ETHIOPIAN FOOD AND DRUG AUTHORITY

GOOD PRACTICE GUIDELINE FOR BLOOD ESTABLISHMENTS

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Contents

Forward

Blood regulation plays a crucial role in ensuring the safety, efficacy, and quality of blood, blood components, and plasma for fractionation. This guideline is established to safeguard both donors and recipients, minimize risks of infections, and ensure that the collection, processing, and distribution of blood meet required standards. Regulations ensure that blood establishments comply with Good Practices in areas such as donor selection, testing, processing, and distribution. In Ethiopia, blood and blood components regulations are primarily governed by the Ethiopian Food and Drug Authority (EFDA), and are aligned with international standards.

The Food and Medicine Administration Proclamation No. 1112/2019 Article 30 provides the legal framework for blood and blood products in Ethiopia. It establishes rules for donation, collection, testing, processing, storage, and distribution, emphasizing that blood should be donated voluntarily and without financial gain. The Proclamation ensures that blood products meet high safety and quality standards before being used.

The guideline provides comprehensive requirements for the collection, testing, and processing of blood and blood products. It emphasizes on following principles:

- **Quality Assurance Systems**: A robust quality management system that ensures consistent and reliable processes.
- **Donor Selection and Screening**: Rigorous donor screening is required to prevent the transmission of infectious diseases, including HIV, Hepatitis B, and C. Donors are evaluated based on health status and medical history to reduce risks.
- **Testing and Quality Control**: All donated blood is tested for transfusion transmittable infection (TTI) and components (e.g., red blood cells, platelets, plasma) are verified for potency, purity, and sterility. Quality control mechanisms ensure that blood products meet safety standards.
- **Good Manufacturing Practices (GMP)**: GMP ensures that blood establishments maintain consistent, validated processes and that all equipment is properly maintained and calibrated. Personnel must be adequately trained to ensure safe handling of blood products.

- **Traceability and Record Keeping**: Blood products must be fully traceable from donor to recipient, with records maintained at every stage. This ensures prompt recalls in case of safety and quality concerns.
- **Ethical and Humanitarian Considerations**: Blood donation must be voluntary, with no financial compensation, as emphasized by both national and international regulations. Proclamation 1112/2019 mandates that blood products used for life-saving purposes or research must not financially benefit the donor or recipient.

Blood establishments need to be routinely inspected by appropriate regulatory bodies to ensure compliance with laws, standards and guidelines. These inspections verify that establishments meet required standards for donor safety, blood quality, and adherence to GMP, thereby maintaining public trust and ensuring safe healthcare services. Blood regulation is also integral to the safe and effective use of blood and blood products in healthcare systems. By establishing clear laws and standards for the collection, testing, processing, and distribution of blood, these regulations help to prevent the transmission of infectious diseases and ensure that blood transfusions contribute to saving lives without introducing additional risks.

Finally, I extend my heartfelt gratitude to all those who directly participated in the development process, including the staff of EFDA, the Technical Working Group members, development partners, workshop participants, and those who contributed indirectly. Your tireless efforts made this guideline possible. I strongly encourage all concerned stakeholders to make the best use of the guideline and provide feedback to the EFDA for its improvement and future revisions.

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Ethiopian Food and Drug Authority

Acronyms and Abbreviations

CAPA	Corrective Action and Preventive Action
CPP	Critical process parameters
CQA	Critical quality attributes (CQAs)
DQ	Design Qualification
EFDA	Ethiopian Food and Drug Authority
GMP	Good Manufacturing Practice
IQ	Installation qualification
ISBT	International Society for Blood Transfusion
NRA	National Regulatory Authorities
NAT	Nucleic acid amplification techniques
OQ	Operation Qualification
PQ	Performance Qualification
PQR	Product Quality Review
QRM	Quality Risk Management
SOP	Standard Operating Procedure
URP	User Requirements Specification
VMP	Validation Master Plan
WHO	World Health Organization
ASL	Approved Supplier List

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1. Introduction

Blood and blood component transfusion is a critical intervention in modern healthcare, often essential for saving lives, particularly in vulnerable populations such as children, women of childbearing age, and patients with severe medical conditions. Ensuring the safety and quality of blood and blood components is fundamental to reducing risks associated with transfusion, such as the transmission of infections (e.g., HIV, Hepatitis B, syphilis, and Hepatitis C) and adverse reactions.

