVIG, which are currently imported at a high cost. A substantial need for FVIII was also identified.

A preliminary analysis suggests that to improve the quality of recovered plasma to be suitable to fractionators as an API, the following would need to be considered: a) consolidate or rationalize the number of blood establishments processing plasma; b) standardize testing protocols for all blood donations; c) enhance the cold chain and freezer storage capacity; and, d) improve quality assurance measures, in particular to implement GMP in blood establishments producing plasma for fractionation. A cost-effectiveness analysis should underpin the decision-making process. These measures will, no doubt, improve safety of blood components for transfusion. A cost analysis for these measures is not yet available.

In an effort to improve the management of the blood system in Indonesia, the government has issued regulations that put all blood services under the
umbrella of the Ministry of Health, creating a National Blood Committee that involves all pertinent stakeholders in the country. These regulations also emphasize the government’s responsibility in managing, guiding, monitoring and financing the blood system, and state that plasma can be fractionated into plasma derivatives either inside Indonesia or by fractionators abroad.

The role of this National Blood Committee is to develop an organizational structure that is appropriate to ensure that the blood programme can be run efficiently and effectively, as well as to review the established IRC Standards on blood services with the intent to upgrade them into national standards. At a national level, a GMP document on blood establishments is also under review, and an independent regulatory body to evaluate the blood system has been delegated to the national authority for control of medicines.

In order to be cost effective, PDMP other than albumin and immunoglobulin would need to be produced from the plasma, which will require prompt blast freezing of separated plasma, so that blood coagulation factors can also be produced, better meeting the country’s needs at a reasonable cost. Cost effectiveness will improve as volumes of acceptable plasma for fractionation increase. Indonesia is willing to accept international assistance in working towards these requirements, and government endorsement and commitment is a major asset. Strengthening of technical capacity of the NRA will be supported by WHO.

A.3 Production of plasma for fractionation: Main challenges in India

In India, there are over 2500 blood establishments, which vary greatly in size and local practices. About 10 million units of whole blood are collected each year from a population of over 1 billion people. However, about 80% of these units are transfused as whole blood. The remaining 20% could generate about 400 000 litres of plasma, but much of this is transfused as plasma or cryoprecipitate, or discarded, so the potential volume of plasma possibly available for fractionation would be about 150 000 to 200 000 litres per year.

India’s usage of plasma derivatives per capita is less than that of developed countries, and there are frequent shortages of PDMP. India depends upon the import of plasma products, as it does not have capability of processing plasma within the country itself.

There have been some contract fractionation activities of Indian plasma for the last 5–7 years. However, much work is still required so that higher volumes of recovered plasma meet the GMP requirements for fractionation in accordance with international standards. A detailed gap analysis needs to be performed. It would be expected to identify at least the following needs: Consistent national regulations applied to all blood banks, central coordination of blood establishments with standard procedures and testing protocols enabling determination of residual risk, endorsement of component therapy for patient transfusions, robust cold chain (i.e. blast freezing, cold storage capacity and reliable maintenance of the frozen state during transport), a comprehensive quality assurance programme, and an effective information technology system.
for donor tracking and traceability. Upgrading of production standards in blood establishments would require effective enforcement and implementation of GMP and qualification of GMP inspectors regarding production of blood components. Furthermore, enforcement of blood-specific regulations and quality evaluation of blood safety-related in vitro diagnostic devices will be needed. The quality of these tests would have a significant impact on the plasma residual risk, a fundamental consideration when discussing quality of plasma.

Given the size and complexity of India, a practical approach would be to select a few states where effective enforcement and implementation of GMP for the production of plasma for fractionation would be likely to succeed. This could provide a solid basis to motivate and support further developments in a reliable manner for other parts of the country. Based upon the experience of other countries, pursuing contract fractionation while planning a local fractionation facility would seem a prudent approach.

A cost-effectiveness analysis should be performed. The costs of implementing the requirements above should be compared to the savings from importing less plasma derivatives from a wide variety of sources. Testing should be centralized as well as procurement of supplies, at least at the state level. An additional benefit to be expected would be increased quality of all components for transfusion.

