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

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

**Albumin**  A plasma derivative used for patients who need 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 the blood by centrifugation and/or filtration into its components, and returning unrequired components to the donor. The term “plasmapheresis” is used for the 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 banks, blood centres, blood transfusion units, blood services and blood transfusion services.

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

**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.

**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, which is deficient in people with haemophilia A. Also called “antihaemophilic factor”.

**Factor IX**  Blood coagulation factor IX, which is deficient in people 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**  A (large-scale) process by which plasma is separated into individual protein fractions, which are then purified further for medicinal use (variously referred to as “plasma derivatives”, “fractionated plasma products” or “plasma-derived medicinal products”). The term “fractionation” is usually used to describe a sequence of processes, including plasma protein separation steps (typically precipitation or chromatography).
purification steps (typically ion-exchange or affinity chromatography), and one or more steps for the inactivation or removal of bloodborne infectious agents (viruses and, possibly, prions).

**Fractionator**  An organization that performs plasma fractionation to manufacture plasma-derived medicinal products.

**Good manufacturing practice**  The part of quality assurance that ensures products are consistently produced and controlled to the quality standards appropriate to their intended use, and as required by the marketing authorization or product specification. Good manufacturing practice is concerned with both production and quality control.

**Hepatitis A virus**  A non-enveloped, single-stranded RNA virus; the causative agent of hepatitis A.

**Hepatitis B virus**  An enveloped, double-stranded DNA virus; the causative agent of hepatitis B.

**Hepatitis C virus**  An enveloped, single-stranded RNA virus; the causative agent of hepatitis C.

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

**Immunoglobulin**  Also known as “immune globulin” and “gamma globulin”. Used in the treatment of primary immunodeficiency and a number of other conditions. Polyvalent immunoglobulin is prepared from a large number of donors. Hyperimmune or specific immunoglobulins are prepared from plasma containing high levels of antibody to a certain infectious agent or antigen, such as rabies, tetanus, hepatitis B and Rhesus factor.

**Incidence**  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 or licensee of the object product in its manufacture and use and bring to it a competitive advantage. Know-how can be supported further with privately maintained expert knowledge on the operation, maintenance, use and application of the object product and of its sale, use or disposal.

**Manufacture**  All operational processes or steps – including purchase and 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**  World Health Organization terminology referring to a national medicines regulatory authority, which should promulgate and enforce medicines regulations.
**Nucleic acid amplification technique**  A testing method to detect the presence of a targeted area of a defined nucleic acid (for example, viral genome) using 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 the continuous filtration or centrifugation of anticoagulated blood.

**Plasma-derived medicinal products**  A range of medicinal products obtained by the fractionation process of human plasma. Also called “plasma derivatives”, “plasma products” and “fractionated plasma products”.

**Plasma for fractionation**  Recovered or apheresis plasma used for the production of plasma-derived medicinal products.

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

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

**Recovered plasma**  Plasma recovered from a whole-blood donation and used for fractionation into plasma-derived medicinal products.

**Source plasma**  Plasma obtained by apheresis for further fractionation into plasma-derived medicinal products.

**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 implemented properly, and approval of the plasma for fractionation or plasma products by the relevant national regulatory authority.

**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).

**Window period**  The time interval from when a person is infected with an agent to when a blood sample from that person first yields a positive result in a test for that agent (for example, with corresponding antibodies). A blood donation during this period can transmit infection to the transfusion recipient. The nucleic acid amplification technique shortens this period compared with serological testing.
Executive summary

This report describes activities undertaken during phase II of a World Health Organization (WHO) and European Commission project for enhancing the availability, safety and quality of blood products in low- and middle-income countries. The specific aim of the activities described in this report and in the preceding phase I report was to help countries develop robust technical and regulatory capacities and procedures for ensuring the consistent quality and safety of blood components manufactured in not-for-profit blood establishments.

During phase I an assessment was made of the needs, challenges and opportunities that were likely to be associated with efforts to improve production standards in blood establishments in low- and middle-income countries. This involved reviewing the volume of plasma separated from whole blood that is currently wasted worldwide and identifying key steps needed to improve the situation. The volume of wasted plasma is expected to increase as the volume of blood collected to meet the need for red blood cells increases. Countries will therefore be faced not only with greater levels of lost revenue but also with the significant and growing financial and environmental implications of discarding plasma. Findings of phase I are published in a separate report.

Following the completion of phase I, and in line with key stakeholder inputs on how best to build on its findings, WHO initiated a two-year programme of activities in Indonesia – phase II of the project – in order to demonstrate proof of concept in a selected pilot country. The analysis and activities undertaken are discussed in this report. In full collaboration with relevant partners, WHO undertook the development, management and monitoring of a series of activities that encompassed situation assessments, gap analysis and training workshops in Indonesia. The information obtained through situation assessment and gap analysis at various points was used to identify the main challenges to be addressed and to inform the development of activities for progressing towards the overall project goal of improving access to safe blood products through local production and technology transfer in blood establishments.

As a result of this analysis, WHO training workshops were developed and held on blood testing, risk assessment, and enforcement and implementation of good manufacturing practice in blood establishments. Mock inspections were conducted in parallel in three blood establishments in Jakarta, Tangerang and Bekasi in Indonesia; rather than constituting a true inspection of compliance, these mock inspections were intended to familiarize participants with the objectives of such inspections and the practical processes involved. The information put together and discussed with the participants during the training activities is summarized in the report.

This report also includes a summary of conclusions and proposed follow-up actions to be taken in Indonesia. WHO acknowledges the continued efforts being made in Indonesia to strengthen the regulation of blood products, including the formal adoption of a health ministerial decree to strengthen regulation of the entire national blood system by the Indonesian Ministry of Health and the National Agency for Drug and Food Control. WHO will provide further support through the assessment of good manufacturing practice implementation and standard operating procedures in a selected pilot blood establishment in order to evaluate compliance with international quality assurance
regulations; in particular, WHO will hold further training in national blood-screening policy and regulation involving key stakeholders and experienced experts in the definition of national standards in Indonesia. In all cases, further progress requires an increase in the technical capacity and expertise of regulatory authorities allied to the transfer of crucial manufacturing technologies and know-how.

The achievements and lessons learnt in phase II will be promoted and communicated via WHO websites, international conferences, educational seminars and other channels. WHO will continue to work towards its ultimate goal of supporting low- and middle-income countries in all regions of the world in their efforts to raise production standards and strengthen the regulatory oversight of blood establishments producing plasma for fractionation into plasma-derived medicinal products for their populations.
1. Introduction

1.1 Improving access to safe blood products

Blood products include not only blood components – whole blood, red blood cells, platelets and plasma manufactured from single donations and intended for direct transfusion – but also plasma-derived medicinal products such as albumin, polyvalent and specific immunoglobulins and blood coagulation factors that are manufactured on an industrial scale from thousands of pooled plasma units. In high-income countries, each unit of whole blood collected is separated into therapeutic blood components to allow for optimized and selective component therapy, based on the therapeutic needs of patients. In stark contrast, ensuring access to safe and essential blood components made from voluntary non-remunerated whole-blood donations often presents a major challenge in low- and middle-income countries, where local quality and safety standards in blood establishments urgently need to be established, strengthened and implemented.

Over the past three decades, the inadvertent transmission of infectious disease agents such as human immunodeficiency virus (HIV) and hepatitis B and C viruses as a result of blood transfusion has demonstrated the absolute necessity of validated quality systems and effective regulation in this area. Such requirements apply not only to the preparation of blood components for transfusion but also to the preparation of plasma as a raw material for the manufacture of medicinal blood products. Unless far greater attention is paid to ensuring the availability, safety and quality of blood and blood products, particularly in low- and middle-income countries, efforts to achieve the health-related Millennium Development Goals for reducing child mortality, improving maternal health, and combating HIV and acquired immunodeficiency syndrome (AIDS), malaria and other diseases cannot succeed.