Plasma derived medicinal products are manufactured from human blood plasma. It can be obtained from whole blood donations (recovered plasma) or by apheresis procedures (source plasma). Plasma is the source of a wide range of medicinal therapeutic products that are used for the treatment and prevention of a variety of life threatening injuries and diseases often associated with protein deficiency states.

In Ethiopia, the Food and Medicine Administration Proclamation No. 1112/2019 Article 30, Sub-Articles 2 establishes strict regulatory requirements for blood donation, collection, processing, and distribution. These provisions emphasize principles of humanity and prohibit financial gain in the use of blood products while mandating that all blood components meet safety and quality standards before use. In addition, Sub Article 3 of this article states Blood and blood components for transfusion or further manufacturing or processing may not be put into use unless its safety and quality are in compliance with applicable regulatory requirements.

Globally, the World Health Organization (WHO) underscores the necessity of a robust quality assurance system in blood collection and processing, ensuring adherence to Good Practice Principles. These principles spanning quality management, personnel qualification, documentation, premises, equipment, and material management are vital for the consistent production of safe, quality and efficacy of blood and blood components, and the protection of donors and recipients.

This guideline outlines requirements from donor selection, blood collection, processing and quality control of blood, blood components and plasma derivatives through the distribution of final blood products. It focuses on quality management systems that ensure the safety, quality

and efficacy of blood and blood components. By adhering to local and international standards, these guidelines aim to enhance the safety and reliability of blood transfusion as a life-saving medical intervention.

2. Terms and Definitions

The definitions given below apply to the terms used in these guidelines.

Good manufacturing practice (GMP):-All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations

Apheresis:-The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/or filtration into its components, and returning those not required to the donor.

Blood collection:-The procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution, under conditions designed to minimize microbial contamination, cellular damage and/or coagulation activation of the resulting blood donation.

Blood component:-A constituent of blood (erythrocytes, leukocytes, platelets, cryoprecipitate and plasma) that can be prepared by various separation methods and under such conditions that it can be used either directly for therapeutic purposes or for further processing/manufacturing.

Blood establishment:-Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components (including plasma for fractionation),when intended for transfusion or further industrial manufacturing.

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

Calibration:-The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

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

Computerized system: -system includes the input of data, electronic processing and the output of information to be used either for reporting or for automatic control.

Contract acceptor: -An establishment or institution that performs particular work or services under a contract for a different institution.

Contract giver:-An establishment or institution that is subcontracting particular work or services to a different institution and sets up a contract defining the duties and responsibilities of each side.

Donor:-A person in defined good health conditions who voluntarily donates blood or blood components, including plasma for fractionation.

Distribution:-The act of delivery of blood and blood components to other blood establishments, hospital blood banks or manufacturers of blood- and plasma-derived medicinal products. It does not include the issuing of blood or blood components for transfusion.

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

HBsAg, hepatitis B surface antigen:-The antigen on the periphery of the hepatitis B virus.

HBV, Hepatitis B virus:-An enveloped double-stranded DNA virus that is the causative agent of hepatitis B.

HCV, hepatitis C virus:-An enveloped single-stranded, RNA virus that is the causative agent of hepatitis C.

HIV, human immunodeficiency virus: An enveloped, single-stranded RNA virus that is the causative agent of the acquired immunodeficiency syndrome (AIDS).

HTLV 1 and 2, human T-cell lymphotropic virus, types 1 and 2

Enveloped, single stranded RNA viruses those are typically cell-associated.