Recently, a blood act has been submitted to the cabinet of India, regarding national blood policy, regulatory reforms, consolidation of blood banks, rational use of blood, and a plan for development of plasma products, but it has not yet been passed.

A.4 A brief update from Saudi Arabia

The Kingdom of Saudi Arabia has a blood donation rate of 16 per 1000 population. Components are produced from about 80% of the collections, and about half of the plasma is wasted. There are 258 blood banks, both government and private, not including the hospital blood banks. The private blood banks are not under Ministry of Health management. The Saudi Arabia Food and Drug Administration (FDA) regulates blood products, but not yet the blood establishments. All plasma derivatives are imported, and there is no contract or local fractionation. There is a plan, with government and financial support, for a local fractionation facility that could also accommodate plasma from other neighbouring countries. Transfer of technology will be needed to support production of plasma for fractionation, as a first phase.

B. Plasma contract fractionation programmes

When discussing technology transfers in relation to pharmaceutical products, it is often difficult to provide solid evidence that the technology and know-how transfer have an impact on local access to a given product. In the case of blood products, and in a context of worldwide shortages due to limitation in the supply of the raw material, evidence is available to confirm this. Technology
and know-how transfer to LMIC has mostly focused on the improvement of the collection procedures of plasma for fractionation to allow contract fractionation by an established facility, usually located in a more regulated environment (14).

Transfer of production technology for PDMP has been understandably limited until now, not only because of the technical difficulties in the implementation of a new facility and in the recruitment and training of skilled operators, but also due to the initial human and infrastructural efforts that are needed to generate a sufficient volume of quality plasma justifying the investment in a domestic facility. A logical intermediate phase in the consideration for a domestic facility is a phase of contract fractionation whereby the increasing volume of quality plasma being generated by a country is sent for contract fractionation abroad helping to improve access to safe blood products within a reasonable timeframe.

In the past 15 to 20 years, several countries have started contract plasma fractionation agreements. In a few cases, such as Iran (17, 20, 21, 25) and Brazil (19), steps towards the construction of a domestic facility and technology transfer have been taken following a phase of contract fractionation.

B.1 Iran

The Iran Blood Transfusion Organization (IBTO) is an integral part of the national health system and was established and financially supported by the government. IBTO has a nationwide network and is responsible for all activities related to blood transfusion including donor recruitment, blood collection, testing, preparation of blood components and distribution of blood and blood components to the health centres.

Blood components are distributed free of charge to public and private hospitals, whereas PDMP incur a cost to hospitals or patients. In 2011, about 2 million units of whole blood were collected. As component production has increased to >95%, transfusion of whole blood has declined drastically.

Serological testing for HIV, HBV, HCV and syphilis is performed on all donations, and recently a pilot NAT programme was started. Iran tests its donations using EU and FDA licensed IVD, and has full look-back and traceability capability. The percentage of HBV confirmed donations has decreased to 0.25%, partly due to national strategies of controlling HBV in the general population, but also due to stricter donor selection. The HCV and HIV positive rates in blood donors have also respectively declined to 0.07% and 0.004% in 2010.

With the shift to component therapy, surplus recovered plasma became gradually available, providing Iran with the opportunity to optimize its use for manufacture of PDMP and the use of these products started to increase. The importation of PDMP was consuming a substantial part of the national health budget.
Iran started a contract fractionation programme in 2005 in order to use the surplus recovered plasma for producing PDMP. Initially, 40,000 litres of plasma were used per year, but this volume has increased to about 150,000 litres in 2011. Iran considered its options for providing the essential PDMP as continued importation, contract fractionation or local fractionation, and chose contract fractionation initially. The selection of a fractionator was not easy, as different fractionators had different specific requirements, but agreement was achieved on these and annual plasma volume, duration of contract and product profile. IBTO has undergone multiple audits by the fractionators and national regulatory authorities of the fractionator’s country. Challenges in maintaining the cold chain were met, and difficulties in transporting the plasma across international borders were also overcome. Mini-pool NAT is performed by the fractionators, with any possible positive results reported back to IBTO.

