

Annex 3

Guidelines on management of blood and blood components as essential medicines

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Guidelines published by the World Health Organization (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 WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.

Abbreviations

EM	essential medicine
GMP	good manufacturing practice(s)
GPP	good preparation practice(s)
GvHD	graft versus host disease(s)
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
PRP	platelet-rich plasma
RBC	red blood cell
RTTI	relevant transfusion-transmitted infection(s)
SOP	standard operating procedure

1. Introduction

Essential medicines (EMs) are defined by WHO as 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 in appropriate dosage forms, with assured quality and affordability. The WHO Model List of Essential Medicines¹ was first generated in 1977 and has been updated every 2 years since then.

This list of EMs includes a core list of minimum medicine needs for a basic health-care system (that is, 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. A number of human plasma-derived medicinal products (PDMPs) – namely, factor VIII concentrate and factor IX complex concentrate (coagulation factors II, VII, IX and X) – were added to the 2nd edition of the complementary list of EMs in 1979, followed by the addition of human normal immunoglobulin to the 15th edition in 2007. In the 18th edition of the complementary list published in 2013, factor VIII concentrate and factor IX complex concentrate were replaced with coagulation factor VIII and coagulation factor IX respectively. Furthermore, anti-D, anti-rabies and anti-tetanus immunoglobulins were added to the 19th edition of the core list of EMs in 2015.

In the 2010 World Health Assembly resolution WHA63.12 concern was expressed about the unequal levels of access globally to blood products,² particularly PDMPs (also called plasma derivatives). Such inequality of access left many patients without needed treatment, and many of those with severe congenital and acquired disorders without adequate plasma-derivative treatments. In this resolution, the World Health Assembly urged WHO 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.

¹ See: <http://www.who.int/medicines/publications/essentialmedicines/en/>

² The term “blood products” used in resolution WHA63.12 means blood, blood components and plasma derivatives/PDMPs.

Requirements for implementing effective national blood regulation are described in the WHO *Assessment criteria for national blood regulatory systems* (1).

In accordance with resolution WHA63.12, and in recognition of the fact that achieving self-sufficiency in the supply of safe blood is an important national goal in preventing blood shortages and meeting the transfusion needs of the patient population, blood and blood components (whole blood, red blood cells (RBCs), platelets and fresh frozen plasma) were added to the 18th edition of the core list of the WHO Model List of Essential Medicines 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 transfusion, and that this can be accomplished by promoting voluntary non-remunerated blood donation. Defining blood and blood components as EMs (that is, as biological therapeutic products or simply “therapeutics”) could also contribute to self-sufficiency by: (a) drawing 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 (b) 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 is additionally 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 (for example, fresh frozen plasma used instead of factor VIII and factor IX for the treatment of patients with haemophilia A and B respectively), contributing to an essential need for plasma components. Furthermore, plasma components are used for the treatment of several plasma protein deficiency diseases that are not treated with PDMPs.

Effective blood regulation is crucial for 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 WHO undertake 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.

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 – with the latter in some cases being perceived as part of medical practice rather than the preparation of a biological therapeutic product. There is therefore 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 the context of blood and blood components for transfusion, quality requirements for the preparation of blood components may in some jurisdictions not be called “good manufacturing practices” (GMP) – for example in Europe they are called “good practices”. However, in general, WHO recognizes, and has developed, specific GMP for the preparation of blood components (2). In this GMP document WHO defines 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. In order to support the implementation of comparable regulatory systems for blood components for transfusion, the alternative term “good preparation practices” (GPP) will be used in the current document. The implementation of GPP that are equivalent to the WHO GMP for blood establishments (2) will ensure that blood components have similar safety and quality profiles regardless of where they are prepared.

2. Purpose and scope

These WHO Guidelines are intended 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 the regulation of drugs produced under current GMP (cGMP) but is adapted to address the specific attributes of blood and blood components for transfusion that distinguish them from PDMPs and from 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 based on the model

provided in these Guidelines would involve application of the analogous “GPP” for such products.