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

Mobile site:-A unit or site used for the collection of blood and/or blood components, operating temporarily or at movable locations off-site from a permanent collection site, under the responsibility of a blood establishment.

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

Near-miss event:-An incident that, if not detected in a timely manner, would have affected the safety of the recipients or donors.

Plasma for fractionation:-The liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration and/or centrifugation of anti-coagulated blood in an apheresis procedure, intended for further manufacturing.

Production:-All operations involved in the preparation of blood components, from collection through processing to completion as a finished product (blood component).

Qualification:-A set of actions used to provide documented evidence that any piece of equipment, critical material or reagent used to produce the final product and that might affect the quality or safety of a product works reliably as intended or specified and leads to the expected results.

Quality:-The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs, and the consistent and reliable performance of services or products in conformity with specified requirements. Implied needs include safety and quality attributes of products intended both for therapeutic use and as starting materials for further manufacturing.

Quality assurance:-A part of quality management focused on providing confidence that quality requirements will be met.

Quality management:-The coordinated activities that direct and control an organization with regard to quality.

Quality management system:-A management system that directs and controls an organization with respect to quality and that ensures that steps, processes, procedures and policies related to quality activities are being followed.

Quality risk management (QRM):-A systematic process for the assessment, control, communication and review of risks to the quality of the product across the product's life cycle.

Quarantine:-The status of starting or packaging materials, intermediate, bulk or finished products that are isolated physically or by other means while a decision is awaited on their release for use or rejection.

Regular donor:-A person who routinely donates blood, blood components or plasma in the same blood establishment in accordance with the minimum time intervals.

Repeat donor:-A person who has donated before in the same establishment but not within the period of time considered as regular donation.

Repeatedly reactive:-A donation is considered to be repeatedly reactive if it is found reactive in a screening test, is retested in duplicate using the same assay, and at least one of the repeat tests is also reactive.

Validation:-Actions for proving that any operational procedure, process, activity or system leads to the expected results. Validation work is normally performed in advance according to a defined and approved protocol that describes tests and acceptance criteria.

Approved Supplier: - Is any vendor that has proven to meet a company's specific requirements. Approved supplier status usually means that the supplier is eligible for inclusion on the official list of potential sources for goods or services, referred to as an ASL

3. Scope

This guideline applies to collection, processing, testing, packaging, storage and distribution of blood and blood components including plasma for fractionation intended either for transfusion or as a starting material for further processing/manufacture of plasma derived medicinal products (PDMP).

4. Objectives

The objective of this guideline is to ensure donor safety, guarantee the quality, safety, and efficacy of blood and blood products, promote the application of good practice and ensure compliance with regulatory requirements.

5. General Principles

The general principles outlined in Ethiopian pharmaceutical Good Manufacturing Practice (GMP) guideline are applicable to the implementation of this guideline.

6. Manufacturing requirements

6.1. Personnel and Organization

6.1.1. Sufficient personnel with the necessary qualifications and experience should be available to carry out activities related to the collection, testing, processing, storage, and distribution of blood and blood components. Personnel should be trained and assessed for competence in performing their tasks.

6.1.2. Only personnel who have read, understood, and demonstrated competence in all relevant standard operating procedures (SOPs) and competent should be involved in manufacturing and distribution processes, including collection, quality control and quality assurance.

6.1.3. All personnel should receive initial and ongoing training appropriate to their specific tasks. Training programs shall be in place to ensure that personnel have necessary knowledge of Good Practice. Training records shall be maintained.

6.1.4. Training should be provided to all personnel, whose duties require access to preparation areas or laboratories, including technical, maintenance and supportive staff.

6.1.5. Written policies and procedures should be established to describe the approach to training. These should include records of training sessions, their content, and assessments of their effectiveness.

6.1.6. The contents of training programs should be periodically assessed and the competence of personnel should be regularly evaluated.