Table A1 below indicates the product yield for the four major derivatives, along with annual usage for the country. The PDMP received under this contract fractionation programme provide for 100% of IVIG used in Iran, as well as 15% of the FVIII, 100% of the FIX, and 40% of the albumin requirements. The differential cost between imported products and those obtained via the contract fractionation programme are shown in the table, resulting in actual annual savings of more than US$ 11 million in 2011. FVIII and albumin are still imported, but using a bid process for all the remaining needs of the country. Availability of PDMP produced from Iranian plasma in the market has inevitably forced the providers of commercial products to offer more reasonable prices for their products in order to hold their share of Iran’s market.

<table>
<thead>
<tr>
<th>PDMP</th>
<th>Yield/L by contract fractionation</th>
<th>Average annual consumption</th>
<th>% market share met by contract fractionation</th>
<th>Average cost € 2010</th>
<th>Annual direct savings from contract fractionation US$ (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>4.5g</td>
<td>650kg</td>
<td>100%</td>
<td>29.5</td>
<td>8 million</td>
</tr>
<tr>
<td>F VIII</td>
<td>160 IU</td>
<td>140m IU</td>
<td>15%</td>
<td>0.20</td>
<td>544 000</td>
</tr>
<tr>
<td>F IX</td>
<td>200 IU</td>
<td>15m IU</td>
<td>100%</td>
<td>0.21</td>
<td>777 000</td>
</tr>
<tr>
<td>Albumin</td>
<td>24.5g</td>
<td>8500 kg</td>
<td>40%</td>
<td>1.9</td>
<td>1.8 million</td>
</tr>
</tbody>
</table>

Based on the annual number of whole blood donations, IBTO is able to produce about 250,000 litres of surplus plasma annually. Therefore in order to use this plasma for improving availability and affordability, and due to lack of any national fractionation facility, IBTO determined to pursue its contract fractionation programme. Although improving the blood safety profile of the country through improving quality assurance system has been one of the main objectives of this project, the programme has also significantly improved availability of PDMP in the country.

In summary, Iran’s contract fractionation programme has substantially improved: the quality assurance system and blood safety for its national transfusion service, accessibility and affordability of plasma derivatives, and resource allocation in the national health system.
B.2 Brazil

Approximately three million blood donations are collected each year in Brazil by nearly 200 blood establishments, which comprise a nationally-coordinated network of 27 state blood transfusion services, representing a donation rate close to 2%. Hemobras is the state-owned not-for-profit organization created for the manufacture of plasma derivatives, and it is currently responsible for plasma contract fractionation. The Agência Nacional de Vigilância Sanitária (ANVISA) is the NRA, which is responsible for regulation of all medicines in the country.

The volume of plasma potentially available each year for plasma fractionation in Brazil is in the range of 400 000 litres. In 2000, consideration was given to creating a local plasma fractionation plant. The possible options were:

1) Import 100% of the country’s needs for plasma derivatives

Importing would provide safe and improved medicines and avoid the risk and expense of building and operating a fractionation plant. However, this would put the country at risk, as worldwide demand for derivatives is increasing and it can surpass production capacity, resulting in much higher prices and affordability difficulties as well as shortages. Recovered plasma would continue to be wasted in this scenario; currently very few companies are authorized to incinerate plasma in Brazil and the cost is US$ 5 per litre. There is also the ethical issue of non-remunerated donors’ displeasure upon learning of the plasma from their donation being wasted, which could negatively affect future blood donations and thereby the blood supply.

2) Engage in a contract fractionation programme

Contract fractionation would result in an improved national blood system as the quality of recovered plasma (and thereby the cellular components as well) would be improved. This should reduce the amount of plasma wasted. It would help ensure adequacy of supply of plasma derivatives for the country and result in lower prices compared to importing. However, it is unlikely that a single contract fractionator could accommodate all 400 000 litres of plasma that Brazil would need to offer.