The scope of these Guidelines includes elements that:

- make reference to resolution WHA63.12 (2010) regarding the approach that must be taken to assure the quality, safety and availability of blood and blood components for transfusion (see section 1 above);
- clarify the specific nature of blood and blood components as biological therapeutic products of human origin (see section 3 below);
- focus on the ethical aspects of blood donation, such as the need to protect donors against exploitation, and to establish voluntary non-remunerated donations of blood and blood components for transfusion (see section 4.1 below);
- recognize the necessity to implement standards and controls, a quality assurance system and good practices for blood and blood component preparation (see sections 4.2 and 4.3 below);
- highlight the similarities and differences between blood and blood components and conventional biological medicines and biopharmaceuticals (see section 5 below);
- focus on the need to sustain nationally regulated blood systems (see sections 6 and 7 below).

3. Blood and blood components as biological therapeutic products

3.1 Historical background of blood transfusion

The first successful transfusion of human blood, as a treatment for 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 into the patient. This was followed by several technological advancements in transfusion medicine (3, 4), which included:

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

- Developments in blood component manufacturing between the mid and 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 °C.
- The implementation of specific serological and nucleic-acid-based tests for various infectious disease pathogens, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and syphilis 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: (a) donor selection using questionnaires to elicit risk factors for relevant transfusion-transmitted infections (RTTI) (5); (b) aseptic collection (6); (c) laboratory testing, and quarantine measures (2); (d) bacterial detection in platelets and pathogen reduction (7, 8); and (e) the use of data-management software. Further information on these aspects is provided below in section 4.

3.2 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 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/haemorrhagic shock, which requires immediate blood transfusion in order to prevent organ failure and death. Blood transfusion is also used as a supportive therapy for surgery, chemotherapy, and stem cell and organ transplantation, as well as the treatment of serious acute and chronic diseases caused by deficiencies or defects in plasma proteins or cellular blood components, in order to avoid complications such as life-threatening haemorrhage or 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. This is because several of these diseases are due to deficiencies or defects in a single blood component or plasma protein (for example, abnormal or low RBC counts for anaemia (including abnormal haemoglobin for thalassaemia); low platelet counts for thrombocytopenia; and clotting factor deficiency for haemophilia). Plasma derived from whole blood or apheresis can also serve as the 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 of PDMPs, thereby providing one of the possible pathways towards self-sufficiency in PDMPs. Examples of diseases and conditions that are treated with blood or blood component transfusion are listed in Table A3.1 (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 A3.1

Examples of indications for use of essential blood and blood components

Blood/blood component	Examples of indications ^a
Whole blood	RBC replacement in acute active blood loss with hypovolaemia. Therapy in the indications below when no specific blood components are available.
RBCs	Supplement oxygen-carrying capacity (for example, RBC replacement to treat symptomatic anaemia; blood loss during surgical intervention, trauma and haemolysis; and bone marrow failure; and to support patients with haemoglobinopathies).
Platelets	Prevention or treatment of bleeding due to platelet deficiency or dysfunction, or massive blood loss (for example, in patients with decreased platelet production due to congenital or acquired bone marrow failure; platelet-destructive conditions; dilutional thrombocytopenia; and functionally abnormal platelets).

Table A3.1 *continued*

Blood/blood component	Examples of indications ^a
Plasma	<p>Management of patients who require multiple coagulation factors (for example, bleeding patients; and patients undergoing invasive procedures).</p> <p>Treatment of patients with clinically significant coagulation abnormalities.</p> <p>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.</p> <p>Plasma exchange in patients with thrombotic thrombocytopenic purpura.</p> <p>In order to preserve factor VIII, 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 factor VIII deficiency. Plasma frozen within 24 hours could also be used.</p>

^a Additional specific medical indications apply to further processed blood components such as washed and irradiated components and cryoprecipitate.

3.3 Risks of blood and blood components

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

- As the collection of blood requires a venepuncture to be performed, 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 an RTTI. This risk must be minimized by the use of standardized and validated techniques and disinfectants for aseptic venepuncture. Moreover, thorough adherence to aseptic technique with closed systems and appropriate microbiological sterility testing should be implemented.
- In the case of several pathogens causing severe disease (including HIV, HBV and HCV) an exposed donor harbouring an RTTI may feel well and wish to donate despite being at risk of transmitting

infections to patients. Therefore, it is crucial to: (a) collect blood from voluntary non-remunerated donors, as they are known to have lower rates of RTTI; (b) exclude from donating, through enquiry, any person who has been at increased risk of acquiring such an infection; and (c) test all donors for RTTI using validated assays that have been approved by relevant regulatory authorities.