In 2010 the Sixty-third World Health Assembly in resolution WHA63.12 expressed concerns about the unequal access globally to blood products, particularly plasma-derived medicinal products (1). This inequality leaves many patients in need of transfusion and those with severe congenital and acquired disorders without adequate treatment. As a result of insufficient regulatory control and failure to implement appropriate production practices in blood establishments, plasma collected in low- and middle-income countries is often unacceptable for contract fractionation, with considerable wastage of plasma. Resolution WHA63.12 urged World Health Organization (WHO) Member States to take all 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 ... in order to ensure that regulatory control in the area of quality and safety of blood products across the entire transfusion chain meets internationally recognized standards”.

Resolution WHA63.12 also requested WHO to guide Member States in their efforts to raise quality standards in blood establishments, to reduce the risk of transmission of infectious diseases, and to enforce the implementation of blood-product regulations in order to improve the availability of safe blood products. It was recognized that this would require the establishment of quality systems and implementation of good manufacturing practice and appropriate regulatory control, including the use of validated in vitro diagnostic devices capable of detecting transfusion-transmitted infections.
The activities summarized in this report and in the phase I report (2) were developed as a direct response to the need to enhance the availability, safety and quality of blood products in low- and middle-income countries. The activities form part of an overall WHO and European Commission project seeking to optimize the use of blood donations, improve blood transfusion safety, decrease plasma wastage and increase the availability of safe plasma-derived medicinal products. During phase I, a general assessment was made of the needs, challenges and opportunities likely to be associated with efforts to improve production standards in blood establishments in low- and middle-income countries. This involved reviewing the volume of plasma separated from whole blood that is currently wasted worldwide and identifying key steps needed to improve the situation.

Estimations made during phase I indicated that each year more than 9 million litres of recovered plasma are discarded worldwide (2). This level of wastage represents a lost opportunity to improve health and comes with significant direct and indirect costs. It is estimated that the therapeutic products that could be manufactured from such a quantity of plasma, provided it meets good manufacturing practice requirements for fractionation, could be used to treat more than 200 000 people with bleeding disorders and primary immunodeficiency. In addition to the direct economic costs and environmental implications of disposal, the severe shortage of plasma derivatives in low- and middle-income countries also leads to poor or no treatment and increased mortality and morbidity rates, including among children, and thus to increased associated national health care expenditure.

Project activities in phase II were designed to help achieve the specific goal of ensuring production practices in blood establishments meet the international quality standards required for the use of plasma as a starting material for the preparation of plasma-derived medicinal products. They were developed in full accordance with the objectives set out in resolution WHA63.12 for promoting access to good-quality safe blood products at the global level, and with an overarching WHO/European Commission framework for improving public health by increasing the availability, affordability and accessibility of medical products (3). A WHO-led process to support the implementation and upgrade of production standards for recovered plasma in blood establishments that could lead to the overall strengthening of activities within such establishments and the subsequent delivery of significant public health benefits is described in this report.

1.2 Rationale for phase II activities

Analysis of the opportunities and main barriers associated with the local production of good-quality recovered plasma as a starting material for the manufacture of plasma derivatives in blood establishments in low- and middle-income countries clearly highlighted the potential for improving access to safe blood products. The production of plasma meeting all requirements for further fractionation was considered to be a reachable objective where there was both government commitment and a satisfactory blood-collection system fully supported by good manufacturing practice implementation and well-planned technology transfer. Where successful, efforts to improve the quality of recovered plasma in local blood establishments based on voluntary non-remunerated local donation would improve access to a greater range of safe blood products. In addition, there would also be a concomitant and dramatic increase in the safety and effectiveness of current red blood cell and platelet production and transfusion, which is of key importance in reducing mortality and morbidity caused by transfusion-transmitted infections. The inability of low- and
middle-income countries to meet required quality standards for recovered plasma was identified as the major barrier to ensuring suitability of plasma for fractionation into essential plasma-derived medicinal products. Although generally relevant quality criteria already existed in this respect, specific aspects such as testing strategies varied, depending on the epidemiology of the country and even on particular fractionators. It was felt that WHO could directly facilitate the efforts needed in this area to improve plasma quality. In some low- and middle-income countries, this may have required initial external funding in addition to technical expertise in order to improve the infrastructure of blood establishments. As quality systems and the introduction and implementation of a robust culture of adherence to good manufacturing practice to support the standardization of production processes in blood establishments are essential prerequisites, the time and resources needed to bring about improvements cannot be underestimated and depend on the current status of national blood establishments’ operations.

In light of these considerations, furthering the adoption and implementation of regulations specific to blood products was considered to be of utmost importance. WHO undertook to support Member States by coordinating a series of activities in continuation of the efforts already made in this area. It was envisaged that the degree of assistance needed to build up the technical capacities of blood establishments and national regulatory authorities would depend on the country selected. In any case, the technical capacity of the national regulatory authorities would need to be strengthened in order to define and apply the appropriate national blood standards for ensuring the quality, safety and efficacy of locally made products before initiating contract or local fractionation.

1.3 Demonstrating proof of concept – why Indonesia?

During a stakeholder meeting at the end of phase I, it was suggested that demonstrating proof of concept and effectiveness in the upgrading of national quality-assurance systems in blood establishments in one country would, if successful, greatly encourage other low- and middle-income countries to follow the approach taken. Although substantial volumes of plasma are discarded in many countries with no access to plasma derivatives, a selective focus had to be applied based on likely feasibility and baseline cost–benefit analyses. Government support for the proper regulation of blood establishments and fractionators would be an essential aspect of any improvement process and would need to be assured from the start. Two further criteria identified for determining success were that results should be obtained in a short period of time and should require only a modest budget.

Of the many countries evaluated for this project, Indonesia, with its clear appreciation of the ethical and economic implications of discarding plasma, appeared to be best suited to initiate the required steps. Crucially, the Indonesian Government had indicated its strong commitment to strengthening the regulation of its national blood programme, improving and securing its blood supply, and ensuring the fractionation of recovered plasma. Moreover, the Indonesian regulatory authority for medical products, the National Agency for Drug and Food Control, had publicly indicated its commitment to enforcing good manufacturing practice regulations in all blood establishments involved in the production of plasma for fractionation and had requested WHO support in the training of regulatory staff in the evaluation, assessment, inspection and quality control of blood products. Support for the project was also expressed by the Indonesian Red Cross, with strong indications given of the willingness and readiness of all parties to initiate the necessary activities. Obtaining
comparable levels of governmental commitment to the implementation and enforcement of a culture of good manufacturing practice was not considered feasible in other proposed project settings, particularly given the envisaged maximum project duration of two years.

The blood programme in Indonesia was managed, guided and coordinated by the National Blood Committee (Figure 1), established in 2011, which had indicated its willingness for Indonesian plasma to be fractionated domestically or abroad. Blood donation in Indonesia is voluntary and non-remunerated, with increasing national donation rates and progress being made towards blood components therapy. Since plasma-fractionation activities benefit from economies of scale and require large volumes of good-quality plasma in order to be cost-effective, it was considered that any proof of concept achieved in Indonesia, with the fourth largest population in the world and a potentially high volume of available plasma, would help to attract support and assistance from both Asian and European plasma fractionators. It was estimated that a total of approximately 70 000 litres of potentially usable plasma for fractionation were discarded each year by 10 Indonesian Red Cross blood transfusion units alone.