3) Build and operate a domestic plasma fractionation facility

Management of fractionation contracts is not easy, and requires significant work and dedication even if there is a good relationship between the plasma providers and the plasma fractionators. Fractionating locally could have the advantage of providing access to and incorporation of a complex biological technology, and would also require improvements in the blood component production systems. Since plasma is free of direct costs in Brazil, this would be the option with the lowest long-term costs. However it requires high initial capital investment and takes years to consolidate. There is also a risk of failure of the technology transfer, as has been demonstrated in several other places over the past decade; this is due to the complex engineering and highly technological demands of a biotech pharmaceutical plant.
Brazil's decision was to engage in contract fractionation and build a local fractionation plant. As neither contract fractionation nor having a local plant alone would be able to satisfy 100% of Brazil's demand for FVIII and IVIG, any remaining needs for FVIII and IVIG would be met by importing these products.

The four conditions needed for financial viability of a local fractionation plant were identified as: availability of suitable plasma; an established regular market for plasma derivatives (now about US$ 1 billion per year in Brazil); the technology; and, a strong regulatory system. In 2009, Hemobras assumed responsibility for managing plasma as an API for the country, since that is a requirement for success both for contract fractionation and for local fractionation. It was realized that it would be very difficult to succeed in fractionating plasma locally without having the experience of contract fractionation.

The current annual volume of plasma available for contract fractionation is 150 000 litres, (plus or minus 25%). Plasma discarded by blood establishments before being sent to the fractionators (before or during preparation) is still too high in that only 33% of plasma is sent for fractionation due to technical reasons or low volume. The fractionator performs annual audits of the blood establishments, but has only audited 130 so far, as the remaining 70 are small. Of those audited, 115 have been approved and 14 rejected. Even for those approved, 21% of units were rejected initially, but that has improved to 11%, with a goal of reducing this rate to 3% or less. The prevalence of positive TTI markers is lower in blood establishments that have been approved than in the rejected ones. Overall, the wastage of plasma is 44%. Only 2% of the blood establishments supply more than 60% of the plasma they produce. The ten largest suppliers of plasma are able to provide 54.6% of the total volume of plasma sent to Hemobras.

The wastage of plasma could be related to the lack of compliance with GMP, as well as to difficulties in maintaining the cold chain in Brazil's tropical climate. It is important for the blood establishments to work closely with their partner in fractionation. Government commitment is also needed to consider the production of plasma as a priority. These will require a change in organizational culture.

Combining the approaches of contract fractionation and transfer of technology is viewed as fundamental. Brazil has been able to assume some steps and activities progressively, and some phases of technology transfer can be anticipated. NAT mini-pool testing will become mandatory in Brazil in 2013.

The derivatives to be produced under contract fractionation are albumin, IVIG, FVIII and FIX. The minimum yields for each product are shown in Table A2.
Table A2: Minimal yield for plasma products

<table>
<thead>
<tr>
<th>Product</th>
<th>Minimal yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>24 g/L ±5%</td>
</tr>
<tr>
<td>IVIG</td>
<td>4.8 g/L ±5%</td>
</tr>
<tr>
<td>FVIII</td>
<td>115 IU/L ±8%</td>
</tr>
<tr>
<td>FIX</td>
<td>220 IU/L ±5%</td>
</tr>
</tbody>
</table>

The supply of plasma derivatives obtained from contract fractionation meets 36% of Brazil’s needs for Albumin, 30% for IVIG, 15% for FVIII and 39% for FIX. Since it is mandatory to meet the FVIII needs of the country, the Ministry of Health will import plasma-derived FVIII, and, if necessary, recombinant FVIII.

Assessing the cost effectiveness of contract fractionation in Brazil is important. When comparing import prices with prices of the products from contract fractionation from Brazilian plasma, the annual savings are US$ 26 million (this is a 44% reduction in import price, and so very cost effective) (Table A3). Management of indirect costs of this contract is not included in these figures.