- Donors who have tested positive on a first or previous donation must be systematically deferred – that is, the donation must not enter the processing and testing cycle. To achieve this it is recommended that: (a) a national blood donor registry (for example, as part of the blood management system) is maintained at all points of donation; and (b) donors are registered using a unique-identifier system. Conditions for the potential re-entry of donors (for example, 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 these is blood group incompatibility. Therefore, careful blood group typing and documentation is essential to avoid errors (for example, 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 – that is, documenting and reporting adverse events and reactions, and initiating corrective actions where necessary. The management of risks associated with blood transfusion needs to be part of the quality management system developed by the blood establishment.

4. Preparation of blood and blood components

4.1 Ethical aspects of blood donation

To ensure the safety of both donors and patients, transactions of human blood and blood components should comply with the well-acknowledged principles of biomedical ethics – namely, autonomy, beneficence, non-maleficence and justice. Dignity also applies to donors in the sense of prohibiting the use of 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, which include:

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

- Providing information to the donor regarding the potential risks associated with the donation, the risk of donating infected blood, and the donor's responsibility with respect to patient safety and well-being.
- Obtaining the donor's consent to the donation and to 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 PDMPs 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. Their use in research requires ethics approval and a separate and specific informed consent. Under national laws, exceptions may apply in situations where the donation is anonymized.
- Encouraging "non-directed donations" (that is, donations made independently of the needs of a particular patient) in order to prevent coercion by known donors/family members, as such coercion could result in a reluctance to disclose behaviours associated with infectious risks. An exception could be made for designated donations based on medical reasons (for example, for patients with rare blood types where no compatible non-directed donations are available).
- Minimizing the impact of deferrals on donors (for example, health concerns, or feelings 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 to follow up with deferred donors as appropriate.
- Protecting donor health and safety during the collection of blood and blood components and, if needed, dealing with donor adverse reactions and obtaining medical care for the donor for an appropriate period of time after the collection.
- Informing donors of abnormal test results and ensuring that reactive infectious disease test results are confirmed and the donors counselled with respect to further investigation and management by an appropriately specialized physician.
- Protecting donors against exploitation.
- Avoiding incentives that could influence an individual's decision to donate.
- Protecting personal data and making them accessible only to authorized personnel such as physicians or the responsible person.

4.2 Description of key product preparation steps

4.2.1 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. The measurement of haemoglobin is essential and a limited physical examination, including vital signs (for example, pulse, blood pressure and temperature), may be performed either routinely or where the donor's condition raises suspicions of any possible anomaly, in accordance with national standards. Each time donors donate, standardized donor-screening questionnaires should be used to elicit information on their medical and social history in order to determine that: (a) they are in good health and will not be harmed by donating blood; and (b) they are not at increased risk of infection with communicable bloodborne diseases. A confidential interview should be conducted by trained personnel to clarify the answers obtained in the questionnaires.

The standard operating procedures (SOPs) of the blood establishment should specify the donor-exclusion criteria as well as the donor-deferral time frames, taking into account both the specific local epidemiology and internationally accepted standards and guidance, such as the Pan American Health Organization guidelines on prospective donor education and selection (14). Donors should also be informed about the necessity to provide post-donation information to the collection facility on any illness or any other information relevant to the safety of donated blood that was unknown prior to donating.

Donors should be tested for selected transfusion-transmissible infectious agents such as HIV, HBV, HCV 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 in which 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 the residual risks that can result from: (a) limitations associated with the donor-screening process (for example, inaccurate responses to screening questions); (b) recent ("window-period") infections (15); (c) assay failures; (d) known pathogens for which testing is not performed; and (e) unknown pathogens. Essential measures for maintaining and/or enhancing the safety of the blood supply should be implemented, and should include quality management as well as the continuous monitoring of new infectious disease threats and timely implementation of appropriate risk-mitigation strategies involving donor screening and/or infectious-disease testing.