Figure 1 Structure of the Indonesian National Blood Committee

CHAIR
Dr Ratna Rosita, MPHM; Secretary General of Ministry of Health

VICE CHAIR
Chair for Blood of Indonesian Red Cross

SECRETARY
Director of Basic Health Care – Ministry of Health

VICE SECRETARY
Director of Indonesian Red Cross – Central Blood Centre

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Chair of Blood Donor Association
Chair of National AIDS Control

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Dr Djumhana, Hematology Assc.
Professor Salam, Blood Transf. Doctor Assc.
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Indonesia was selected as the first country in which to demonstrate proof of concept and effectiveness in the upgrading of national quality-assurance systems in blood establishments. WHO undertook to develop, manage and monitor the two-year phase II project, which was to be based on a combination of situation analysis and assessment followed by training workshops focused on identified high-priority quality assurance themes agreed with the country stakeholders. In terms of regional impact, it was recognized that if the efforts made in Indonesia were successful, then there were several other large countries in the region that could participate in a process of regional cooperation focused on the transfer of technology to both blood establishments and plasma-fractionation programmes. It was further intended that many of the lessons learnt from the experience of implementing activities in Indonesia would inform and support the rollout of vital capacity-building processes in other countries and regions, wherever appropriate funding and levels of commitment could be secured.

1.4 Project resources, monitoring and evaluation

The phase I and phase II project activities were developed, managed and implemented by the Blood Products and Related Biologicals Programme of the WHO Essential Medicines and Health Products Department. This programme coordinates the development of the WHO norms and standards for the regulation and control of the quality and safety of blood products (4). The programme has long been involved in the coordination of international expert networks in the biological field, including the WHO Blood Regulators Network (5), comprising leading regulatory authorities in the blood area. The programme also has broad experience in technical capacity-building activities in all WHO Regions.

The project manager took responsibility for the organization and coordination of the project activities, which were undertaken in collaboration with relevant country-level stakeholders and established expert networks linked to the programme. A highly experienced team was selected with relevant implementation experience in the areas of blood collection, production of blood components and plasma for fractionation, plasma contract fractionation programmes, plasma fractionation technology and global regulatory issues in blood safety.

The achievements and lessons learnt in phase II will be promoted and communicated via WHO websites, international conferences, educational seminars and other channels.
2. Situation assessment and gap analysis

A systematic process of situation assessment was initiated in March 2012 during a country visit in which the WHO team met with the National Blood Committee and relevant representatives from the Indonesian Ministry of Health, the Indonesian National Agency for Drug and Food Control and the Indonesian Red Cross (Annex 1). At this meeting, detailed presentations and discussions provided the foundation for an improved understanding of various aspects of the national blood service system. The situation assessment process culminated in August 2013 with a meeting on blood regulation and control involving senior governmental, regulatory and Indonesian Red Cross stakeholders. During this meeting, the gaps and challenges to be addressed were explored in a series of seminars on national blood regulation and standards involving 70 participants (Annex 2).

Indonesia is the fourth most populous country in the world, with more than 250 million inhabitants. As part of efforts to improve the management of the blood system in the country, the Indonesian Government passed a law in 2009 to make safe blood services an integral part of health services. These regulations emphasized and set out the responsibilities of the Indonesian Government in providing safe and accessible blood services based on the needs of the population. Key elements included recognition of the public health need for safe blood products regulated by the Indonesian Government, recognition of the requirement that blood collection should take place only within official blood centres and be based on voluntary non-remunerated donation, and recognition that plasma derivatives could be produced either domestically or abroad by approved fractionators. In 2011 further national regulations were issued reiterating and reinforcing the responsibilities of central and local government agencies in managing, guiding, monitoring and financing the blood system, ensuring safe and accessible blood services, and promoting further research and development activities. The regulations specifically required that plasma for fractionation should be supplied by official blood establishments, that fractionation be performed only at legally recognized facilities licensed by the Ministry of Health and that met all required standards, and that the price of plasma fractionation products would be regulated by the Indonesian Government.

There are two blood services organizations in Indonesia – one managed by the Indonesian Government and one managed by the Indonesian Red Cross. Responsibility for the monitoring and coordination of both systems rests with the Ministry of Health Directorate of Basic Health Care, Subdirectorat of Special Health Care, Elderly and Blood Services. A total of 211 Indonesian Red Cross and 164 Indonesian Government blood transfusion units were operating across Indonesia in 2013 (Figure 2). In an effort to increase access to blood products, the Indonesian Government established blood centres in Government hospitals that had previously lacked such activities. Indonesian Red Cross blood centres are classified into three types based on criteria such as facility workflow, available human resources, and the extent and quality of service activities.
The National Blood Committee was established to bring together all pertinent stakeholders in Indonesia to improve coordination between Indonesian Red Cross and Indonesian Government blood services and to move towards a nationally coordinated blood system. Following its establishment, the National Blood Committee assisted the Ministry of Health to develop a national programme in accordance with a national blood policy based on an effective and efficient organizational structure. As part of this process, the existing Indonesian Red Cross standards on blood services are reviewed with the intention of upgrading them to national standards for blood services. The broad range of tasks of the National Blood Committee included:

- provision of considered inputs to the Minister of Health to inform decisions on national policies for blood services;
- developing and improving community advocacy and education initiatives to consolidate and sustain levels of voluntary blood donation;
- preparing and developing education and training programmes for blood services personnel;
- developing a strategic and operational system for blood services financing;
- improving blood services technologies and knowledge levels;
- improving the operational and technical management of blood services;
- promoting research and development;
- coordinating with all Indonesian Government institutions and relevant international bodies.
In 2011 more than 2.3 million units of whole blood were collected (Figure 3), primarily in Indonesian Red Cross blood centres, equating to a donation rate of around 8 units per 1000 people. The blood came from first-time donors (40%) and repeat donors (60%). Although 64% of the blood collected in the Indonesian Red Cross blood centres was processed into its major components, efforts were mounted to increase the national blood donation rate in order to increase efficiency of use, as only 70% of national needs were being met. Most donations were serologically tested by enzyme-linked immunosorbent assay, some by rapid tests and some by nucleic acid amplification technique assays. An average volume of 100–125 ml of plasma per bag was obtained. The largest Indonesian Red Cross blood centres are located on Java and are capable of processing 80–90% of the whole blood collected into blood components. It was estimated that approximately 70 000 litres of potentially usable plasma for fractionation were discarded each year by just 10 Indonesian Red Cross blood centres. Data also showed that approximately 10% of the total plasma separated from whole blood is used for transfusion.

Figure 3 Number of blood donations in Indonesia, 2005–2013

The Indonesian Red Cross estimated that meeting the appropriate international quality standards needed to allow fractionation of the 70 000 litres of discarded plasma could be achieved within three years, thus allowing for the production of human albumin and intravenous immunoglobulin, which are currently imported at high cost. Indonesia also has a substantial need for factor VIII. The estimated combined market value of all three lost blood products was of the order of US$ 18.8 million.

Audits conducted in Indonesian blood establishments by three plasma fractionators highlighted numerous critical, major and minor deviations from established best practices. Critical deviations in particular were observed in the areas of management quality assurance, use of information technology systems, whole-blood collection procedures,
production of labile blood products, and testing and screening activities. These included
the absence of quality policies, targets and performance indicators, lack of equipment
design and protocols for product release, and the absence of a systematic approach to
the documentation and validation of crucial activities.

In 2013 the total number of blood donations in Indonesia was more than 2.7 million
(Figure 3). As national campaigns continue to be undertaken to increase the blood donation
level to 2% of the population (about 4.4 million donations) in order to meet the demand
for red blood cells, the potential volume of wasted plasma will rise if no action is taken.
Separated into its major components, such an increased volume of whole blood would
yield an estimated 500,000 litres of plasma, assuming the separation rate from whole
blood also increases. As the volume of collected plasma rises, both the indirect public
health costs resulting from the lost plasma-derived medicinal products and the direct
financial and environmental costs of discarding the plasma will increase significantly. Based
on a conservative price of plasma for fractionation (US$ 50 per litre), the plasma has a
potential value of US$ 25 million per year. In addition, the cost of destroying approximately
40,000 litres of unused plasma each year at three blood centres in Jakarta was estimated
to be US$ 50,000.

