EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2016

GUIDELINES ON MANAGEMENT OF BLOOD AND BLOOD COMPONENTS AS ESSENTIAL MEDICINES

© World Health Organization 2016

Adopted by the Sixty-seventh Meeting of the World Health Organization Expert Committee on Biological Standardization, 17-21 October 2016. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.
Recommendations and guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for blood establishments/banks that prepare blood and blood components intended for transfusion. If an NRA so desires, these Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Guidelines be made only on condition that modifications ensure that the blood and blood components are at least as safe and efficacious as that prepared in accordance with the recommendations set out below.
CONTENTS

1. INTRODUCTION ................................................................................................................................. 6

2. BLOOD AND BLOOD COMPONENTS AS BIOLOGICAL THERAPEUTIC PRODUCTS ......................... 9
   2.1 Historical Background of Blood Transfusion .................................................................................. 9
   2.2 Indications for Essential Blood and Blood Component Therapy ..................................................... 9
   2.3 Risks of Blood and Blood Components ......................................................................................... 12

3. PREPARATION OF BLOOD AND BLOOD COMPONENTS .................................................................... 13
   3.1 Ethical Aspects of Blood Donation ................................................................................................. 13
   3.2 Description of Key Product Preparation Steps .............................................................................. 14
      3.2.1 Donor Suitability Assessment ................................................................................................. 14
      3.2.2 Collection and Component Preparation ................................................................................. 15
      3.2.3 Additional Testing .................................................................................................................. 16
      3.2.4 Labelling ................................................................................................................................ 16
      3.2.5 Storage .................................................................................................................................... 17
      3.2.6 Distribution and Shipping ....................................................................................................... 17
      3.2.7 Haemovigilance ..................................................................................................................... 17
      3.2.8 Good Preparation Practices/Quality Systems ......................................................................... 18
   3.3 Associated Substances and Medical Devices ............................................................................... 18

4. COMPARISON OF BLOOD COMPONENTS WITH PDMP ................................................................... 20
   4.1 General ........................................................................................................................................... 20
   4.2 Product Safety and Quality ............................................................................................................ 20
   4.3 Product Efficacy ........................................................................................................................... 21

5. THE BLOOD REGULATORY SYSTEM ............................................................................................... 22
   5.1 Guiding Principles .......................................................................................................................... 22
   5.2 Regulatory Framework .................................................................................................................... 22
      5.2.1 General ................................................................................................................................... 22
      5.2.2 Legislation .............................................................................................................................. 23
      5.2.3 Regulations ............................................................................................................................ 23
      5.2.4 Non-Binding Instruments ....................................................................................................... 26
   5.3 The Regulatory Authority ............................................................................................................. 26
5.3.1 Organization of the Regulatory Authority ............................................. 26
5.3.2 Functions of the NRA ........................................................................... 26

6. THE BLOOD SUPPLY SYSTEM .................................................................. 27
   6.1 Organization of the Blood Supply System ............................................ 27
   6.2 Functions of Blood Establishments/Banks ........................................... 27

7. THE BLOOD TRANSFUSION SYSTEM ......................................................... 28

8. STEP-WISE IMPLEMENTATION OF A NATIONALLY REGULATED BLOOD
   SYSTEM ........................................................................................................ 29

9. REFERENCES ............................................................................................... 32

10. APPENDIX .................................................................................................... 34

11. AUTHORS AND ACKNOWLEDGMENT ..................................................... 36
ABBREVIATIONS

EM  Essential Medicine
GMP  Good Manufacturing Practices
GPP  Good Preparation Practices
GvHD  Graft Versus Host Disease
HBV  Hepatitis B Virus
HCV  Hepatitis C Virus
HIV  Human Immunodeficiency Virus
HLA  Human Leukocyte Antigen
NRA  National Regulatory Authority
PDMP  Plasma-Derived Medicinal Product
RBC  Red Blood Cells
RTTI  Relevant Transfusion Transmitted Infection(s)
SOP  Standard Operating Procedures
WHA  World Health Assembly
WHO  World Health Organization
1. INTRODUCTION

Essential medicines (EMs) as defined by the World Health Organization (WHO) are those medicinal products that satisfy the health care needs of the majority of the population. They should therefore be available at all times, in adequate amounts and appropriate dosage forms, with assured quality, and affordability. A WHO Model List of EMs was first generated in 1977 and has been updated every two years since then (http://www.who.int/medicines/publications/essentialmedicines/en/).

This list of EMs includes a core list of minimum medicine needs for a basic health care system (i.e., the most efficacious, safe and cost-effective medicines for priority conditions that are selected based on current and estimated future public health relevance), as well as a complementary list of medicines for priority diseases for which specialized diagnostic or monitoring facilities, specialist medical care and/or specialist training are needed. Some human plasma-derived medicinal products (PDMPs), i.e., factor VIII concentrate and factor IX complex concentrate (coagulation factors II, VII, IX and X) were added to the 2nd complementary list of EMs in 1979, followed by the addition of human normal immunoglobulin to the 15th list in 2007. In the 18th list published in 2013, factor VIII concentrate and factor IX complex concentrate were replaced with coagulation factor VIII and coagulation factor IX, respectively. Further, anti-D, anti-rabies and anti-tetanus immunoglobulins have recently been added to the 19th core list of EMs in 2015.

In the World Health Assembly 2010 resolution WHA63.12, the WHA expressed its concern about the unequal access globally to blood products, particularly PDMPs (also called plasma derivatives), leaving many patients without needed treatment and many of those with severe congenital and acquired disorders without adequate plasma derivative treatments. In this resolution, the WHA urged Member States “to take all the necessary steps to update their national regulations on donor assessment and deferral, the collection, testing, processing, storage, transportation and use of blood products, and operation of regulatory authorities 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.” The requirements for implementing effective national blood regulation are described in the WHO Assessment Criteria for National Blood Regulatory Systems (I).

In accordance with the resolution WHA63.12, and in recognition of the fact that achieving self-sufficiency in the supply of safe blood is an important national goal to prevent blood shortages and to meet the transfusion needs of the patient population, blood and blood components (whole blood, red blood cells, platelets, and fresh frozen plasma) were added to the 18th core list of the WHO Model List of EMs in 2013. Self-sufficiency in this context means that the national needs of patients for safe blood and blood components, as assessed within the framework of the national health system, are met in a timely manner, and that patients have equitable access to safe blood for

---

1 The term “blood products” used in WHA resolution 63.12 means blood, blood components and plasma derivatives/PDMPs.
transfusion, and this can be accomplished by promoting voluntary non-remunerated blood donation. Defining blood and blood components as EMs (i.e. biological therapeutic products or therapeutics) could also contribute to self-sufficiency by: (i) calling attention to the role of national governments in providing the necessary organizational and other support required for assuring a safe and adequate blood supply; and (ii) encouraging countries to develop and ensure compliance with safety and quality standards as well as good practices in product preparation for transfusion.