4.2.2 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), constitute 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 either a manual or automated procedure. The manual method involves the centrifugation of a unit of whole blood at low speed to obtain RBCs 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 RBCs, plasma and a buffy coat containing platelets and leukocytes. The buffy coats derived from approximately 4–6 units are then pooled and centrifuged at low speed to separate the platelets from the leukocytes. The RBCs, whole blood and platelet components should be leukocyte reduced by the use of pre-storage filters. Leukocyte reduction is needed to reduce the risk of:

- platelet refractoriness due to alloimmunization against human leukocyte antigen (HLA) and platelet-specific antigens in multiply transfused patients;
- febrile non-haemolytic transfusion reactions (FNTRs);
- transmission of leukocyte intracellular pathogens such as human cytomegalovirus (HCMV);
- transmission of variant Creutzfeldt-Jakob disease.

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: (a) pooling; (b) irradiation for the prevention of graft versus host diseases (GvHD); (c) the use of filter systems for the reduction of micro-aggregates; (d) washing to remove plasma; and (e) applying pathogen reduction (currently using photochemical methods) to enhance safety from infections. Donations from family members should be leukocyte-reduced and irradiated to prevent transfusion-associated GvHD.

The 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.

4.2.3 Additional testing

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

- 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.
- Quality control testing should be performed on a statistically based proportion of components to ensure ongoing assessment of the quality of the procedures used for product preparation. The frequency of quality control testing, the test parameters (for example, haemoglobin, haematocrit, platelet count, factor VIII concentration and sterility) and acceptance criteria should all be established for each type of component. Test results should be 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.

4.2.4 Labelling

The “labelling” of blood and blood components refers to both information appearing on the direct product label and/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 of product preparation, the list of pathogens for which discretionary testing is performed (for example, cytomegalovirus or hepatitis E virus), the storage conditions and expiry date (and time of day if applicable). Standardized labels that can be universally read (such as those printed using machine-readable ISBT 128 standard terminology) should be used. The list of pathogens for which testing was performed and found to be negative should appear either on the product label or in accompanying documentation.

4.2.5 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 period after collection (preferably within 8 hours for fresh frozen plasma, or within 24 hours). Whole blood and RBCs should be refrigerated (at 1–6 °C) and platelets should be stored at 20–24 °C under agitation.

4.2.6 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.

4.2.7 Haemovigilance

4.2.7.1 Documentation

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

4.2.7.2 Adverse reaction reporting and investigating

There should be a system in place for reporting and investigating serious donor reactions, and serious or unexpected adverse recipient 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.

4.2.7.3 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 transfusion-transmissible infectious agent – and to identify recipients who received blood or blood components from a donor who is later confirmed positive for such an infectious agent.

Trace-back procedures should also be established to investigate any report of a suspected RTTI in order to: (a) identify a potential implicated donor;

(b) determine whether any donor who contributed to the transfusion is infected with (or positive for serological markers of) the implicated infectious agent; (c) trigger a recall of in-date blood or blood components contributed by that donor; and (d) notify consignees and recipients of components collected from that donor. The NRA should also be notified as required.

4.2.8 Good preparation practices/quality systems

4.2.8.1 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 (2). These elements include:

- organization and personnel (including training);
- maintenance of facilities/premises;
- equipment qualification, calibration and maintenance;
- quality control programme for products, supplies and services;
- donor selection, blood collection, testing, processing, storage and distribution, and record-keeping;
- SOPs containing step-by-step instructions for all activities undertaken during product preparation, as well as specifications for the resulting blood components;
- process validation;
- change control;
- corrective and preventive measures;
- quality monitoring;
- management of risks, documentation, nonconformities, audits and contracts.

4.2.8.2 Nonconformity and deviation reporting and investigating

There should be a system in place to ensure that any nonconformities 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 the NRA, if applicable), and for quarantining and/or recalling products whose safety may have been compromised.