Table A3: Cost-effectiveness of contract fractionation in Brazil

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost for import (US$)</th>
<th>Annual supply from contract fractionation</th>
<th>Annual cost (US$) of contract fractionation</th>
<th>Annual cost (US$) for importing the amount supplied by contract fractionation</th>
<th>Difference (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>50/g</td>
<td>720 000 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F VIII</td>
<td>0.22/IU</td>
<td>17 250 000 IU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F IX</td>
<td>0.23/IU</td>
<td>33 000 000 IU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5/g</td>
<td>3 600 000 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33 300 000</td>
<td>59 985 000</td>
<td>26 685 000</td>
</tr>
</tbody>
</table>

The Ministry of Health, ANVISA and Hemobras are working together on quality systems, educational activities, offering assistance to blood establishments for improved preparation, storage and quality control of plasma. Hemobras is reimbursing the blood establishments for additional logistic costs incurred to improve plasma quality and availability.
C. Local plasma fractionation activities

Two examples of not-for-profit local fractionation activities in LMIC were discussed. It is important to highlight that these activities started 30 years ago when standards for plasma for fractionation were not as strict as they are today.

C.1 Argentina

Argentina has a plasma fractionation facility that has been developed as a means to make use of the plasma generated by blood establishments that is not used for transfusion (70 to 80% of the plasma produced).

Initially, the improvement in the quality of plasma to meet requirements for fractionation represented a financial burden on blood establishments that was counteracted by the beneficial impact on public health and better availability of PDMP. Discarding plasma has a cost.

The expenditures needed to attain GMP in the manufacture of plasma for fractionation are necessary investments in the production and control of plasma as an API (i.e. facilities, equipment, personnel, screening tests, quality systems, traceability, etc.). Benefits include better utilization of all blood components, which are strategic resources, resulting in better provision of the country’s needs for plasma products. This leads to an improvement in public health, at a reduced cost.

Engaging in a contract fractionation programme results in greater benefit from available plasma, and ensures a national supply of essential products. There is no need for the major financial investment required for installing a plant, while allowing secure access to plasma products at lower cost, even in periods of global shortages, because the cost of fractionation is much lower than the cost of importing finished products. In parallel, contract fractionation improves the national blood system. Nevertheless, there may be some costs directly linked to the production of plasma of the quality required for fractionation, and one should keep in mind that the fractionator will require a minimum amount of plasma before engaging in this activity. The fractionator and the local blood collection system should work closely together to solve problems and upgrade the collection system. Finally, technical problems in the fractionation plant may occur, causing product shortages.

The decision to build a local facility or to undertake contract fractionation should take into consideration the ability to obtain enough plasma of the required quality to make the project cost effective, the heavy capital investment necessary for facilities, equipment and technology transfer for a range of critical plasma products, and the requirements for local expertise and infrastructure in industrial development (highly specialized engineering, water production, equipment maintenance, etc.). When a country decides to develop production methods, the time involved in developing and scaling them up may be quite long, as well as that needed to provide the personnel with adequate professional training.
Having such elements under consideration, a plasma fractionation project was initiated in 1974 as part of the University of Cordoba in Argentina. Until 1994, the volume of plasma fractionated remained low (about 20 000 litres/year), only two products were generated, with low yields, and plasma quality problems were encountered, leading to constant financial losses. In 1995, a plasma quality work plan was established with the blood establishments (including audits by the fractionator), which led to gradually increasing volumes of plasma fractionated up to 100 000 litres, and expanding the product range to coagulation factor VIII and several hyperimmune IGs, making the plant cost effective in 2012. Factor IX and prothrombin complex concentrate are under development. In 2011, this fractionation centre could cover 65%, 60%, and 5% of the national needs in IGs, albumin, and FVIII, respectively. The facility has an R&D department for new products and process developments. Today, the products are considered to comply with national and international requirements, and the plant is inspected annually by Argentina's regulatory authorities, and occasionally by those from Chile and Uruguay. From 2013, it is planned that the local NRA will inspect blood establishments producing plasma for fractionation.

The establishment of this project has significantly improved the national blood system and reduced public health expenditures. Plasma product prices from the local producer are the lowest in the country and act as a regulator of market prices. Argentina could maintain the national supply of plasma products even during economic crisis (2001).

The financial arrangement between blood establishments and the fractionator implies that the former receives a proportion of the product outputs to compensate for the cost of plasma, or equipment or supplies to improve plasma quality. The remaining plasma products are sold to compensate for the production cost and ongoing technological upgrading. As a result of this programme, the Argentinian public health system covers part of local needs of plasma products free of charge, and another part at a lower price than that of imported products.