Assuring the quality, safety and availability of blood and blood components additionally is linked to promoting self-sufficiency in essential PDMPs. If more plasma is collected by apheresis or recovered from whole blood than is needed for transfusion, it may be used as a starting material for fractionation and thereby, support self-sufficiency in PDMPs, provided that the plasma meets required quality standards. As noted above, PDMPs such as coagulation factors and human immunoglobulins have been recognized as EMs since 1979 and 2007, respectively, and have been regulated in several countries as biological therapeutic products for decades to ensure they meet internationally recognized standards for safety, quality and efficacy. However, given the unequal access globally to PDMPs, some countries still rely primarily on the use of whole blood and plasma for various diseases and conditions that could be treated with PDMPs (e.g., fresh frozen plasma instead of Factor VIII and FIX for the treatment of patients with Haemophilia A and B, respectively), contributing to the essential need for plasma components. Further, plasma components are used for the treatment of several plasma protein deficiency diseases that are not treated with PDMPs.

Effective blood regulation is critical to the establishment of blood components as EMs. However, blood and blood components may not meet the legal definition of medicines in all countries and this could have an impact on the approach that must be taken to assure their quality, safety and availability (compared to the approach employed for conventional medicines). Consequently, in 2014, the International Conference of Drug Regulatory Authorities (ICDRA) recommended that the WHO undertakes a project to provide guidance on the management of blood and blood components as EMs. This project involved the WHO Blood Regulators Network (BRN), in cooperation with the WHO Expert Committee on Biological Standardization (ECBS).

Blood and blood components are either prepared by blood establishments and distributed to hospitals and other facilities, or prepared by hospital blood banks for use in the treatment of various diseases, and in some cases, the latter is perceived as part of medical practice rather than the preparation of a biological therapeutic product. There is concern that blood and blood components could be prepared in facilities including hospitals that are not subject to appropriate regulatory oversight. Consequently, the regulatory system should apply to all facilities.
In some jurisdictions - in the context of blood and blood components for transfusion - quality requirements for the preparation of blood components may not be called “Good Manufacturing Practices” (e.g. in Europe they are called “Good Practices”). However, in general, WHO recognizes and has developed specific GMP for blood components preparation (2). In that WHO GMP document the relevant aspects of quality system requirements for blood establishments, including the relevant aspects of GMP that are applicable and necessary for the preparation of blood components for transfusion, are defined. In order to support the implementation of comparable regulatory systems for blood components for transfusion, the alternate term “Good Preparation Practices (GPP)” will be used within this document. Implementation of GPP that are equivalent to the WHO GMP for blood establishments (2) will ensure that these products have similar safety and quality profiles regardless of where they are prepared.

These Guidelines intend to provide a framework for establishing regulatory oversight of blood and blood components for use in transfusion as EMs. The underlying concept is that blood and blood components are biological therapeutic products of human origin whose preparation should be subject to regulatory standardization and oversight to assure their quality, safety and efficacy. The framework provided in these Guidelines is similar to that which is widely applied to regulation of drugs produced under current Good Manufacturing Practices (cGMP), but is adapted to address the specific attributes of blood and blood components for transfusion that distinguish them from PDMPs and pharmaceutical medicines (drugs) in general. In jurisdictions where the legal frameworks in place for medicines manufactured under cGMP for pharmaceuticals would not apply to blood and blood components, parallel regulation on the model of these Guidelines would apply analogous “GPP” for these products. The scope of these Guidelines includes elements that:

a) Make reference to WHA63.12 (2010) regarding the approach that must be taken to assure the quality, safety and availability of blood and blood components for transfusion (discussed above);
b) Clarify the specific nature of blood and blood components as biological therapeutic products of human origin (see section 2);
c) Focus on the ethical aspects of blood donation such as the need to protect donors against exploitation and the establishment of voluntary non-remunerated donations of blood and blood components for transfusion (see section 3.1);
d) Recognize the necessity for blood and blood component preparation to implement standards and controls, a quality assurance system and good practices (see sections 3.2 and 3.3);
e) Highlight the similarities and differences between blood and blood components and conventional biological medicines and biopharmaceuticals (see section 4); and
f) Focus on the need to sustain nationally regulated blood systems (see sections 5 and 6).
2. BLOOD AND BLOOD COMPONENTS AS BIOLOGICAL THERAPEUTIC PRODUCTS

2.1 Historical Background of Blood Transfusion

The first successful transfusion of human blood, as a treatment of postpartum haemorrhage, was performed in 1818 by a British obstetrician, Dr. James Blundell, who drew blood from the patient’s husband and, to prevent the blood from coagulating ex-vivo, infused it directly to the patient. This was followed by several technological advancements in transfusion medicine (3, 4), which include, among others:

a) A number of discoveries in the early 1900s that led to the introduction of blood typing, cross matching and antibody identification in order to prevent the immunological risks associated with blood transfusion;

b) The development of blood banks in early to mid-20th century due to the discovery that blood collected in anticoagulant solution can be stored for several days when refrigerated;

c) Developments in blood component manufacturing between mid to late 20th century, which included the use of interconnected, sterile, disposable plastic containers for collection and preparation of blood and blood components, collection by apheresis, and the storage of platelets at 22 ± 2 ºC; and

d) The implementation of specific serological and nucleic acid-based tests for various infectious diseases (e.g., syphilis, HBV, HCV and HIV) in the mid to late 20th century to reduce transfusion-transmitted diseases.

Over time blood collection and component preparation have become increasingly complex, and currently include among others: donor selection using questionnaires to elicit risk factors for relevant transfusion transmitted infections (RTTI) (5), aseptic collection (6); laboratory testing, and quarantine measures (2), bacterial detection in platelets and pathogen reduction (7, 8) and the use of data management software, as explained in Section 3.