4.3 Associated substances and equipment

Associated substances and equipment used during blood and blood component preparation include:

- anticoagulant solutions and additive solutions for RBCs and platelets;
- blood pressure and pulse monitors, thermometers, haemoglobin analysers, etc. that are used to assess donor health;
- 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;
- in vitro screening test kits used for donor testing, and systems for microbial detection, compatibility testing and quality control testing (including automated systems);
- pathogen-reduction technology systems;
- computerized blood management systems, specifically systems that analyse 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 substances and equipment are generally regulated as medical devices, except for the anticoagulant 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. Furthermore, even though device manufacturers are responsible for the validation of the software in automated devices, in some cases additional validation is required prior to implementation – particularly when the equipment needs to be programmed according to the specific needs of the blood establishment/bank. This further complicates the preparation process for blood and blood components and underscores the need to comply with internationally recognized standards.

5. Comparison of blood components with PDMPs

5.1 General

These WHO 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 that distinguish them from PDMPs. PDMPs may already be regulated as medicines under an existing framework. The following sections highlight both the similarities and the differences between blood and blood components and PDMPs to assist in determining quality requirements that could be applied to blood and blood components.

5.2 Product safety and quality

Conventional biological medicines are typically manufactured on an industrial scale using complex proprietary processes that vary between manufacturers. One example is the manufacturing of PDMPs, which may involve, among other steps: (a) the pooling of thousands of plasma units; (b) 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; (c) viral inactivation/removal techniques to enhance product safety; and (d) formulation, filling and lyophilization. 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: (a) closed single-use systems are used for product preparation to reduce the risk of contamination/cross-contamination; (b) each component is derived from one donation or from a limited number of donations; and (c) 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 photochemical 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 an NRA. 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 those used for the preparation of blood and blood components, there are also similarities with respect to the following:

- a reliance upon the availability of healthy donors and the need to protect donors;
- the risks associated with RTTI and the donor screening and testing measures required to mitigate these risks;

- 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, look-backs and trace-backs;
- the need to validate new or modified procedures employed for product manufacturing or preparation;
- 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;
- the need for segregation and holding (that is, quarantine) of donations/products until they are released for distribution to prevent the release of potentially unsafe products;
- the need for product storage and transportation at appropriate temperatures and 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 GMP (adapted to blood and blood components) when relevant and appropriate – and which includes elements such as the testing of starting materials, in-process quality testing and controls (for example, bacterial detection and other quality control tests), labelling that reflects product identity and assures traceability, and adverse event reporting (see section 4.2.8 above). Consequently, the regulation of blood and blood components as biological therapeutic products would ensure the consistent implementation of appropriate standards for product quality, safety and efficacy. Such regulation would apply to all blood establishments/banks involved in the preparation of these products.

5.3 **Product efficacy**

As with other biopharmaceuticals, PDMPs are subjected 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: (a) their efficacy has been established through historical use; and (b) 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 technologies or processing steps (for example, pathogen-reduction technologies) as these could potentially alter their biological characteristics.

6. The blood regulatory system

6.1 Guiding principles

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

- sustain nationally regulated self-sufficient blood systems;
- protect donors against exploitation and prohibit financial gain;
- 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;
- ensure that the regulations for blood and blood components and for PDMPs are complementary, and incorporate the essential elements and core functions specified in the *WHO Assessment criteria for national blood regulatory systems (1)*.

6.2 Regulatory framework

6.2.1 General

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

The regulatory system should consist of a regulatory framework administered by an 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 that 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 and the capacity to respond quickly to rapid technological advances, while providing the required authority and capacity to take immediate action during crises and emergencies.

6.2.2 Legislation

The legislation or 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 the preparation of blood and blood components, as well as the use of 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:

- Definition of the therapeutic products and devices to be regulated.
- Prohibitions that prevent the preparation or sale of potentially unsafe products (for example, products that are adulterated or prepared under unsanitary conditions).
- Assignment of an NRA with legal powers to administer, enforce and verify compliance with the legislation and regulations (for example, powers for inspection, seizure and forfeiture and for the establishment of a list that sets out the classes of products to be regulated).
- The offences and punishment of persons who deliberately contravene the legislation or regulations.
- Definition of the areas for which regulations should be developed and granting of the authority to develop the regulations necessary for carrying the purposes and provisions of the legislation into effect. These areas should include those covered below in section 6.2.3.