6.1.7. The training programs should be reassessed for any critical change in environment, equipment or processes. Training needs should be identified, planned, delivered and documented appropriately to ensure the continued validation of systems and equipment.

6.1.8. Only individuals authorized through defined procedures and properly documented may participate in the collection, processing, testing, and distribution processes, including quality control and quality assurance.

6.2. Organization and Responsibilities

6.2.1. The organization should have an adequate number of personnel with the necessary qualifications and experience. Management holds ultimate responsibility for determining and providing adequate and appropriate resources (human, financial, material, facilities, and equipment) to implement and maintain the quality management system. Management must also continually improve the system's suitability and effectiveness through active participation in management reviews. Responsibilities assigned to any one individual should not be so extensive as to compromise quality.

6.2.2. There should be an organizational chart that clearly depicts the relationships among key personnel within the managerial hierarchy. Key personnel must include the following functions, along with their designated substitutes:

- **Responsible Person**
- **Processing Manager**: Responsible for overseeing all processing **activities.**
- **Quality Control Manager**: Responsible for all quality control activities.
- **Quality Assurance Manager**: Responsible for ensuring the implementation of appropriate quality systems and protocols for the safe and secure release of materials, reagents, and blood components.

6.2.3. A physician should have the responsibility and authority for all medical matters, including consultative and support services related to donor and/or patient care and safety.

6.2.4. All personnel should have up-to-date job descriptions clearly outlining their tasks and responsibilities. The responsibilities for processing management and quality assurance should be assigned to different individuals who operate independently.

6.2.5. Personnel in responsible positions should have adequate authority to fulfill their responsibilities. Duties may be delegated to designated deputies with satisfactory qualifications.

6.2.6. There should be no gaps or unexplained overlaps in the responsibilities of personnel involved in the application of Good Practices.

6.2.7. Individual responsibilities should be clearly defined, and personnel should be assessed to confirm their understanding. Records of this assessment should be maintained, and personnel signature lists should be available.

6.3. Hygiene and Sanitation

6.3.1. There should be written safety and hygiene instructions in place, adapted to the activities to be performed.

6.3.2. Visitors or untrained personnel should not preferably enter the processing and laboratory areas. If entry is unavoidable, they should be provided with prior information, particularly regarding personal hygiene and required protective clothing. They should also be closely supervised during their presence.

6.3.3. The organization is responsible for providing instructions on hygiene and health conditions relevant to quality of blood components. Staff should report any health problems that could impact the quality of blood components. All staff members working in processing and laboratory areas must strictly follow these procedures. Instructions should include when and how to wash hands.

6.3.4. Measures should be taken to ensure that individuals with infectious diseases or open lesions on exposed body surfaces do not engage in the preparation of blood components. Medical examinations should be conducted on a regular basis to ensure fitness for work and personal health. Procedures should be in place to ensure personnel report health conditions that may affect the quality of blood or blood components.

6.3.5. A written procedure outlining the requirements for wearing protective equipment in different areas. The requirements should align with the activities being carried out.

6.3.6. Activities such as eating, drinking, chewing, smoking, and storing food, drinks, smoking materials, or personal medication should be prohibited in processing, testing, and storage areas. Any unhygienic practices within preparation areas or any other areas where blood or blood components could be adversely affected should also be strictly forbidden.

6.4. Premises

6.4.1. General Principle

6.4.1.1. Premises, including mobile sites, should be located, constructed, adapted, and maintained to suit the activities being carried out. The layout should enable the work flow in a logical sequence, minimizing the risk of errors and allowing for effective cleaning and maintenance to reduce contamination risks.

6.4.1.2. Lighting, temperature, humidity, and ventilation should be appropriate to ensure that they do not adversely affect blood components during processing and storage or compromise the accurate functioning of equipment.

6.4.1.3. Premises should be designed and equipped to prevent the entry of insects or other animals.

6.4.1.4. Steps should be taken to prevent unauthorized access. Processing, laboratory testing, storage, and quality control areas should not be used as thoroughfares by personnel who are not assigned to those areas.