2.2 Indications for Essential Blood and Blood Component Therapy

Human blood is a complex fluid which circulates in the vascular system and is composed of plasma (the liquid portion which contains proteins and a variety of small molecules) and cellular elements that include red blood cells (RBCs), white blood cells and platelets.
Blood and blood components perform numerous vital functions in the body (9, 10). Consequently, severe blood loss could result in life-threatening conditions such as hypovolaemic/hemorrhagic shock, which requires immediate blood transfusion in order to prevent organ failure and death. Blood transfusion is also used as supportive therapy for surgery, chemotherapy, and stem cell and organ transplantation, as well as treatment of serious acute and chronic diseases that are caused by deficiencies or defects in plasma proteins or cellular blood components in order to avoid complications of plasma protein deficiencies and cytopenia (e.g. life-threatening hemorrhage) and to improve quality of life by reducing anaemia-related symptoms. As blood systems developed, transfusion evolved from whole blood transfusion to targeted therapy with specific blood components because several of these diseases are due to deficiencies or defects in a single blood component or plasma protein (e.g., abnormal or low RBC counts for anaemia, including abnormal hemoglobin for thalassemia; low platelet counts for thrombocytopenia; and clotting factor deficiency for haemophilia). Plasma derived from whole blood or apheresis could also serve as starting material for the manufacturing of PDMPs. In this regard, the transfusion of cellular blood components instead of whole blood could serve to generate additional plasma for further manufacturing into PDMPs, providing one of the possible pathways towards self-sufficiency for PDMPs. Examples of the various diseases and conditions that are treated with blood or blood component transfusion are listed in Table 1 (11, 12).

The increasing global demand for access to safe blood and blood components for transfusion has led to the manufacturing or development of various types of equipment and tests used for their preparation. These technological advancements, along with the large number of components prepared annually, have resulted in a significant increase in the complexity of blood and blood component preparation, which further underlines the need for the development of standards for blood banking, and for the inspection of blood establishments/banks to verify compliance with these standards. However, the implementation of internationally accepted standards such as the WHO GMP Guidelines (2) is currently not mandatory in all countries. Regulatory controls should be established worldwide in order to enhance the safety and quality of blood and blood components intended for transfusion.
Table 1. Examples of Indications for Use of Essential Blood and Blood Components

<table>
<thead>
<tr>
<th>Blood/Blood Component</th>
<th>Examples of Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td>RBC replacement in acute, active blood loss with hypovolaemia.</td>
</tr>
<tr>
<td></td>
<td>Therapy in the indications below, where no specific blood components are available.</td>
</tr>
<tr>
<td>RBCs</td>
<td>Supplement oxygen-carrying capacity (e.g., RBC replacement in symptomatic anaemia, blood loss by surgical intervention, trauma and haemolysis, bone marrow failure, and support of patients with haemoglobinopathies).</td>
</tr>
<tr>
<td>Platelets</td>
<td>Prevention or treatment of bleeding due to platelet deficiency or dysfunction or massive blood loss (e.g. patients with decreased platelet production due to congenital or acquired bone marrow failure, platelet destructive conditions, dilutional thrombocytopenia and functionally abnormal platelets).</td>
</tr>
<tr>
<td>Plasma</td>
<td>Management of patients who require multiple coagulation factors (e.g., bleeding patients, patients undergoing invasive procedures).</td>
</tr>
<tr>
<td></td>
<td>Treatment of patients with clinically significant coagulation abnormalities.</td>
</tr>
<tr>
<td></td>
<td>Treatment of patients with selected coagulation factor or rare specific plasma protein deficiencies for which a more appropriate alternative therapy such as specific coagulation concentrate or recombinant products is not available.</td>
</tr>
<tr>
<td></td>
<td>Plasma exchange in patients with thrombotic thrombocytopenic purpura.</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> In order to preserve FVIII, plasma frozen within 8 hours of collection is preferable for indications requiring labile coagulations, or for the preparation of cryoprecipitate for use in the correction of FVIII deficiency. Plasma frozen within 24 hours could also be used.</td>
</tr>
</tbody>
</table>

**Note:** Additional specific medical indications apply to further processed blood components such as washed and irradiated components and cryoprecipitate.
2.3 Risks of Blood and Blood Components

Blood transfusion carries the risk of transmitting infections, if the donated blood contains pathogens.

a) The collection of blood requires a venipuncture. Pathogenic bacteria could be transferred into the donation from a contaminated skin area, and subsequently proliferate (particularly in platelets) to clinically significant numbers capable of causing a transfusion transmitted infection. This risk must be minimized by the use of standardized and validated techniques and disinfectants for aseptic venipuncture. Moreover, thorough adherence to aseptic technique with closed systems and appropriate microbiological sterility testing should be implemented.

b) In the case of several pathogens causing severe disease (including HIV, HBV and HCV), an exposed donor harboring a RTTI may feel well and wish to donate despite being at risk of transmitting infections to patients. Therefore, it is of crucial importance to: (i) collect blood from voluntary non-remunerated donors, as they are known to have lower rates of RTTIs; (ii) exclude from donating any person who has been at increased risk of acquiring such an infection through inquiry, and (iii) test all donors for RTTI using validated assays that have been approved by relevant regulatory authorities.

c) Donors who have tested positive on a first or previous donation must be systematically deferred, i.e. the donation must not enter the processing and testing cycle. To achieve this it is recommended that: (i) a national blood donor registry (e.g. as part of the Blood Management System) be maintained at all points of donation; and (ii) the donors be registered with a unique identifier system. Conditions for potential re-entry of donors, e.g. after proven clearance of the infection or demonstration of a false-positive test, may be defined.

There are also a number of adverse reactions due to immunological mechanisms, the most relevant of which is blood group incompatibility. Therefore, careful blood group typing and documentation is essential to avoid errors, e.g. giving the wrong blood to the patient.

The risks associated with blood transfusion necessitate traceability from donor to patient and vice versa, and a system of haemovigilance, i.e. documenting and reporting adverse events and reactions and initiating corrective actions where necessary. Management of risks associated with blood transfusion need to be part of the Quality Management System developed by the blood establishment.
3. PREPARATION OF BLOOD AND BLOOD COMPONENTS

3.1 Ethical Aspects of Blood Donation

To protect donors’ and patients’ safety, transactions of human blood and blood components should comply with the well-acknowledged principles of biomedical ethics: autonomy, beneficence, non-maleficence and justice. Dignity also applies to donors in the sense of prohibition of using the human body as a source of financial gain (13).