The gap analysis suggested that increasing the quantity of recovered plasma suitable for
fractionation would require:

• consolidation or rationalization of the number of blood centres, where feasible;
• strengthening of quality-assurance systems, including for donor management, to
  address major weaknesses identified during audits by plasma fractionators;
• standardization of testing protocols for all blood donations;
• installation of blast freezers and enhanced freezer storage capacity.

It was recognized that in order to implement improvements, a broad range of challenges
need to be addressed. For example, the existence of numerous small laboratories
conducting donor-screening tests is a recognized weakness, and their consolidation is a
high priority. Many Indonesian Government blood centres are small hospital facilities that
would not meet good manufacturing practice standards for several years and would not
be able to produce plasma for further fractionation; the Ministry of Health is working to
upgrade standards.

The large number of highly diverse blood centres made the harmonization of blood-
collection practices and regulation of good manufacturing practice challenging. Although
some degree of centralized control of critical safety and quality-assurance production steps
could be realistic, along with strategically restricting the implementation of such steps to
suitably competent blood centres, the blood-collection and blood-production activities in
many centres does not comply with good manufacturing practice standards and there is
a pressing need to increase the number of personnel and upgrade their capabilities and
expertise. The existence of two systems within the national blood supply requires a strong
and independent standards-setting national authority to ensure harmonization of quality-
assurance procedures and uniform quality of plasma for both transfusion and fractionation.

Stronger regulation is needed for the in vitro diagnostic devices used to detect HIV and
hepatitis B and C viruses in blood donations, particularly as some centres are using rapid
tests. There are no centralized systems for the purchasing or quality control of in vitro
diagnostic devices, and the licensing of tests is authorized by a separate Ministry of Health section. There is a recognized need to strengthen coordination and reporting systems to improve communication channels between blood centres and the Ministry of Health. Improved communication is also necessary to sustain and improve blood-collection systems and to optimize donations by avoiding wastage. In some cases, underestimation of the regulatory and technical complexity of implementing good manufacturing practice in blood establishments masked the high level of risk inherent in directly constructing domestic fractionation facilities using untested and non-validated technologies.

Cost–effectiveness analysis would underpin and support the required decision-making and investment processes in these and other areas. For example, the prompt blast freezing of separated plasma would permit the production of blood coagulation factors, albumin and immunoglobulin, with beneficial impacts on cost–effectiveness and public health. Cost–effectiveness will also increase as potential plasma volumes for fractionation increase.

In summary, in the absence of national blood standards and independent regulatory supervision of blood establishments, the safety of the blood supply would remain suboptimal and be determined only by the degree of professional competency of individual centres. Regulators need to work with blood services management to determine standards, highlighting the acute need for an independent regulatory authority to help blood services meet current international requirements. Absence of an independent, well-functioning regulatory system for the licensing of blood establishments and blood products has resulted in practical difficulties in the official registration of plasma products fractionated from plasma prepared at the Indonesian Red Cross Blood Transfusion Service.

The Government of Indonesia is strongly committed to improving its national blood services and to putting in place the regulatory and other requirements that will allow the significant volume of currently discarded plasma to be used for the good manufacturing practice–assured manufacture of vitally important blood products. A regulatory structure for biological medicines is already in place at the National Agency for Drug and Food Control, with a clear intention expressed to incorporate the regulation of blood establishments. In addition, following discussions in 2013 with senior representatives from the Ministry of Health, the National Blood Committee, the National Agency for Drug and Food Control and the Indonesian Red Cross blood centres, a commitment was made to initiate the preparation of a national decree to strengthen overseeing and implementation of quality assurance systems in blood establishments. The National Agency for Drug and Food Control would then be part of the national system with responsibility for ensuring the regulatory compliance of blood establishments in its capacity as an independent regulatory entity (referred to locally as “Badan POM”). A proposal to add a good manufacturing practice guideline for blood establishments based on published WHO guidance to the National Agency for Drug and Food Control national regulatory manual is considered another welcome step.

Despite broad recognition of the need for concerted efforts to upgrade the quality and hence usability of plasma through implementation of good manufacturing practice overseen by an independent regulatory authority, it is clear that substantial progress is needed to reduce plasma wastage in Indonesia. During discussions with senior representatives from the Ministry of Health, the National Blood Committee, the National Agency for Drug and Food Control and the Indonesian Red Cross blood services, an approach was developed to address these challenges based on a programme of WHO training activities.
3. World Health Organization training activities

3.1 Introduction

Following discussion of the outcomes of the situation assessment process described above, it was agreed that a series of WHO training activities would be undertaken to help relevant stakeholders in Indonesia to advance collectively through the decision-making processes required in blood establishments. There is, for example, a recognized need to promote improved understanding of the importance of blood-testing strategies as part of effective risk assessment in blood components. Furthermore, there is a need for stakeholders to appreciate the crucial requirement for pre-established national blood standards against which good manufacturing practice can be applied before its implementation and enforcement in blood establishments (6–8).

A major urgent need was identified as building the technical and regulatory capacity of blood establishments and the national regulatory authority through the use of WHO good manufacturing practice training workshops, including the holding of mock inspections, and thus introducing a “production culture” to blood establishments. Educational activities on the regulatory and technical requirements of plasma for fractionation were also seen as high-priority steps. In particular, technical support in the selection and use of viral test kits is needed, encompassing scientific considerations such as the sensitivity and specificity of different tests, the local epidemiological situation, donor characteristics, evolution of testing technologies, and understanding of the risks and limitations of the assays used. Furthermore, a number of key elements for ensuring the production of plasma in accordance with good manufacturing practice could potentially be implemented within a two-year timeframe. These key elements 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 devices, improving the cold chain for plasma, introducing quality-assurance systems, and developing good manufacturing practice expertise within blood establishments and the national regulatory authority.

WHO workshops in the following areas were conducted to familiarize relevant focal points and responsible officers with the decision-making processes and associated activities needed to achieve the specific project objectives:

- assessment criteria for national blood regulatory systems (Figure 4);
- blood-testing technologies and risk assessment (Figure 5);
- enforcement and implementation of good manufacturing practice in blood establishments, including practical mock inspections of selected blood establishments (Figure 6).
Intended training outcomes included increasing national capacity in Indonesia for inspecting and ascertaining whether blood establishments complied with WHO good manufacturing practice requirements for the collection of quality-assured blood for the production of plasma as a starting material for the manufacture of plasma-derived medicinal products. This required strengthening the technical capacity of the National Agency for Drug and Food Control to define and enforce appropriate quality, safety and efficacy requirements for blood products. It was considered that such advances would
contribute to the overall phase II objective of establishing a quality-assured system in Indonesia to enable the negotiation of plasma contract fractionation programmes and thereby improve the supply of good-quality, affordable and locally sourced blood products.

The workshops were generously hosted by the National Agency for Drug and Food Control, which also provided WHO with logistical support. Participants included representatives of the National Agency for Drug and Food Control central and regional office inspectorates, relevant Indonesian Ministry of Health directorates, the National Blood Committee, the Indonesian Red Cross, the relevant Indonesian Ministry of Health blood transfusion services, and other technical units in Indonesia, including the HIV reference laboratory. It was originally intended that project training activities would also be open to participants from other countries in the WHO South-East Asia Region in order to maximize their impact and promote regional cooperation with regulatory authorities and blood establishments in other countries. For practical reasons, however, this had to be limited due to the large number of participants from Indonesia. The lists of participants for the workshops are provided in Annexes 3, 4 and 5.