Regional activities
Looking at the situation in other Latin American countries, large amounts of plasma (between 700 000 and 1 000 000 litres) are discarded each year. This plasma could be used for fractionation if its quality could be improved. The use of PDMP is very low compared to international benchmarks, and very uneven across the different countries in the region. Product shortages are frequent and prices are higher in countries without a fractionation programme. For instance the use of IG is 14 kg/million people in Argentina compared to 0.7 in Peru; and that of FVIII 2.2 IU/capita compared to 0.6.

Uruguay and Chile are performing contract fractionation with Argentina (10 000 and 20 000 litres/year, respectively), and Ecuador is expected to enter into an agreement with Argentina. The Latin American continent has two other not-for-profit plasma fractionation centres, located in Cuba and Venezuela.
Brazil, as stated elsewhere in this report, is performing contract fractionation with France (annual volume of 140 000 litres);

The way to move forward strategically in order to improve access to safe essential plasma products requires taking advantage of the available, locally-discarded plasma and enhancing its quality for use for fractionation. This will contribute to better meet the needs of the population in the Latin American region, and to improve public health at lower costs. The major area of focus should be the implementation of GMP in blood establishments including the establishment of blood donor databases and the development of the supervision of blood establishments by NRAs (licenses and inspections).

C.2 South Africa

South Africa’s locally-collected plasma surplus is supplied to the National Bioproducts Institute (NBI), a not-for-profit company, for further processing into PDMP. The resulting products are sold on a cost recovery basis and operating surpluses are used to fund NBI ongoing capital and technology projects. The product portfolio is determined by public health considerations and customer demand and includes a range of liquid and lyophilized PDMP: blood coagulation factors; polyvalent and hyperimmune immunoglobulins (IV & IM); albumin and a fresh-plasma product (lyophilized). Blood coagulation factors, polyvalent IVIG and IMIG; anti-D, anti-tetanus and anti-rabies immunoglobulin products are included in the South Africa Essential Medicines List.

Plasma is procured at a price determined by a cost recovery model. Plasma contributes, on average, 40% of product costs. NBI and SANBS are self-funded using a fee-for-service/product model. The NBI product range meets >80% of SA therapeutic requirements in terms of range and quantity for PDMP.

Approximately 920 000 donations of whole blood are collected each year in South Africa. All donations are screened serologically and by NAT for HIV, HBV and HCV and 98% of usable donations are processed into blood components. All recovered plasma is shock frozen to <-30°C within 24 hours of collection. Additionally, NBI also tests all plasma for HAV and parvovirus B19.

NBI audits local plasma suppliers to monitor and improve quality and safety standards that meet NBI’s requirements. Over the past 10–15 years this process has contributed to the strengthening of infrastructure of the national blood system in South Africa on several levels: a) re-engineering the cold chain to improve plasma quality and maximize plasma availability; b) adoption of closed system for plasma extraction to reduce the risk of contamination; c) introduction of blast plasma freezing to improve quality of fresh frozen plasma (FFP) for fractionation and therapeutic use; d) strengthening of GMP process control and information technology systems.

Improved health care in South Africa has increased the demand for blood, blood components and PDMP. NBI is currently undertaking several compliance and capacity projects to be completed by mid-2014. New sources of plasma will be required to take up the additional capacity created. Local and regional support
for the local fractionation industry is essential for sustainability and future growth. A fragmented market will impact directly on the cost effectiveness and viability of the local industry due to the nature of plasma as an API from which at least three products need to be extracted per litre processed.

FVIII usage in South Africa in 2011 was 0.87 IU/capita. Statistically, 65% haemophilia A patients are identified. National initiatives are in place to increase patient identification. The South African Haemophilia Foundation (SAHF) in conjunction with the World Federation of Haemophilia (WFH) has set a target for South Africa of 1.0 IU/capita, as part of the Global Alliance for Progress (GAP). This translates a requirement for 252 000 litres of FFP.

Overall, public health benefits from local manufacture result in available, accessible, affordable and comprehensive range of essential medicines to prevent infectious diseases and therapeutic proteins to manage rare and neglected medical conditions; it also provides security of supply.