Respecting the rights and ensuring the safety and well-being of both donors and patients is fundamental. Consequently, blood donation should begin with a consideration of a number of ethical issues. These include the following:

a) Encouraging voluntary non-remunerated blood donation which serves as an important foundation for a safe and sustainable blood supply;

b) Providing information to the donor regarding the potential risks associated with the donation, the risk of donating infected blood, and the donor’s responsibility to patient safety and well-being;

c) Obtaining the donor’s consent to the donation and the use of the donation either for transfusion or for further manufacturing of PDMPs. The donor must be mentally competent and the consent given voluntarily. Collection of plasma for PDMP should be undertaken only after ensuring sufficient plasma for transfusion. The use of blood and blood components for other purposes should only be allowed when self-sufficiency in blood and blood components for transfusion is already ensured. The use for research requires ethics approval and a separate and specific informed consent. Under national laws, exceptions may apply in situations where the donation is anonymised;

d) Encouraging “non-directed donations” (i.e., donations made independent of the needs of a particular patient) in order to prevent coercion by known donors/family members as this could result in a reluctance to disclose behaviors associated with infectious risks. An exception could be made for designated donations based on medical reasons (e.g. for patients with rare blood types, where no compatible non-directed donations are available);

e) Minimizing the impact of deferrals on donors (e.g., health concerns, feeling of rejection or discrimination) by educating staff on donor deferral criteria and communication to ensure they are able to explain the reasons for deferral to donors and follow up with deferred donors as appropriate;

f) Protecting donor health and safety during the collection of blood and blood components and, if needed, taking care of donor adverse reactions and obtaining
medical care for the donor after the collection for an appropriate period of time;

g) Informing donors of abnormal test results and ensuring reactive infectious disease test results are confirmed and the donors counselled with respect to further investigation and management by an appropriately specialized physician;

h) Protecting donors against exploitation;

i) Avoiding incentives that could influence an individual’s decision to donate; and

j) Protecting personal data and making it accessible to relevant personnel only, e.g. physician, responsible person.

3.2 Description of Key Product Preparation Steps

3.2.1 Donor Suitability Assessment

Blood and blood component preparation begins with the health screening of carefully recruited donors. Risk based health criteria and acceptable limits should be taken into consideration during the donor selection phase of the donation procedure. Measurement of hemoglobin is essential and a limited physical examination including vital signs (e.g., pulse, blood pressure, and temperature) may be done routinely, or only if the donor’s condition raises suspicion of any possible anomaly in accordance with national standards. Each time a donor donates, standardized donor screening questionnaires should be used to elicit information on the donor’s medical and social history in order to determine whether: (i) he/she is in good health and will not be harmed by donating blood; and (ii) he/she is not at increased risk of infection with communicable blood-borne diseases. A confidential interview should be conducted by trained personnel to clarify the answers obtained to the questionnaires.

The establishment’s standard operating procedures (SOPs) should specify the donor exclusion criteria as well as the donor deferral time frames taking into account specific domestic epidemiology and internationally accepted standards such as the Pan American Health Organization Guidelines on Education and Selection of Prospective Donors (14). Donors should also be informed about the necessity to provide post-donation information to the collection facility of any illness or other relevant information that was unknown prior to donating, which may be relevant for the safety of donated blood.

Donors should be tested for selected RTTI agents such as HBV, HCV, HIV and Syphilis to prevent the use of blood and blood components from infected donors. The testing requirements for additional infectious disease agents should be based on epidemiological data for the geographical region where the donations are made.
It should be noted that while donor suitability assessment significantly reduces the risk of disease transmission to recipients, there are still concerns about residual risks resulting from limitations associated with the donor screening process (e.g., inaccurate responses to screening questions), recent (“window period”) infections (15), assay failures, known pathogens for which testing is not performed or unknown pathogens. Measures that are essential for maintaining and/or enhancing the safety of the blood supply should be implemented, and should include quality management, as well as continuous monitoring of new infectious disease threats and timely implementation of appropriate risk mitigation strategies involving donor screening and/or infectious disease testing.

3.2.2 Collection and Component Preparation

After local skin disinfection using a defined and validated disinfection procedure, blood should be collected aseptically into single use blood bags that meet a suitable regulatory standard. The blood bags, which contain anticoagulant solutions (and preservative/additive solutions where applicable), comprise a closed system. The use of blood bags with diversion pouches can further reduce the risk of contamination with skin microbiota by preventing the initial blood flow from entering the blood bags.

Blood components may be prepared using manual or automated procedures.

a) The manual method involves the centrifugation of a unit of whole blood at low speed to obtain RBC and platelet rich plasma (PRP), the transfer of the PRP into a satellite blood bag, and centrifugation of the PRP at high speed to obtain the platelets and plasma. Alternatively, whole blood can be centrifuged at high speed to obtain three layers consisting of RBC, plasma and a buffy coat containing platelets and leukocytes. The buffy coats derived from approximately 4 to 6 units are then pooled and centrifuged at low speed to separate the platelets from the leukocytes. The RBC, whole blood and platelet components should be leukocyte reduced by the use of prestorage filters. Leukocyte reduction is needed to reduce the risk for

i. platelet refractoriness due to alloimmunization against HLA and platelet specific antigens in multiply transfused patients;

ii. febrile non-haemolytic transfusion reactions (FNTRs);

iii. transmission of leukocyte intracellular pathogens such as human cytomegalovirus (HCMV); and

iv. transmission of variant Creutzfeldt Disease (vCJD).

b) The second method of component preparation is an automated procedure that involves the use of apheresis machines that separate whole blood into its components, transfer the desired components into containers, and return the remaining components to the donor. Some apheresis machines have built-in leukocyte reduction mechanisms.
Blood and blood components may also be subject to additional processing steps such as pooling, irradiation for the prevention of GvHD, the use of filter systems for the reduction of micro aggregates, washing to remove plasma, and applying pathogen reduction (currently using photochemical methods) to enhance safety from infections. Donations from family members should be leucocyte reduced and irradiated to prevent transfusion-associated graft versus host diseases (TA-GvHD).

SOPs used by blood establishments/banks should specify limits for the volumes collected at each donation, as well as the frequency of donation, in order to protect donor health and safety.

### 3.2.3 Additional Testing

In addition to testing donors for RTTI, blood and blood components should also be subject to the following:

a) Each donation intended for transfusion should be tested for ABO and RhD blood groups. Testing for red cell antibodies of potential clinical significance is also recommended, particularly for first time donors and donors with a history of pregnancy or transfusion since their last donation. Additional testing is required for specialized products such as HLA-matched and phenotyped components; and

b) Quality control testing should be performed on a statistically based proportion of components prepared to ensure ongoing assessment of the quality of the procedures used for product preparation. The frequency of quality control testing, the test parameters (e.g., haemoglobin, haematocrit, platelet count, factor VIII concentration, sterility) and acceptance criteria should be established for each type of component, the results analysed on an ongoing basis, and appropriate corrective action taken when values deviate from acceptable limits. Bacterial detection in platelets may also be performed (note: in some countries each platelet component is subject to bacteriological testing for the detection of bacterial contamination).