In these and related activities, the international standards developed and established by WHO in its existing range of technical documents, guidelines and recommendations addressing specific aspects of plasma for fractionation and the implementation of good manufacturing practice in blood establishments were a key resource. Workshop support documents included WHO's Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products (10), Recommendations for the production, control and regulation of human plasma for fractionation (11), Guidelines on good manufacturing practices for blood establishments (12), Blood products and related biologicals: catalogue (13) and Assessment criteria for national blood regulatory systems (14). Workshop presentations were based on these guidelines and related European regulations. Relevant background materials were distributed to all participants in electronic and printed form.

For the workshop on blood-testing technologies and risk assessment, facilitator support was provided by experts from the WHO Collaborating Centre for Quality Assurance of Blood Products and In Vitro Diagnostic Devices at the Paul-Ehrlich-Institut. Activities conducted during the subsequent workshop on the enforcement and implementation of good manufacturing practice in blood establishments included three parallel mock inspections held in the Jakarta, Bekasi and Tangerang blood transfusion units made available by the Indonesian Red Cross. These mock inspections were facilitated by three senior good manufacturing practice inspectors from the Therapeutic Goods Administration (Australia), Paul-Ehrlich-Institut (Germany) and Swissmedic (Switzerland), all of whom had specialist knowledge of blood establishments.

Feedback from workshop participants indicated that the WHO training activities would strongly contribute to the development of appropriate technical expertise in the enforcement and implementation of good manufacturing practice in blood establishments. Participants from Malaysia requested the development of similar activities either in their country or as part of a regional WHO project.
3.2 World Health Organization workshop on blood-testing technologies and risk assessment

In vitro diagnostic device batch testing by a national regulatory authority allows for the independent checking and monitoring of manufacturer production consistency. This requires significant human and laboratory resources and expertise, however, and alternative approaches can be used based on monitoring the information provided by the manufacturer. In all cases, the evaluation of in vitro diagnostic devices used for blood-safety testing should be a continuous process that incorporates regular re-evaluation and recertification as part of improving the detection capacity of testing and meeting region-specific needs. This will require monitoring of the evolution and distribution of viral genotypes and of the circulation of new virus variants.

The specific objectives of the workshop were to:

• ensure appropriate understanding of the benefits and limitations of blood-safety testing systems in complying with national blood policies and allowing for risk assessment;
• provide a sound technical rationale for the evaluation and regulation of in vitro diagnostic devices used for blood-safety testing and for the use of appropriate strategies and systems for such testing;
• discuss the estimation of residual risk of missed infections in the context of different epidemiological and testing scenarios.

Before the core sessions addressing these objectives, a series of presentations were given by representatives from the Ministry of Health and Indonesian Red Cross Central Blood Transfusion Service on blood-safety testing in Indonesia, the relevant markers to be tested, the setting of defined standards, and the current rates of viral markers in the blood-donor population. The resulting overview of the situation in Indonesia was important in ensuring shared understanding of the wide diversity of blood establishments in Indonesia and of the prospects for establishing national standards and related tendering requirements, both for testing algorithms and for the types and evaluation of in vitro diagnostic device tests to be used.

Main workshop topics included the essential features, evaluation and control of blood-safety testing systems and their associated benefits and limitations, the relative characteristics of serological and nucleic acid amplification technique assays, and assuring the quality of laboratory performance. Key concepts addressed in the evaluation of testing systems included the minimum requirements defined by leading regulatory agencies for manufacturer evaluations of tests related to blood safety. In addition, comparison of the features of different internationally available assay types provided an overview of current enzyme-linked immunosorbent assays, rapid tests, and nucleic acid amplification technique and confirmatory assays, and their advantages and disadvantages. Consideration was given to the standardization and evaluation of tests based on internationally agreed reference preparations and on specific regional requirements, and the minimum number of test samples required for statistical significance. Attention was also given to the definition, properties and acceptance criteria of adequate control materials, and to the manufacture, storage, distribution and use of appropriate reference control preparations. This included consideration of the use of WHO international standards and reference panels and of the ways such preparations could support the analytical quality control of in vitro diagnostic
devices. Based on these considerations, further discussions were held on the evaluation and regulation of in vitro diagnostic devices used for blood-safety testing and on estimating the residual risk of missed infections in blood components. Based on the outcomes of the session, the current status of regulatory oversight in Indonesia was discussed. The highlights of the information presented and discussions held are summarized below.

3.2.1 Evaluation and regulation of in vitro diagnostic devices used for blood-safety testing

Assays used for screening blood safety are defined as high-risk devices and require stringent evaluation and clear establishment and dissemination of the essential requirements that need to be met for their use. In vitro diagnostic device regulation should incorporate both pre-marketing and post-marketing supervision. Pre-marketing regulatory oversight should focus on the evaluation of region-specific quality considerations for in vitro diagnostic devices, such as sensitivity and prevalent viral genotype or variant coverage, through assessment of manufacturer studies based on samples representative of the region. Selective performance evaluations should also be conducted to determine assay sensitivity, potentially based on the use of regional specimens and WHO international standards and reference panels. Assessment of potential issues of specificity would be based on regional co-infection patterns in the population or medication practices. In all cases, the essential requirements for all in vitro diagnostic devices to be used need to be established and published in the country. Collaboration is required between the regulatory authority and blood establishments in the selection of specific samples for use in regionally appropriate reference panels for quality control of the tests to be licensed. The Paul-Ehrlich-Institut would be willing and able to provide further technical support to any committed process for improving approaches in this area.

Such pre-marketing oversight allows for comparative data to be obtained on different assays, for the differentiation of types of assay and for confirmation of manufacturer data. Intended outcomes include the definition of minimum acceptance criteria based on regional needs, calculation of the residual risks of blood component or plasma pool contamination in relation to specific assays, testing algorithms and strategies, and the use of cost–benefit analyses to inform decision-making. In vitro diagnostic device regulatory oversight approaches should cover both screening and confirmatory assays (serological and nucleic acid amplification technique) and should have the potential to be applied to diagnostic assays. In addition, the testing laboratories responsible for such evaluations should act on behalf of, and communicate regularly with, the national authority responsible for regulatory approval.

As part of post-marketing regulatory oversight, data on the use of different devices in the country should be collected and assessed, including data on user complaints, for example arising from adverse incidents. Specific investigations, including laboratory testing, may need to be conducted to follow up on potential incidents, with the findings potentially used to redefine the quality requirements, communicate with the manufacturer or improve assays.

In summary, any regulatory mechanism put in place should be based on the use of measures that allow the effective regulation of all assays used in blood-safety testing. The regulatory mechanism should incorporate a means of refusing the approval of any assays found to be unsuitable for meeting the blood-safety needs of the country, for example in terms of
prevalent viral genotype or variant coverage or sensitivity, and a process for immediately withdrawing any previously approved assays from the market.

Blood screening test failures should become evident during retrospective investigation of any reported infection of the recipient or donor seroconversions, assuming the process is traceable. Relevant information may also be obtained from investigations of implausible screening results. The standard and performance of post-marketing in vitro diagnostic device surveillance activities could be assessed through an external quality assessment scheme. This would require regular rollout and participation and notification of poor assay results to the competent regulatory authority.

3.2.2 Estimation of residual risk of missed infections

The residual risk of virus transmission to recipients of non-inactivated blood components, including plasma, cannot be eliminated completely using any blood-safety testing strategy or system. The same consideration therefore applies to the risk of viral contamination of plasma pools used to manufacture plasma-derived medicinal products. Although serological testing covers part of the acute and all of the chronic phases of infection with HIV and hepatitis B and C viruses, and nucleic acid amplification technique assays additionally cover part of the very early infection phase, residual risks persist due to the existence of the viraemic window phase tested negative by all assays, test failures and undetected viral variants or genotypes.