Detailed guidance regarding provisions that could be included in national acts or legislation may be found in the list of documents provided in the Appendix to these Guidelines.

6.2.3 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 to 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 ensure that they remain current with regard to technological advances and emerging threats.

An alternative and more 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 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 advances and emerging threats.

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

- Static or fixed – this approach references requirements in a specific version of a standard at a defined date to ensure that amendments to the standard do not automatically become part of the regulations. In this approach, a regulatory amendment will be required to reference subsequent versions of the standard.
- Ambulatory or flexible – this approach references requirements in the standard as amended from time to time to automatically make any amendments part of the regulations. In this approach, 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 for which the procedures used for their preparation and storage are well established.

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

- protection of donor health and safety;
- prevention of infectious-disease transmission from donors to recipients;
- prevention of adverse reactions due to immunological mechanisms in transfusion recipients;
- 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:

- Standards for the collection and processing of blood and blood components, which include the methods used for their preparation (see section 4 above).
- GPP (consistent with GMP in some jurisdictions) to assure the quality, safety and availability of these products.
- The use of test kits, blood-collection sets, anticoagulant/additive solutions and other collection equipment that have been approved by the NRA.

- Importation and exportation of blood and blood components – although self-sufficiency in blood and blood components is a basic principle.
- The definition of clinical trials and the requirement for clinical trials of blood and blood components prepared using new technologies (for example, pathogen-reduction technologies) that could potentially alter their biological characteristics.
- Pre-approval of applications/submissions to determine if the data submitted support the claims made for product safety and quality and, if applicable, for efficacy (this may include on-site evaluations of the facility and processes used for product preparation).
- The issuance of authorization by the NRA to carry out product preparation activities.
- The review of applications/submissions for post-approval changes.
- The submission of applications for (or amendments to) registration, accreditation or blood establishment licensing.
- The registration of blood establishments/banks and importers or the issuance of licences to such facilities based on evidence of compliance with GPP.
- The authority of the NRA to issue, refuse, suspend, reinstate or cancel an authorization, registration or accreditation, or facility licence.
- The provision of information to the NRA regarding serious reactions in donors and recipients by the holders of blood and blood component registration or authorization and licences.
- The performance of risk–benefit evaluation and investigation of the root cause of nonconformity, deviation and adverse events reports.
- Powers of inspectors, which allows for 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 of corrective actions.

Consideration should be given to the adoption of internationally recognized standards, such as the examples cited in these Guidelines (2, 5, 6, 14), that set out detailed requirements for the activities described in section 4 above. Regardless of the approach taken, all 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 that require the investigational testing and pre-approval of applications for associated substances (such as anticoagulant, additive and preservative solutions)

and relevant medical devices (such as in vitro screening and diagnostic test kits, blood-collection equipment and 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.

6.2.4 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 regulatory requirements. Since they are not legally binding, they allow flexibility with respect to their interpretation and are adaptable to change. However, if a failure to implement these non-binding instruments were to result in a serious adverse event, the blood facility in question would need to explain why the guidance was not followed.

6.3 The regulatory authority

6.3.1 Organization of the regulatory authority

The regulatory authorities in different 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 in the level of regulatory oversight. While recognizing that huge difficulties exist in some regions, it is recommended that countries move towards the establishment of an NRA in order to ensure consistency across the country in both regulatory requirements and oversight.

6.3.2 Functions of the NRA

The key functions of the NRA with respect to blood and blood components are described in the WHO *Assessment criteria for national blood regulatory systems* (1). Such functions 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 (for the individual elements of such requirements see section 6.2.3 above).

The WHO assessment criteria document also contains additional information on: (a) the essential elements necessary to establish the legal basis, authority and general characteristics of an NRA; (b) the core functions of an NRA required for the comprehensive oversight of blood and blood components; and (c) major criteria, indicators and associated ratings to assist NRAs in assessing their performance and identifying areas for improvement.

7. The blood supply system

7.1 Organization of the blood supply system

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

7.2 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. Such facilities are responsible for: (a) performing the activities described in sections 4.1, 4.2 and 4.3 above; and (b) implementing the 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.