### 3.2.4 Labelling

Labelling of blood and blood components includes information appearing on the direct product label or contained in accompanying documentation. More specifically, the product label should include the product type, blood groups, a unique donation code that is traceable to the donor, the site for product preparation, the list of pathogens for which discretionary testing is performed (e.g., cytomegalovirus or hepatitis E virus), the storage conditions and expiry date (and time if applicable). Standardized labels that can be universally read such as those printed using machine readable ISBT 128 should be used. The list of pathogens for which testing was performed and found negative should appear either on the product label or in accompanying documentation.
3.2.5 Storage

Blood and blood components should be stored under specified conditions in order to maintain their safety and quality. Units determined to be safe and released for transfusion should be segregated from untested units, and access to storage areas should be restricted to designated personnel. Plasma components should be frozen within a specified time period after collection (preferably within 8 hours for fresh frozen plasma, or within 24 hours). Whole blood and RBC should be refrigerated (1°C – 6°C), and platelets should be stored at 20-24°C under agitation.

3.2.6 Distribution and Shipping

To ensure the safety and quality of blood and blood components, they should be formally released to hospitals for further storage in hospital blood banks or for transfusion after verifying that they meet all safety and quality standards, and are appropriately packaged prior to transportation. The shipping containers should be validated to maintain acceptable storage conditions for the blood and blood components.

3.2.7 Haemovigilance

3.2.7.1 Documentation

There should be a documentation system to assure bidirectional traceability of blood components between donors and patients as a foundation of haemovigilance.

3.2.7.2 Adverse Reaction Reporting and Investigating

There should be a system in place for reporting and investigating serious donor reactions, and serious or unexpected recipient adverse reactions reported by hospitals. In the case of recipient reactions, measures should be taken to notify those in possession of co-components when applicable, and to quarantine and/or recall the co-components. NRAs should also be notified as required. System-wide corrective actions should be implemented where feasible and appropriate.

3.2.7.3 Look-back and Trace-back

Blood establishments should have a look-back procedure in place in order to identify previous donations (and related blood components) from a donor who, on subsequent testing, is confirmed positive for a RTTI; and recipients who received blood components from a donor who later is confirmed positive for a transfusion-transmissible infectious agent.
Trace-back procedures should also be established to investigate a report of a suspected transfusion-associated infection in order to: (i) identify a potential implicated donor; (ii) determine whether any donor who contributed to the transfusion is infected with, or positive for serologic markers, of the implicated infectious agent; (iii) trigger a recall of in date blood components contributed by that donor; and/or (iv) notify consignees and recipients of components collected from that donor. NRAs should also be notified as required.

3.2.8 Good Preparation Practices/Quality Systems

3.2.8.1 Key Requirements

It is recommended that blood establishments/banks comply with relevant elements of GPP to assure the quality and safety of blood and blood components. These include the following (see reference #2 for details):

a) Organization and personnel (including training);
b) Maintenance of facilities/premises;
c) Equipment qualification, calibration and maintenance;
d) Quality control program for products, supplies and services;
e) Donor selection, collection, testing, processing, storage, distribution and record keeping;
f) SOPs containing step-by-step instructions for all activities employed for product preparation as well as specifications for the resulting blood components;
g) Process validation;
h) Change control;
i) Corrective and preventive measures;
j) Quality monitoring; and
k) Management of risks, documentation, non-conformities, audits and contracts.

3.2.8.2 Non-conformity and Deviation Reporting and Investigating

There should be a system in place to ensure that non-conformities and deviations that occur during blood and blood component preparation are documented, investigated for their causative factors and followed up by corrective actions. This should include a system for notifying those in possession of the implicated products (and NRAs, if applicable), and for quarantining and/or recalling products whose safety may have been compromised.

3.3 Associated Substances and Medical Devices

Several associated substances and equipment are used during blood and blood component preparation. These include, among others:
a) Anticoagulant solutions and additive solutions for RBCs and platelets;

b) Blood pressure and pulse monitors, thermometers, haemoglobin analyzers, etc., which are used for donor health assessment;

c) Apheresis equipment, automated blood processors, blood bag collection systems, centrifuges, automated red cell washers, gamma and X-ray irradiators, sterile connection devices, automated blood extractors, plasma freezers, etc., that are used for blood and blood component collection and/or processing;

d) *In vitro* screening test kits used for donor testing, systems for microbial detection, compatibility testing and quality control testing, some of which are automated;

e) Pathogen reduction technology systems; and

f) Computerized blood management systems, specifically systems that analyze data regarding the suitability of blood and blood components for transfusion (note: the classification of blood management systems as medical devices depends on the specifications of the product and the national medical devices legislation).

These materials and equipment are generally regulated as medical devices, except for the anticoagulants and additive solutions, which may be regulated as either drugs or devices. Blood establishments/banks need to ensure that the materials and devices being used for the preparation of blood and blood components are approved by their regulatory authorities. Further, even though device manufacturers are responsible for the validation of the software in automated devices, in some cases, particularly when the equipment needs to be programmed according to the specific needs of the blood establishments/banks, additional validation is required prior to implementation. This further complicates the process for the preparation blood and blood components and underscores the need to comply with internationally recognized standards.
4. COMPARISON OF BLOOD COMPONENTS WITH PDMP

4.1 General

These Guidelines propose the regulation of blood and blood components under GPP, which consist of cGMP that have been adapted to address the attributes of blood and blood components distinguishing them from PDMPs. PDMPs may already be regulated as medicines under an existing framework. The following sections highlight the similarities and differences between blood and blood components and PDMPs, to assist in determining quality requirements which could be applied to blood and blood components.

4.2 Product Safety and Quality

Conventional biological medicines are typically manufactured at industrial scales using complex, proprietary processes that vary with manufacturers. An example is the manufacturing of PDMPs, which may involve, among others: (i) the pooling of thousands of plasma units; (ii) the concentration and/or purification of one or more plasma proteins using methods such as cryoprecipitation and various fractionation procedures that utilize chromatographic, precipitation and filtration techniques; (iii) viral inactivation/removal techniques to enhance product safety; and (iv) formulation, filling and lyophilisation. In-process testing is performed at various steps to monitor the manufacturing process, and final product testing of each lot is performed to ensure that product specifications are met.

The manufacturing of PDMPs is similar to that of other biopharmaceuticals with respect to the complexity of the manufacturing process and its potential impact on the biological characteristics of the final products. Thus, like other biopharmaceuticals, PDMPs are subject to GMP regulations to ensure the products are consistently safe, efficacious and of high quality.