Regional activities

Namibia Blood Transfusion Service (BTS) identified a need to improve blood safety by adding NAT (for HIV, HCV and HBV) to their blood donation testing. Plasma not required for therapeutic use was being discarded. NBI (South Africa) was approached in 2007 regarding the possibility for procuring surplus FFP from Namibia. During the early stages of the project, Namibia conducted a cost-benefit analysis and decided to outsource the testing of all donations (ABO, Rh typing, serological testing and NAT). In the assessment phase, NBI conducted an on-site audit that revealed operational deficiencies. These included strengthening of quality and information technology systems, improving documentation, plasma freezing and storage and cold chain management. Namibia BTS employed skilled contract staff throughout their upgrade project to facilitate process improvements including the installation of new equipment, a robust information technology system and a re-engineered quality system. Further to an NBI physical audit and submission of necessary information to the regulatory authority in South Africa, approval was obtained to fractionate plasma from Namibia BTS in 2011 and to integrate it with local plasma if required. The next stage of the project is for Namibia and NBI to enter into a plasma supply agreement. Supply of PDMP required by Namibia will be distributed via the pharmaceutical supply chain.

A process road map for other countries to supply plasma to NBI will include the following:

1. Country identifies quantity of plasma that is currently discarded.
2. Country provides NBI with relevant information.
3. NBI will undertake a paper audit analysis.
4. If favourable, NBI will conduct a physical audit and provide a gap analysis.
5. NBI will identify what support it can provide in order to develop plans to close the gap.
6. A shopping basket of requirements will be drawn up – including equipment requirements.

7. The country will then need to undertake a cost-benefit analysis and decide how to proceed.

8. An implementation plan will be drawn up and rolled out, after which NBI will re-audit.

9. Recommend a dedicated project implementation team on the ground to increase chances of success.

10. If the BTS passes the audit, NBI will seek regulatory approval.

11. If regulatory approval is obtained, NBI will enter into a plasma supply (sale) agreement and delivery schedule with the BTS.

12. The supply of PDMP via BTS or appointed pharmaceutical supply chain will also be agreed.

A number of business considerations will also be taken into account:

1. Determine the cost of compliance with NBI plasma specifications.

2. Determine the availability of funding for infrastructure development.

3. Net value of FFP (cost per litre collected vs revenue from sale of FFP).

4. Transport and logistics costs of FFP to NBI.

5. Supply contract duration.


7. Product profile of NBI and suitability for plasma supplier country.

8. Product registration and legislative issues.


Introducing NAT of individual blood donations and improving infrastructure alone may not be sufficient for NBI to obtain approval to process all available FFP from any given country. The robustness of the quality, cold chain and information technology systems will also influence success. A full assessment is necessary for a fair evaluation including epidemiological surveillance data. A preliminary cost-benefit analysis, following initial discussions with Zimbabwe, using a step-wise approval approach, revealed the information summarized in Tables A4a to A4c:
### Table A4a. Phased approach - First Processing Centre approved for supply

<table>
<thead>
<tr>
<th>Product type</th>
<th>Quantity of donations</th>
<th>Litres of plasma</th>
<th>NBI approved prices</th>
<th>Revenue from: plasma + net revenue from sale of PDMP less NAT testing costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP from first processing centre</td>
<td>30 000</td>
<td>7 500</td>
<td>R 500.00</td>
<td>$487 500.00</td>
</tr>
<tr>
<td>Cost of NAT per donation</td>
<td>75 000</td>
<td></td>
<td>-R 192.00</td>
<td>-$720 000.00</td>
</tr>
<tr>
<td>Net revenue from PDMP sales</td>
<td></td>
<td></td>
<td></td>
<td>$64 685.78</td>
</tr>
<tr>
<td>Net revenue</td>
<td></td>
<td></td>
<td></td>
<td>-$167 814.22</td>
</tr>
</tbody>
</table>