8. The blood transfusion system

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

- storing blood and blood components at appropriate temperatures and conditions;
- developing appropriate procedures for further processing of the blood and blood components prior to transfusion – for example, pooling, washing and irradiation, where applicable;
- appropriate pre-transfusion testing of patients and cross-matching to ensure compatibility of the blood component to be transfused;

- maintaining appropriate records to ensure that blood components can be traced to their recipients and from recipients back to their donors;
- documenting and investigating nonconformities and deviations related to the handling of blood and blood components;
- quarantining of blood and blood components that are under investigation by the blood establishments/banks and hospitals;
- reporting adverse events and reactions that are related to the quality of blood components to the blood establishments/banks;
- investigating, evaluating and documenting all adverse transfusion reactions;
- ensuring the appropriate use of blood and blood components by clinicians.

9. Stepwise implementation of a nationally regulated blood system

The implementation of a nationally regulated blood system is fundamental to assuring the quality, safety and availability of blood and blood components in accordance 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 roadmap 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 perform a coordinating function within the blood services. In any case, the political commitment of the ministry of health is necessary to establish a roadmap for implementing a nationally regulated blood system. The main elements of this roadmap 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. The assignment of the main tasks for implementing this roadmap 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) and to implement a nationally regulated blood system is encouraged in order to foster more success over time.

The key stakeholders in the blood system (that is, 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 their individual responsibilities and expected contributions. Regular interaction among stakeholders is essential.

The legislative body should define a legal framework (regulation) applicable to blood and blood components. This would include assigning the NRA to oversee all institutions and health-care professionals supplying blood and blood components.

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

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

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

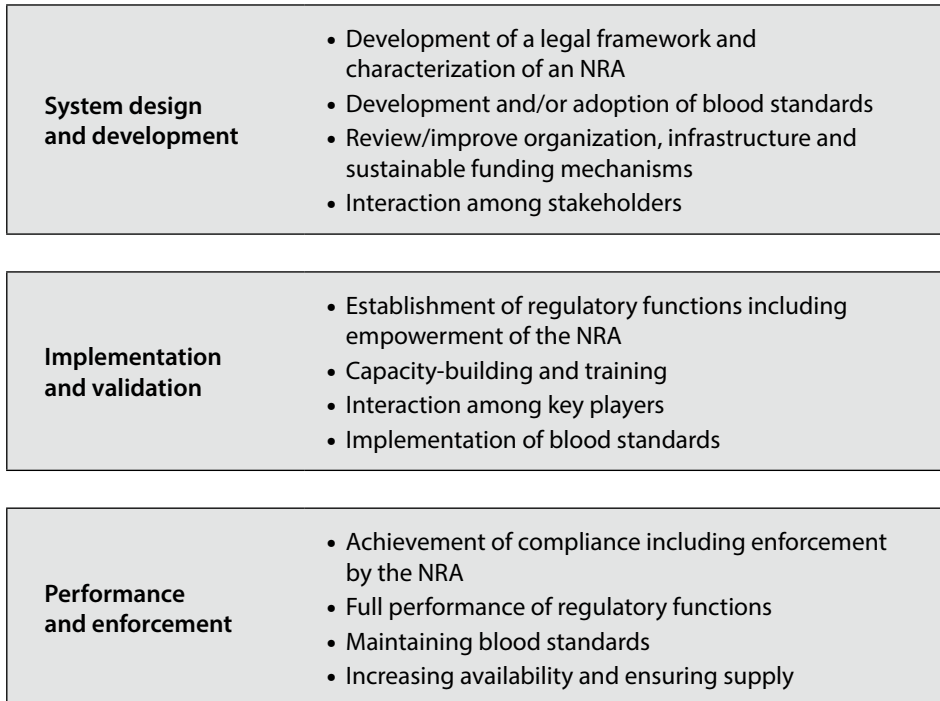
The development of national blood standards covering donor-selection criteria, infectious disease marker testing strategies, quality system requirements and standards for the final products (specifications and/or monographs) will be an essential step. Both during and after the legislative process, these initial standards may continuously be improved and implemented on a national basis. The establishment of such standards should take into account existing national and international guidelines such as the *WHO guidelines on good manufacturing practices for blood establishments* (2). As soon as possible, blood establishments should apply these standards in a consistent manner by implementing appropriate procedures (including SOPs and training) within their quality system.