The preparation of blood and blood components differs from PDMP manufacturing in that: (i) closed, single-use systems are used for product preparation to reduce the risk of contamination/cross contamination; (ii) each component is derived from one or a limited number of donations; and (iii) in some cases, the preparation techniques employed are limited to mechanical or physical methods such as centrifugation, separation and cryoprecipitation (for cryoprecipitates). Additional methods such as leukocyte reduction, pooling, washing, irradiation and photo-chemical methods for pathogen inactivation are also employed. Consequently, blood and blood components can be produced at various facilities, ranging from large blood establishments to small hospital blood banks. There are concerns that not all blood establishments/banks are regulated by NRAs. Even in settings where unregulated blood establishments/banks have adopted manufacturing standards developed by professional organizations, there is no mechanism for verifying compliance with these standards.
Notwithstanding the differences in the complexity of the processes used for the manufacturing of PDMPs and preparation of blood and blood components, there are also similarities with respect to the following:

a) The reliance on the availability of healthy donors and the need to protect donors;

b) The risks associated with transfusion transmitted infections and the donor screening and testing measures that are required to mitigate these risks;

c) The importance of linking the donor with each lot of product manufactured or prepared through appropriate labelling and record keeping to facilitate recalls, and where applicable, trace-backs and look-backs;

d) The need to validate new or modified procedures employed for product manufacturing or preparation;

e) The use of appropriately validated automated systems, particularly when there is a need to track a large number of donors/donations and the results of their screening and infectious disease tests;

f) Segregation and hold (i.e., quarantine) of donations/products until they are released for distribution to prevent the release of unsafe products; and

g) Product storage and transportation at appropriate temperatures/conditions.

These similarities lead to the underlying concept that blood and blood components should be prepared within a quality management system based on the principles of GMPs (adapted to blood and blood components), when relevant and appropriate, that includes, among others, elements such as testing of starting materials, in-process quality testing and controls (e.g., bacterial detection and other quality control tests), labelling reflecting product identity and assuring traceability, and adverse event reporting (see section 3.2.8 for details). Consequently, the regulation of blood and blood components as biological therapeutic products would ensure consistent implementation of appropriate standards for product quality, safety and efficacy. Such regulation would apply to all blood establishments involved in the preparation of these products.

4.3 Product Efficacy

Similar to other biopharmaceuticals, PDMPs are subject to clinical trials in the target population to establish their safety and efficacy before approval for clinical use. Such trials are typically not required for conventional blood and blood components because (i) their efficacy has been established through historical use; and (ii) they are prepared and
stored using established procedures that are published in standards developed by professional organizations. However, clinical trials are currently required for blood and blood components when they are prepared using new technology or processing steps (e.g. pathogen reduction technologies) as these could potentially alter their biological characteristics.

5. THE BLOOD REGULATORY SYSTEM

5.1 Guiding Principles

The management of blood and blood components as EMs should take into consideration, the need to:

a) Sustain nationally regulated self-sufficient blood systems;

b) Protect donors against exploitation and prohibit financial gain;

c) Base blood and blood component standards and controls on a quality management system derived from GPP in order to assure the quality, safety and availability of these products; and

d) Ensure that the regulations for blood and blood components and PDMPs are complementary, and incorporate the essential elements and core functions specified in the WHO Assessment Criteria for National Blood Regulatory Systems (1).

5.2 Regulatory Framework

5.2.1 General

Blood and blood components should be controlled under an appropriate regulatory system in order to promote and enhance their quality, safety, and availability. Elements and functions of an effective national blood regulatory system have been described by WHO, which are applicable both in developed and developing countries (1).

The regulatory system should consist of a regulatory framework administered by a NRA that is responsible for regulating the activities associated with the preparation of these products. Regulatory frameworks consist primarily of legislative instruments such as legislation (or act) and regulations which can be supplemented by non-legislative instruments such as policies, guidelines and guidance documents. Collectively, these instruments allow for the categorization of risk to an appropriate level of control; the
capacity to respond quickly to rapid technological advances; and the authority and capacity to take immediate action during crises/emergencies.

5.2.2 Legislation

The legislation/law serves as the first level of a comprehensive regulatory framework and provides a legal basis for the establishment of a regulatory system. A law is needed that governs (i) the preparation of blood and blood components; and (ii) associated substances and relevant medical devices. The law should define the scope of regulations and provide the legal authority for their development. The following are examples of the kinds of provisions that could be included in legislation:

a) The definition of the therapeutic products and devices to be regulated;

b) Prohibitions that prevent the preparation or sale of potentially unsafe products (e.g., products that are prepared under unsanitary conditions or adulterated);

c) The assignment of a NRA with legal powers to administer, enforce and verify compliance with the legislation and regulations (e.g. powers for inspection, seizure and forfeiture, and for the establishment of a list that sets out the classes of products to be regulated);

d) The offences and punishment for persons who deliberately contravene the legislation or regulations; and

e) The definition of areas for which regulations should be developed and granting the authority to develop the regulations necessary for carrying the purposes and provisions of the legislation into effect. These should include the areas covered under section 5.2.3 (Regulations) below.

Details regarding provisions that could be included in national acts or legislation may be found the list of documents provided in the Appendix.

5.2.3 Regulations

Regulations form the second level of the regulatory framework. They are developed under the authority of the legislation and serve to interpret the legislation and provide policies and standards/technical requirements that are legally binding.

Regulations can be developed using different approaches. In the traditional risk management approach, good practices and standards are written directly into regulations. The process for developing and amending regulations can be lengthy and can take up to several years in some jurisdictions, thus making it difficult to keep current with advances in technology and emerging threats.
An alternative and flexible approach is the development and use of standards that are not directly incorporated into regulations, but can be referenced in the regulations. For example, instead of specifying the requirements for donor screening and infectious disease testing in regulations, the sections of a voluntary or mandatory national or internationally recognized standards containing these requirements could be referenced in regulations to give them the force of law. Since the standards are a stand-alone document, they can be amended rapidly when required without amending the regulations themselves. This approach is particularly useful for standards/technical requirements that are likely to require frequent amendments in response to rapid technological advancements and emerging threats.

The incorporation of standards into regulations by reference may be achieved using one of the following approaches:

a) Static or fixed: Referencing requirements in a specific version of a Standard at a defined date to ensure amendments to the Standard do not automatically become part of the regulations. In the case, a regulatory amendment will be required to reference subsequent versions of the Standard.

b) Ambulatory or flexible: Referencing requirements in the Standard as amended from time to time to automatically make any amendments part of the regulations. In this case, the regulations do not need to be amended to reference subsequent versions of the Standard.

This standards-based approach to regulation could be adopted, at least in part, for blood and blood components where the procedures used for their preparation and storage are well established.

The regulations for blood and blood components should focus on managing risk in four key areas:

a) Protection of donor health and safety;

b) Prevention of infectious disease transmission from donors to recipients;

c) Prevention of adverse reactions due to immunological mechanisms in transfusion recipients; and

d) Prevention of improper handling or processing that could affect product safety, efficacy and quality.