In contrast to the occurrence of test failures or the appearance of viral variants, neither of which can be predicted or calculated, the residual risk arising primarily from window-phase donations that escape screening detection can be estimated. The frequency of such donations is correlated directly with the frequency of recent infections in the donor population (incidence). Donor populations consist of a mix of first-time and repeat donors. For first-time donors, any positive result could reflect either past infections (prevalence) or recent infections (incidence). Among repeat donors, any positive test result represents a recent infection, because the prior donation must have tested negative. By applying knowledge of the incidence of specific infections and test sensitivity, the probability of the prior donation being infectious but escaping screening detection can be calculated. The rate of recent infections escaping detection may be similar, higher or lower among first-time donors compared with repeat donors. The residual risk of virus transmission due to window-phase donations is thus dependent on the incidence of new infections among both first-time and repeat donors, the testing algorithm in place, the sensitivity of the serological and nucleic acid amplification technique-based assays used, the cotransfused plasma volume, and the degree of virus infectivity. Knowledge of these parameters can also allow for calculation of the maximum viral load entering manufacturing plasma pools.

Each testing algorithm used for blood screening will thus be associated with an intrinsic residual risk determined by a combination of the incidence of new infections in the donor population and the duration of the window phase that escapes detection (determined by testing algorithm and test sensitivity). Using these parameters, the incidence rate–window period ratio can be used to quantify residual risk due to window-phase donations in a specific context. Cost–effectiveness calculations, for example based on the model proposed by the International Society of Blood Transfusion Working Party on Transfusion Transmitted Infectious Disease, can then be made by taking into account factors such as donor epidemiology, costs of different screening options, recipient epidemiology, recipient
treatment costs and recipient mortality rates. Examples of residual risk estimation based on a number of testing strategies and epidemiological scenarios were discussed in the context of the production of blood components for transfusion and of plasma for fractionation.

### 3.2.3 Current regulatory oversight of blood-safety testing in Indonesia

There is currently no centralized regulation oversight in Indonesia for pre-marketing and post-marketing evaluation of blood-safety testing, despite the high-risk context in which such testing is required. As a result, there are no nationally applied standards for in vitro diagnostic device blood screening or for blood and plasma quality in terms of transfusion-transmitted infections. In the absence of such standards, efforts to implement the good manufacturing practice-assured production of blood and blood products based on consistent adherence to national blood standards will remain fundamentally constrained. In addition, the involvement of several agencies in the partial and fragmented overseeing of blood testing means that the risk of transmitting transfusion-transmitted infections depends on the testing technologies applied in each case.

The Indonesian Red Cross Central Blood Transfusion Service plays a coordinating role in the Indonesian Red Cross blood supply network and provides a backup blood supply for other blood transfusion services in Indonesia. Thus, the Indonesian Red Cross Central Blood Transfusion Service is responsible for monitoring the implementation of quality-assurance activities in all Indonesian Red Cross blood centres; in the absence of a centralized national regulator, the Indonesian Red Cross Central Blood Transfusion Service also evaluates blood bags, immunohaematological reagents, and assays and equipment for transfusion-transmitted infection screening. As the range and volume of blood bags, reagents and equipment available on the market continue to increase, there is a growing need for quality control of increasing complexity linked to appropriate regulation.

Hepatitis tests are evaluated by the Indonesian Red Cross Central Blood Transfusion Service, while HIV tests are evaluated by the HIV reference laboratory. The evaluation processes typically start at the request of the manufacturer. The Indonesian Red Cross Central Blood Transfusion Service is requesting certification from internationally recognized regulatory agencies and the provision of training support from the manufacturer in the control of a number of consecutive batches. The current regulatory situation, combined with the high incidence and prevalence of viral infections such as hepatitis B, present major challenges for efforts to ensure blood safety in Indonesia.

The essential roles and responsibilities of manufacturers, the regulatory authority and the blood establishments in the evaluation and regulation of in vitro diagnostic devices as set out above were further discussed and clarified in the context of the current situation in Indonesia. International regulations require that manufacturers demonstrate the clinical specificity and sensitivity of in vitro diagnostic devices used for blood-safety testing in the specific regions where the device is marketed. The resulting information is reviewed by the regulatory authority and used as the basis for determining the type of evaluation or quality-control activities to be undertaken. The regulatory authority is then responsible for the pre-marketing review and approval of blood-screening tests, including assessment of their quality and effectiveness. The regulatory authority does not repeat the full evaluation done by the manufacturer. In terms of ensuring ongoing quality control, manufacturers are also required to define the quality-control specifications for demonstrating production consistency. Based on the information provided in all these areas, the regulatory authority
determines whether the proposed specifications meet the standards set in the country and
decides on the type of laboratory testing needed to confirm the consistent attainment of
the pertinent test features claimed by the manufacturer and required for effectiveness in
the relevant territories.

Such processes urgently need to be implemented in Indonesia to ensure the quality and
effective functioning of the in vitro diagnostic device review and evaluation systems in
use to ensure the safety of the blood supply. The implementation of such systems will
enable regulatory authorities and blood establishments to evaluate the risks faced and to
determine the cost–effectiveness of interventions.

3.3 World Health Organization workshop on enforcement and
implementation of good manufacturing practice in blood establishments

Producing safe high-quality plasma is a highly demanding process, and strong commitment
is needed from all involved parties to develop approaches that bring maximum benefits.

National regulatory authorities enforce and implement regulatory requirements and
standards in blood establishments through licensing and regular inspection. Any licensed
blood establishment supplying plasma as a starting material for the manufacture of
plasma derivatives must therefore have met defined requirements for ensuring the
plasma is safe and good quality. A programme of internal self-evaluation must also be in
place to allow blood establishments to assess the ongoing effectiveness of their quality-
assurance systems. Performed by trained, independent and competent personnel, such
quality-assurance systems should provide control of the process, conducted according to a
documented schedule and audit and covering all aspects of production. Such an approach,
however, must not be regarded as a substitute for official inspections performed by the
national regulator.

Evidence gathered during phase I of the project indicated that the production of plasma
meeting all requirements for further fractionation was a reachable objective in low- and
middle-income countries that, among other criteria, were committed to the enforcement
and implementation of good manufacturing practice approaches to blood establishment
production activities. Improving understanding of the need to implement good
manufacturing practice and to build the technical and regulatory capacity required to
ensure its enforcement in blood establishments was therefore a key project element.

Building on the progress made during the previous workshop on blood-testing technologies
and risk assessment, further training activities were carried out related to the enforcement
and implementation of good manufacturing practice in blood establishments. The specific
workshop objectives were to:

• provide technical assistance to the regulatory authorities and relevant blood services
  in the enforcement and implementation of good manufacturing practice in blood
  establishments intending to prepare human plasma for further fractionation into
  plasma derivatives;

• promote the advancement of blood product regulation by the National Agency for Drug
  and Food Control in Indonesia.
Strict adherence to good manufacturing practice in all the collection, reparation, manufacturing and distribution steps is an essential requirement in the production of good-quality blood components. As a result, the enforcement of good manufacturing practice in blood establishments by the competent national regulatory authority has become an important tool through which the quality and safety of blood products can be ensured. Furthermore, developing a common regulatory language to enhance regional, national and international cooperation between regulatory authorities, thus improving understanding between regulatory authorities, blood establishments and plasma fractionators, will greatly facilitate plasma contract fractionation, thereby increasing the availability of blood products.