A parallel national implementation process and regular interaction among the key players will be essential in accelerating the implementation of standards and regulatory functions. Since the process of implementing a regulatory system and reaching an acceptable compliance status may take several years, a political decision will be required to define the time frames

for reaching full compliance with standards and for effective enforcement of regulations by the NRA. A possible stepwise implementation plan for a nationally regulated blood system is outlined in Fig. A3.1.

Fig. A3.1

Stepwise implementation plan for a nationally regulated blood system



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The BRN reviewed all comments received for incorporation into the revised final draft document WHO/BS/2016.2285.

Further changes were subsequently made to document WHO/BS/2016.2285 by the WHO Expert Committee on Biological Standardization.

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Appendix

Examples of existing legislation, regulations and guidance

The documents listed here are provided as examples of existing legislation, regulations and guidance that may be helpful in establishing a national regulatory framework.

Country or region	Relevant legislation, regulations and guidance
Canada	<ol style="list-style-type: none"> <li data-bbox="341 666 1006 729">1. Food and Drugs Act (1985): http://laws-lois.justice.gc.ca/eng/acts/f-27/ (accessed 26 December 2016). <ul style="list-style-type: none"> <li data-bbox="341 753 976 817">• This Act applies to food, drugs (including blood and blood components), cosmetics and devices. <li data-bbox="341 840 1045 904">2. Blood Regulations: http://laws-lois.justice.gc.ca/eng/regulations/SOR-2013-178/index.html (accessed 26 December 2016). <ul style="list-style-type: none"> <li data-bbox="341 928 1052 1044">• 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. <li data-bbox="341 1068 1048 1159">3. Guidance Document: Blood Regulations: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/blood-reg-sang/blood-guid-sang-ligne-eng.php (accessed 26 December 2016). <li data-bbox="341 1183 1000 1274">4. Food and Drug Regulations: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html (accessed 26 December 2016). <ul style="list-style-type: none"> <li data-bbox="341 1297 1006 1414">• These regulations apply to food and drugs. 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 and 8 of these regulations. <li data-bbox="341 1437 1040 1528">5. Medical Devices Regulations: http://laws-lois.justice.gc.ca/eng/regulations/SOR-98-282/index.html (accessed 26 December 2016). <ul style="list-style-type: none"> <li data-bbox="341 1552 1024 1643">• These regulations apply to medical devices, for example, infectious disease test kits, blood-collection sets and apheresis equipment.

Table *continued*

Country or region	Relevant legislation, regulations and guidance
Europe	<ol style="list-style-type: none"> <li data-bbox="341 360 1069 569">1. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 – setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2002_98/dir_2002_98_en.pdf (accessed 26 December 2016). <li data-bbox="341 593 1069 802">2. Commission Directive 2004/33/EC of 22 March 2004 – implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004484.pdf (accessed 26 December 2016). <li data-bbox="341 826 1069 1035">3. Commission Directive 2005/62/EC of 30 September 2005 – implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004486.pdf (accessed 26 December 2016). <li data-bbox="341 1059 1069 1268">4. Commission Directive 2005/61/EC of 30 September 2005 – implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004485.pdf (accessed 26 December 2016). <li data-bbox="341 1292 1069 1366">5. Council of Europe (EDQM) Recommendations & Resolutions: https://www.edqm.eu/en/blood-transfusion-recommendations-resolutions-71.html (accessed 26 December 2016).
The USA	<ol style="list-style-type: none"> <li data-bbox="341 1390 1069 1512">1. United States Food and Drug Administration; subchapter F – Biologics: http://www.ecfr.gov/cgi-bin/text-idx?SID=7f01bf1d25c364e2d287f227cd6833c8&mc=true&tpl=/ecfrbrowse/Title21/21CsubchapF.tpl (accessed 26 December 2016). <li data-bbox="341 1536 1069 1650">2. United States Food and Drug Administration; Blood Guidances: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm (accessed 26 December 2016).