This can be accomplished by including requirements for the following elements in blood regulations:
a) Standards for the collection and processing of blood and blood components, which include the methods used for their preparation, described in Section 3 of this document;

b) GPP (consistent with GMP in some jurisdictions) to assure the quality, safety and availability of these products;

c) The use of test kits, blood collection sets, anticoagulants/additive solutions and collection equipment that have been approved by the NRA;

d) Importation and exportation of blood and blood components, though self-sufficiency is the basic principle for blood and blood components;

e) The definition of clinical trials and the requirement for clinical trials for blood and blood components that are prepared using new technologies that could potentially alter their biological characteristics (e.g., pathogen reduction technology);

f) Pre-approval of applications/submissions to determine if the data submitted supports the claims for product safety and quality, and if applicable, efficacy (this may include on-site evaluations of the processes used for product preparation and the facility);

g) The issuance of authorization by the NRA to carry out product preparation activities;

h) The review of applications/submissions for post-approval changes;

i) The submission of applications for registration, accreditation or blood establishment licence and for their amendments to the NRA;

j) The registration of blood establishments/banks and importers or the issuance of licences to these establishments based on evidence of compliance with GPP;

k) The authority for the NRA to issue, refuse, suspend, reinstate or cancel an authorization, registration, accreditation or an establishment licence;

l) The provision of information to the NRA regarding serious reactions in donors and recipients by the holder of blood and blood component registration or authorization and licence;

m) The performance of risk/benefit evaluation and the investigation of the root cause of non-conformity, deviation and adverse events reports; and

n) Powers of inspectors, which allows the performance of compliance and enforcement activities such as inspection of blood establishments/banks to assess
compliance with regulatory requirements, investigation of nonconformities, and follow up on corrective actions.

Consideration should be given to the adoption of internationally recognized standards (see e.g. references 2, 5, 6, 14) that contain detailed requirements for the activities described in Section 3 of this document. Regardless of the approach taken, the stakeholders should be given an opportunity to comment on the regulations before they are finalized.

There should also be regulations that define ‘investigational test’ and require investigational testing and pre-approval of applications for associated substances (e.g., anticoagulants, additive and preservative solutions) and relevant medical devices (e.g. in vitro screening and diagnostic test kits, blood collection equipment, blood bag systems) that are used during the preparation of blood and blood components. Systems should be put in place to ensure compliance with these regulations.

5.2.4 Non-Binding Instruments

The third level of the regulatory framework consists of policies, guidance documents / guidelines and voluntary standards that can be used to supplement regulations. Typically, these documents may be simpler and faster to introduce than regulations, and can be used to interpret regulations and/or provide details to blood establishments/banks on how to meet the regulatory requirements. Since they are not legally binding, they allow flexibility with respect to their interpretation and are adaptable to change. However, if failure to implement these non-binding instruments were to result in a serious adverse event, the establishment would need to explain why the guidance was not followed.

5.3 The Regulatory Authority

5.3.1 Organization of the Regulatory Authority

The regulatory authorities in various countries may currently be organized at a local, regional or national level. The establishment of regulatory authorities at the local or regional level could lead to differences in the standards and regulatory requirements applied to blood and blood components, as well as the level of regulatory oversight. Recognizing huge difficulties in some regions it is recommended that countries move towards a national regulatory authority (NRA) in order to ensure consistency across the country in both the regulatory requirements and oversight.

5.3.2 Functions of the NRA

The key functions of the NRA for blood and blood components are described in the WHO Assessment Criteria for National Blood Regulatory Systems (1). The functions of the NRA include the development of regulations and standards for the preparation of blood and blood components, and the provision of regulatory oversight to verify
compliance with regulatory requirements (see the elements specified in section 5.2.2 of this document for details).

The WHO Assessment Criteria also contain additional information on; (i) the essential elements necessary to establish the legal basis, authority and general characteristics of NRAs; (ii) the core functions of NRAs necessary for comprehensive oversight of blood and blood component; and (iii) major criteria, indicators and associated ratings to assist NRAs in assessing their performance and identifying areas for improvement.

6. THE BLOOD SUPPLY SYSTEM

6.1 Organization of the Blood Supply System

The blood supply system in various countries may currently be organized at a local, regional or national level with respect to blood collection, testing and processing. The organization of blood systems at the local or regional level could lead to differences in the implementation of standards and regulatory requirements, and consequently, blood and blood components with different safety and quality profiles. It is recommended that countries move towards a nationally regulated and coordinated blood supply system where possible in order to: (i) harmonize procedures and best practices at the national level; and (ii) provide assurance that blood and blood components are of equivalent safety and quality and thereby facilitate the exchange of these products across the country.

6.2 Functions of Blood Establishments/Banks

The blood supply system consists of blood establishments/banks that collect, test, process (including washing, pooling and irradiation) and distribute whole blood and blood components intended for transfusions, as well as plasma intended for further manufacturing into PDMPs. These establishments are responsible for: (i) performing the activities described in Sections 3.1 and 3.2 of this document; and (ii) implementing regulations and standards developed by NRAs for these activities. All facilities that perform these activities, including hospital blood banks that prepare blood and blood components for use within their hospitals, should implement the regulations and standards developed by the NRA.
7. THE BLOOD TRANSFUSION SYSTEM

The blood transfusion system consists of care centers (hospitals, surgical centers, and outpatient facilities, sometimes including ambulances) that utilize blood and blood components for the treatment of patients. These care centers are responsible for carrying out the following activities:

a) Storing blood and blood components at appropriate temperatures and conditions;

b) Developing appropriate procedures for further processing of the blood and blood components prior to transfusion, e.g., pooling, washing, and irradiation, where applicable;

c) Appropriate pre-transfusion testing of patients and crossmatching to ensure compatibility of the blood component to be transfused;

d) Maintaining appropriate records to ensure blood components can be traced to their recipients and from recipients back to their donors;

e) Documenting and investigating non-conformities and deviations related to the handling of blood and blood components;

f) Quarantining of blood and blood components that are under investigation by the blood establishments/banks and the hospitals;

g) Reporting adverse events and reactions that are related to the quality of blood components to the blood establishments/banks;

h) Investigating, evaluating and documenting all adverse transfusion reactions; and

i) Ensuring the appropriate use of blood and blood components by clinicians.
8. STEP-WISE IMPLEMENTATION OF A NATIONALLY REGULATED BLOOD SYSTEM

The implementation of a nationally regulated blood system is fundamental to assuring the availability, quality and safety of blood and blood components in agreement with their listing as EMs. A risk-based strategy is recommended when considering the development of a regulatory model for the blood system and a national road map for its implementation.