Within blood establishments, good manufacturing practice operates as a tool for the introduction and continuous application of quality-assurance principles in all the steps involved in the production of plasma and other blood components. This includes the systematic application of donor-selection criteria for each donation, the use of validated and robust processes, and the release of only those products that comply fully with established safety and quality requirements. Full traceability from donor to recipient of each collection and each product, supported by adequate documentation, is a fundamental requirement in the preparation of plasma for fractionation. Achieving these outcomes requires adherence through good manufacturing practice to the range of pre-established national and international blood standards that are the basis for the licensing of blood and plasma suppliers.

Blood standards are specifications laid down for the preparation of blood and blood components and intended to ensure donor safety and the quality and safety of blood-derived therapeutics. Blood standards must be adhered to across the entire range of relevant steps, from donor assessment and deferral to the collection, testing, processing, labelling, storage and transportation of blood and blood products. National standards should therefore be promulgated in the country to ensure the standardization of blood-product quality and safety and the protection of blood donors. Where national standards are not available, quality standards with an existing wide coverage could be used as the basis for their development – a process that is currently under way in Indonesia.

The enforcement and implementation of good manufacturing practice principles in blood establishments is a new concept in Indonesia. Adhering to good manufacturing practice will help to ensure that the manufacturing and quality control of blood products are in accordance with the developed recognized standards, with consequent minimization of the risk of transmitting both known and emerging bloodborne diseases. This is an essential step in obtaining plasma of a consistent quality that can be used as an acceptable and reliable starting material by fractionators.

It is worth noting that in the case of blood products, quality assurance cannot be based only on batch testing of the final product and must instead be integrated into all stages of manufacture and distribution. Blood establishments providing plasma as a starting material for the fractionation of plasma derivatives must therefore adhere to good manufacturing practice from the very start of the process in order to ensure standardized and uniform production and consistent product quality. This can be achieved through the use of written and accessible instructions for all critical procedures that are followed by all authorized personnel and kept up to date through regular review.
Ensuring that manufacturing processes are under control and that blood and blood components comply with all specifications requires not only suitable facilities and equipment but also appropriate know-how and targeted training, underpinned by good manufacturing practice. This will strengthen the competence of personnel and enable continuous improvements to be made in the collection, preparation and testing of materials. The use of detailed WHO guidelines and recommendations on the good manufacturing practice and process-related aspects of quality monitoring (7) to promote its enforcement and implementation of good manufacturing practice will significantly strengthen efforts to prevent the transmission of transfusion-transmitted infections via blood products in Indonesia and other countries. The overriding public health objective in all settings is to ensure that blood products that do not meet safety and other acceptance criteria are not released.

In all these areas, efforts to build up regulatory authority and blood operator capacities, including through the acquiring of appropriate technical expertise, are urgently needed in many low- and middle-income countries. In all cases, the national regulatory authority should have a sufficient number of inspectors to effectively monitor adherence to national regulatory requirements, including through the direct observation and assessment of the degree to which personnel follow written procedures. This requires appropriate training in good manufacturing practice inspections and familiarity with blood establishments’ technologies and approaches to the quality assurance of plasma.

The WHO guidelines on good manufacturing practices for blood establishments (12) were used as the reference throughout the workshop. This guidance represents the most comprehensive and up-to-date international resource with specific application to blood establishments. Developed to help countries meet international standards, the guidelines provide regulators and blood establishments with the technical elements that need to be addressed in order to ensure compliance. As part of the training sessions, participants familiarized themselves with the guidelines and with the associated WHO recommendations for the production, control and regulation of human plasma for fractionation (11) in preparation for the mock inspections. Participants were also introduced to the practical aspects of performing an inspection during a preparatory session.

3.3.1 Mock inspections of selected blood establishments

Three mock inspections were conducted in parallel in three blood centres in Jakarta, Bekasi and Tangerang, as part of the workshop activities. The purpose of the exercise was to familiarize participants with the objectives of such inspections and with the practical processes involved in their performance. In addition, the mock inspections allowed good manufacturing practice pharmaceutical inspectors to become familiar with blood-bank technologies. None of the participants had previous experience in the enforcement or implementation of good manufacturing practice in blood establishments. The mock inspection process involved explaining the aspects to be evaluated in the context of an inspection, providing the key questions to be raised, and highlighting any potential areas of concern during the critical and major steps.

The mock inspections did not constitute a true inspection. Rather than checking for compliance or identifying deficiencies in the blood establishment, the mock inspections were a practical means of allowing workshop participants to experience the highly specific biological and technological environments within which good manufacturing practice principles were to be applied.
Although a degree of explanatory support was provided to each group by the staff of the blood establishment, interaction within each facility was confined to exchanges between the facilitator and the participants. In each case, the respective facilitator provided the key questions to the participants and coordinated the resulting feedback. The aim was to avoid any direct interference in the activities of staff to minimize the potential risks posed by the presence of such a large group.

Participants were able to observe the processes carried out in each blood establishment, ranging from donor selection to the collection, processing, testing, storage and distribution of blood. Feedback was requested from each of the three groups and then discussed in plenary with all workshop participants and facilitators. Each of the groups was tasked with identifying an example of a critical and a major good manufacturing practice deficiency in blood-establishment collection, processing and testing activities, with reference to the relevant section of the published WHO guidelines.

### 3.4 Assessment criteria for national blood regulatory systems

The WHO assessment criteria for national blood regulatory systems (8) were developed in response to a WHO Blood Regulators Network initiative aimed at promoting robust national regulatory authorities in both developed and developing countries. The document was adopted by the WHO Expert Committee on Biological Standardization in October 2011 following a global consultation process during which comments received from a large number of countries representing all WHO Regions were reviewed by the WHO Blood Regulators Network.

The assessment criteria are intended for use in both developed and developing countries to support benchmarking and assessment processes that could serve to highlight the strengths of the national regulatory authority while also identifying gaps and areas for future development. The availability of global criteria for determining the competencies of a blood regulator also promotes the international standardization of regulatory assessments, which might reduce the burden placed on product developers, and thereby promote the convergence of international regulations and the wider availability of safe blood products, including plasma derivatives.

The criteria are proposed to identify the functions that should be established and undertaken by an effective national regulatory authority to ensure the quality, safety and efficacy of blood and blood products. The scope of products subject to such supervision includes blood, blood components, plasma-derived medicinal products and associated substances, and in vitro diagnostic devices. The criteria are meant to reflect the best practices of a competent blood regulator, while recognizing the distinction between necessary and desirable functions.

It is expected that self-evaluation of the overall situation in Indonesia with the help of this tool will help to identify the main gaps and priorities to inform the development of capacity-building programmes and support the introduction of blood-product regulations at global level. The overall aim is to sustain efforts to respond to resolution WHA63.12 on the availability, quality and safety of blood products.
4. Moving forward in Indonesia

The overall objective of the WHO/European Commission phase II project was to support Indonesia in developing reliable technical and regulatory procedures to ensure the consistent quality and safety of blood components – including plasma for fractionation – manufactured in not-for-profit blood establishments. The setting of appropriate standards and control measures for the manufacture of blood components and the enforcement and implementation of good manufacturing practice in accordance with national regulations were considered key elements to achieving this objective. Applying nationally agreed quality and safety requirements and specifications for blood and plasma collection, preparation, testing and distribution will allow for a harmonized and systematic approach to ensuring compliance at all steps involved in the manufacture of the full range of blood components in blood establishments in Indonesia.

WHO acknowledges the efforts undertaken by Indonesia to strengthen the regulation of blood products as discussed in a closed session held on 27 June 2014 involving the Vice Minister of Health and relevant ministerial departments, the head of the National Agency for Drug and Food Control and the WHO representative accompanied by the project team. As a follow-up, Health Ministerial Decree No. 83 was published at the end of 2014, which aims to strengthen regulation of the national blood system, including implementation of quality-assurance procedures by blood establishments and supervision by the Ministry of Health and the National Agency for Drug and Food Control.