### Table A4b. Phased approach - Second Processing Centre approved for supply

<table>
<thead>
<tr>
<th>Product type</th>
<th>Quantity of donations</th>
<th>Litres of plasma</th>
<th>NBI approved prices</th>
<th>Revenue from: plasma + net revenue from sale of PDMP less NAT testing costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP from first and second</td>
<td>51 000</td>
<td>12 750</td>
<td>R 500.00</td>
<td>$828 750.00</td>
</tr>
<tr>
<td>processing centre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of NAT per donation</td>
<td>75 000</td>
<td></td>
<td>-R 192.00</td>
<td>-$720 000.00</td>
</tr>
<tr>
<td>Net revenue from PDMP sales</td>
<td></td>
<td></td>
<td></td>
<td>$64 685.78</td>
</tr>
<tr>
<td>Net revenue</td>
<td></td>
<td></td>
<td></td>
<td>-$173 435.78</td>
</tr>
</tbody>
</table>

### Table A4c. Phased approach - Third Processing Centre approved for supply

<table>
<thead>
<tr>
<th>Product type</th>
<th>Quantity of donations</th>
<th>Litres of plasma</th>
<th>NBI approved prices</th>
<th>Revenue from: plasma + net revenue from sale of PDMP less NAT testing costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP from first, second &amp; 2nd</td>
<td>60 000</td>
<td>15 000</td>
<td>R 500.00</td>
<td>$975 500.00</td>
</tr>
<tr>
<td>&amp; third processing centre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of NAT per donation</td>
<td>75 000</td>
<td></td>
<td>-R 192.00</td>
<td>-$720 000.00</td>
</tr>
<tr>
<td>Net revenue from PDMP sales</td>
<td></td>
<td></td>
<td></td>
<td>$64 685.78</td>
</tr>
<tr>
<td>Net revenue</td>
<td></td>
<td></td>
<td></td>
<td>-$319 685.78</td>
</tr>
</tbody>
</table>
In conclusion, there are distinct public health benefits to strengthening blood establishments and making good use of the resulting improved quality plasma. The collaboration between the blood transfusion service and fractionation capacity, operating within a well-structured regulatory framework, can have an important impact on health outcomes. This can be achieved by supplying plasma for contract processing.

**D. Regulatory framework: needs for development**

**D.1 Indonesia**

Support was articulated for the WHO approach to strengthening the enforcement and implementation of GMP in blood establishments through national regulatory oversight. Assistance from WHO and experienced countries was considered very helpful. A strategic framework is needed for determining the approach a country would need to take in order to be able to provide plasma of a quality suitable for fractionation. A proposal was made for a roadmap that would consist of four phases:

1. Perform a gap analysis by reviewing the current situation and identifying strengths and weaknesses. Establishment of regulations and guidelines for best practice are needed in this phase, as well as implementation of GMP in the blood establishments.
2. Strengthen regulatory oversight of blood establishments.
3. Ensure plasma meets the quality requirements as an API for fractionation. Pertinent IVD for donor screening should be in place, thereby also optimizing the safety from TTI in blood components for direct transfusion.
4. Support to be sought for transfer of technology to the country, both for contract fractionation or local fractionation, if appropriate. Economies of scale should become feasible.

Within a regional initiative, one country could become the centre for fractionation for surrounding countries, and so convergence of national regulations would be required. WHO can help LMIC with these particular activities, so that the availability of safe, high quality blood products can be assured.

**D.2 Argentina**

Blood products are regulated as medicines in Argentina. In 2010, it was proposed to the Ministry of Health that blood establishments be included in the regulatory framework of medicines. Objectives were developed that included production of plasma as an API in blood establishments.

Further regulation has established requirements for quality assurance systems in blood establishments as suppliers of plasma for the production of PDMP. This regulation is based on international guidelines and standards, pharmaceutical requirements, inspections, and WHO recommendations for the production,
control and regulation of human plasma for fractionation. In 2011, a GMP inspector training programme was initiated.

Opportunities and needs include:

1. Training programmes for inspectors, including interactions with other GMP inspectors with solid experience in inspection in blood establishments.

2. Production of local reference materials and reference panels, specifically panels for validation of IVD. This will help both plasma fractionation and blood establishment laboratories.

3. Sensitize professionals in blood establishments on the importance of GMP compliance, and the impact of the GMP inspections to improve the availability and quality of plasma for further manufacture.