It is recognized that, when implementing a nationally regulated blood system, the starting situation may vary considerably from one country to another. In some countries, the blood system may be fragmented and central coordination completely lacking, whereas in other countries national or regional bodies may provide a coordinating function within the blood services. In any case, the political commitment of the ministry of health is necessary to establish a road map for implementing a nationally regulated blood system. The main elements of this road map should be developed and agreed upon in cooperation with the key stakeholders. This implementation plan may also incorporate an initial review and improvement of the existing structure of the blood system in a country. Assignment of the main tasks for implementation of this road map and the role and mandate of key personnel should be defined and agreed upon as part of the political process. In any case, a cooperative and step-by-step process to restructure the blood system in a country (if needed) as well as the implementation of a national regulatory system is encouraged to foster more success over time.

The key stakeholders in the blood system (i.e., the blood regulatory system, the blood supply system, and the blood transfusion system), should be involved from the beginning in order to understand and define each one’s responsibility and expected contribution. Regular interaction among the stakeholders is essential. Responsibilities of key stakeholders should be defined.

The legislative body should define a legal framework (regulation) applicable to blood and blood components. This includes the assignment of an NRA to oversee institutions and health care professionals supplying blood and blood components.

An NRA is an essential element of a regulatory system. The decision for a regulatory model should take into account existing regulatory structures, capacities and expertise. Establishing regulation of blood and blood components under the NRA for medicines may be the most effective and most rapid way to accomplish this in settings where blood regulation is otherwise lacking. Regulatory frameworks for blood and blood components and PDMPs should be complementary.

Blood establishments, other related health institutions and health care professionals supplying blood and blood components for transfusion should be engaged to contribute
their experience to the establishment of standards and procedures. This may result in improving the existing structures of the blood system. The initial use of existing standards as a starting point for establishing a common language between all key players may be acceptable.

Where applicable, representatives of the plasma fractionation industry should be invited as additional key players to support this process. This should ensure that appropriate standards are implemented and the quality of surplus plasma as a starting material for further manufacturing will be met.

An essential step is the development of national blood standards covering donor selection criteria, infectious disease marker testing strategy, quality system requirements and standards for the final products (specifications/monographs). During and after the legislative process, these initial standards may continuously be improved and implemented on a national basis. Establishment of such standards should consider existing national and international guidelines (e.g. WHO Guidelines on GMP for blood establishments). As soon as possible, blood establishments should apply these standards in a consistent manner by implementing appropriate procedures (SOPs, training, etc.) within their quality system.

A parallel implementation process and regular interaction among the key players is essential for accelerating the implementation of standards and regulatory functions. However, a political decision to define timeframes for reaching full compliance with standards and to effectively enforce these regulations by the NRA is needed, since the process to implement a regulatory system and to reach an acceptable compliance status may take years. A step-wise implementation plan for a nationally regulated blood system is outlined in the following figure.
**Step-wise Implementation Plan**

| System Design and Development | Development of a legal framework and characterization of an NRA  
|                              | Development and/or adoption of blood standards  
|                              | Review/improve organization, infrastructure and sustainable funding mechanisms  
|                              | Interaction among stakeholders |

| Implementation and Validation | Establishment of regulatory functions including empowerment of the NRA  
|                              | Capacity building and training  
|                              | Interaction among key players  
|                              | Implementation of blood standards |

| Performance and Enforcement | Achievement of compliance including enforcement by the NRA  
|                            | Full performance of regulatory functions  
|                            | Maintaining blood standards  
|                            | Increasing availability and ensuring supply |
9. REFERENCES


## 10. APPENDIX

The following list of documents may serve as examples of existing legislation, regulations and guidances helpful in establishing a regulatory framework.

<table>
<thead>
<tr>
<th>Country</th>
<th>Relevant Legislation, Regulations and Guidance</th>
</tr>
</thead>
</table>
   This Act applies to food, drugs (including blood and blood components), cosmetics and devices.  

   These are stand-alone regulations for blood and blood components intended for transfusion and further manufacturing, and were developed under the authority of the Food and Drugs Act.  


   These regulations apply to food, drugs and cosmetics. The requirements for drugs, which may apply to associated substances such as anticoagulants/additive solutions can be found in Part C, Divisions 1, 1A, 2, 5, 8 of these regulations.  

   These regulations apply to medical devices such as infectious disease test kits, blood collections sets, apheresis equipment, etc. |

|---|---|

|---|---|
11. AUTHORS AND ACKNOWLEDGMENT

The WHO Guidelines on the Management of Blood and Blood Components as Essential Medicines were initiated in 2014 by a recommendation of the International Conference of Drug Regulatory Authorities (ICDRA) to the WHO Blood Regulators Network (BRN).

The BRN (Chair: C. Schärer) undertook the project, in cooperation with the WHO Expert Committee on Biological Standardization (ECBS).

The BRN members involved in this project were F. Agbanyo and L. Elmgren (Health Canada, Canada), J. Epstein and G. Michaud (Food and Drug Administration, USA), R. Seitz, M. Heiden and A. Hilger (Paul-Ehrlich-Institut, Germany), C. Schärer and M. Jutzi (Swissmedic, Switzerland), G. Smith and I. Prosser (Therapeutic Goods Administration, Australia), I. Sainte-Marie and W. Oualikene-Gonin (Agence Nationale de Sécurité du Médicament et des Produits de Santé, France), I. Hamaguchi and T. Kondo (Ministry of Health, Labour and Welfare, Japan). The BRN secretariat at WHO consisted of C.M. Nübling and C. Pasztor.

Further input was provided by P. Strengers (International Plasma Fractionation Association) and H. Klein (National Institutes of Health) prior to public consultation.

During the public consultation phase (July 11–September 26, 2016) comments to the draft WHO Guidelines were received from the following organisations: European Blood Alliance (EBA), International Council for Commonality in Blood Bank Automation (ICCBA), International Plasma Fractionation Association (IPFA), International Society for Blood Transfusion (ISBT), Plasma Protein Therapeutics Association (PPTA)

Furthermore, the following individuals commented during the public consultation: M. d’P Alvarez Castello (CECMED), S. Hindawi (Saudi Society of Transfusion Medicine), M.-L. Hecquet and G. Rautmann (both European Directorate for the Quality of Medicines), F. Moftah (Egyptian Society of Blood Services), G. Praefcke (Paul-Ehrlich-Institut), N. Prunier, T. Schneider and G. Folléa (all Etablissement Français du Sang), M. Ruta, B. Peoples, W. Paul, O. Illoh and E. Storch (all Food and Drug Administration, USA), B. Sorensen (Danish Society of Clinical Immunology), K. Tadokoro (Japanese Red Cross Society), J. Yu (WHO).

The BRN reviewed all comments for incorporation into the revised version of the Guidelines which was presented on October 18, 2016, to the WHO ECBS Blood Products and In Vitro Diagnostics Track for comments.

After further revision the WHO ECBS adopted the final version on October 21, 2016.