A number of agreed follow-up actions were also identified during workshops, meetings and closed discussions with senior officials from the Ministry of Health, the National Agency for Drug and Food Control and the Indonesian Red Cross. There was broad recognition of the undeniable need to continue to build the case for the development and application of national standards and requirements for blood-safety testing in Indonesia based on the centralized and independent regulatory supervision of in vitro diagnostic devices. In the absence of universally promulgated national standards and technical requirements with which manufacturers need to comply, there will continue to be a reliance on internal standards decided on a case-by-case basis. Avoiding this situation by defining the minimum quality requirements for in vitro diagnostic devices used for blood screening will reduce the risk of transmission posed by tests of lower quality while also contributing significantly to the national standardization of blood and plasma quality and safety.

Problems arising from the absence of any centralized regulatory control for the pre-marketing and post-marketing evaluation of test kits to ensure blood safety are compounded by the involvement of several different institutional and other agencies. Currently, pre-marketing evaluation for HIV serology is performed by the Hospital Dr Cipto Mangunkusumo, with the report sent to the manufacturer as part of the requirement for marketing authorization set by the General Directorate of Pharmaceutical and Medical Devices in the Ministry of Health. It was agreed that regulations will be issued for the centralized regulatory control of in vitro diagnostic devices used in high-risk contexts (such as those related to blood safety) that would cover both pre-marketing and post-marketing control. Post-marketing control would be achieved through a programme of regular vigilance based on risk analysis and backed up by intermittent campaign activities with the overall aim of continuously checking and evaluating representative batches of in vitro diagnostic devices marketed for use in blood safety-related contexts.
By taking advantage of existing resources, well-defined training programmes could also be established to support and strengthen the proposed shift towards centralized pre-marketing and post-marketing evaluation and quality control of in vitro diagnostic devices used in blood-safety testing. Although the equipment and infrastructure needed to conduct testing are available, they are scattered, with specific responsibilities fragmented across different agencies. There is also a need for capacity-building initiatives among the staff who will conduct the centralized evaluations. Reference laboratories, once they have been specifically designated by the Indonesian Government for the review and evaluation of tests, should act on behalf of and communicate regularly with the national regulatory authority. The current approach in which evaluation reports are sent to the manufacturer as part of the requirement for receiving governmental marketing authorization needs to be phased out. Technical and other support in these areas could be made available from the Paul-Ehrlich-Institut subject to a clear indication of commitment towards a centralized organizational approach. In an optimally regulated environment, blood establishments would then proactively assume responsibility for monitoring their laboratory performance, ensuring appropriate control as part of quality management in their centres.

The development of national standards and requirements covering all aspects of blood collection and processing, and the passing into law of a national decree conferring responsibility on the National Agency for Drug and Food Control for centralized regulatory control of all aspects relating to the quality and safety of blood products, are thus recognized as absolute prerequisites for strengthening blood-safety requirements and standards in Indonesia. It was agreed that the Directorate General of Health Care, the Directorate General of Pharmaceutical and Medical Devices and the National Agency for Drug and Food Control would take responsibility for advancing the necessary processes.

Based on the limitations observed during the training process in the context of blood establishments, the priority now is to strengthen the knowledge and capacities of quality-assurance staff in blood establishments and of good manufacturing practice pharmaceutical inspectors from the National Agency for Drug and Food Control, who could then be qualified as inspectors for blood-bank technologies. The basic knowledge of pharmaceutical inspectors of good manufacturing practice is currently not sufficient, and the number of inspectors to be trained needs to be adjusted in line with current national priorities. The number of participants involved in the WHO workshops conducted to date was too large and would need to be reduced to ensure efficiency.

A process of qualification of blood establishments preparing recovered plasma for fractionation was also requested from WHO to advance the possibility of plasma being provided from Indonesia for further fractionation. During meeting discussions, the Indonesian Red Cross Blood Transfusion Service specifically requested support for the implementation of good manufacturing practice in five blood establishments considered to fulfil the plasma quality standards for further fractionation. In the context of the project, one approach to support efforts in this direction would be to focus on a process of targeted capacity building in one selected blood centre in Indonesia. This would involve the development of a training module for each of the main steps in the plasma production process. Thus, in parallel with the development and promulgation of national blood standards and the implementation of regulatory considerations, a structured capacity-building programme for qualifying one blood establishment would be put in place. Such a programme would aim to complete the
training activities already developed during the WHO workshops and would need to be adjusted to meet current national priorities in this area.

This approach would be more efficient as the modules could be used for continued capacity building in the country. The main objective would be to prepare the modules in situ to ensure the direct interaction of blood-establishment staff with the experts providing support. A planned programme would need to be properly discussed and developed, with careful consideration given to the profile of the relevant responsible staff from the Indonesian Red Cross and the National Agency for Drug and Food Control. Such an approach could then provide a solid basis for future expansion efforts in Indonesia. In terms of the shortcomings highlighted during previous fractionator audits, the approach should allow the blood establishment time to adapt to the standard operating procedures and requirements set out during the development of the modules. The overall process would be developed based on current WHO guidelines for good manufacturing practice in blood establishments (12). The criteria to be used to select the blood centre will be defined by Indonesia.

4.1 Conclusions and follow-up actions

Although substantial progress has been made in providing safe whole blood and red blood cells and in increasing the levels of blood donation, the challenge remains of how best to support and assist the investments and efforts needed to improve the knowledge base, infrastructure, production standards and regulatory control of blood establishments across Indonesia in order to improve the quality of the blood collected. For example, some local blood establishments where quality and safety standards need to be established or strengthened may have only basic facilities and a shortage of qualified staff.

The proposals for moving forward presented in this report derive from the assessments and observations made and from discussions held during the WHO training activities. As part of this, the development of national standards for the collection, processing and quality control of human blood products needs to be continued. In addition, significant progress remains to be made in introducing a culture of standardization of production processes in blood establishments to ensure consistency in the quality and safety of plasma to be used as a starting material for further fractionation.

A parallel process will also be required whereby national standards are established and applied sequentially according to the demands of the country. At the same time, this approach will provide technical capacity that could be expanded in Indonesia through internal training activities and exchange of personnel. One possibility would be to structure the upgrading of the quality standards in relation to the different activities of the blood establishments, starting with establishments whose work involves the full range of blood components, including plasma for fractionation. By emphasizing the positive impact that such a move will have on public health, national standards can be established for blood establishments producing plasma for further fractionation, thereby avoiding the discarding of large volumes of plasma.

Despite partial attempts to set policy standards for blood screening, it was acknowledged that the absence of national blood standards covering all aspects of blood collection and processing that could be applied throughout Indonesia represented a serious obstacle to progress. The development and promulgation of national blood standards, including
for the regulatory supervision of in vitro diagnostic devices used in blood safety, will undoubtedly facilitate the implementation and enforcement of good manufacturing practice within blood establishments. It was agreed that one follow-up action would be the development, by the appropriate Ministry of Health regulatory authority, of a national blood-screening policy supported by national standards for the use of in vitro diagnostic devices in blood screening. As part of this, another training workshop would be needed involving the Ministry of Health Directorate General of Health Care and Directorate General of Pharmaceutical and Medical Devices related to the definition of national standards for blood products in Indonesia.

In summary, major progress has been made over the duration of this project in improving understanding of the elements that impact on the production of blood components in blood establishments. There still remains a need for stakeholders in Indonesia to better understand the entire blood chain, from donor to patient, in particular in what is related to the production of good-quality plasma for fractionation and its impact on the quality and safety of plasma-derived medicinal products. As in many other low- and middle-income countries, the regulation and oversight of quality-assurance systems in blood establishments require an ongoing process that will take time. The results of this project and its further proposals were presented for consideration and review to the Blood Track of the WHO Expert Committee on Biological Standardization in October 2014.
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