6.4.1.5. Facilities should allow for easy maintenance and cleaning. Open drains should be avoided.

6.4.1.6. Temperature and humidity requirements for preparation areas should be defined based on the operations conducted and the external environment.

6.4.1.7. Preparation areas should be equipped with adequate lighting, particularly in zones where visual checks are conducted.

6.4.1.8. Component sampling may be performed within the processing area, provided that it does not pose a risk to other components.

6.4.2. Blood donor area

6.4.2.1. There should be a designated area for conducting confidential personal interviews and assessments of individuals to evaluate their eligibility to donate. This area must be separate from all processing areas.

6.4.2.2. The premises should meet health and safety requirements for both staff, including mobile blood collection teams, and donors.

6.4.3. Blood collection area

6.4.3.1. Blood collection should be conducted in a dedicated area designed for the safe withdrawal of blood from donors. This area should be appropriately equipped for the

initial treatment of donors who experience adverse reactions or injuries related to blood donation. It should be organized to ensure the safety of both donors and personnel while minimizing the risk of errors during the collection procedure.

6.4.3.2. Before premises are approved for mobile donor sessions, their suitability should be assessed based on the following criteria:

- Adequate size to allow proper operation and ensure donor privacy.
- Safety for both staff and donors.
- Availability of ventilation, electrical supply, lighting, and ancillary facilities.
- Reliable communication, interim blood storage, and transport provisions.

6.4.3.3. The blood collection area and procedures should ensure that blood is collected in a safe and clean environment to minimize the risk of errors and microbial contamination.

6.4.3.4. Attention should be given to the arrangement of donor beds and the handling of blood bags, samples, and labels to maintain efficiency and safety.

6.4.4. **Mobile collection Site**

6.4.4.1. Premises for mobile collection sites should be adequate in design for the conduct of operations and should allow for the logical flow of staff, donors and products in order to minimize the risk of errors.

6.4.4.2. The blood collection at mobile sites should be planned thoroughly. Ancillary areas (rest and refreshment rooms) should be separated from donation or storage areas, but observation of donors during post-donation refreshment should still be ensured.

6.4.4.3. Before premises are accepted for mobile donor sessions their suitability should be assessed against the following criteria:

- Sufficient size to allow proper operation and ensure donor privacy;
- Safety for staff and donors;
- Ventilation, electrical supply, lighting, hand-washing facilities, reliable communication, sufficient space for blood storage and transport, and suitable temperature conditions.

6.4.5. **Blood testing and processing areas**

6.4.5.1. There should be a dedicated laboratory area for testing, separate from the blood donor and blood-component processing areas. Access should be restricted to authorized personnel and used solely for its intended purpose.

6.4.5.2. Laboratories should be designed to suit operations to be performed, providing sufficient space to avoid mix-ups and cross-contamination. Adequate storage should be available for samples and records.

6.4.5.3. Special provisions may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, and extreme temperatures

6.4.6. **Storage area**

6.4.6.1. Storage areas should allow for the secure and segregated storage of different categories of blood and, blood components, and materials, including quarantined and released materials. Access should be restricted to authorized personnel.

6.4.6.2. Contingency plans should be in place to address equipment or power failures in the main storage facility.

6.4.6.3. Storage facilities should be clean and free from litter, dust, and pests (e.g.., insects, and rodents).

6.4.6.4. Storage areas should have sufficient capacity to allow orderly storage of various categories of materials and blood components, including packaging materials, intermediate and finished components, and quarantined, released, rejected, returned, or recalled items.

6.4.6.5. Storage areas should be designed or adapted to maintain predefined storage conditions. Special storage requirements (e.g., temperature, humidity) should be provided, monitored, and alarmed for deviations from defined limits.

6.4.6.6. Receiving and dispatch areas should protect materials from weather conditions. Reception areas should allow containers of incoming materials to be cleaned before storage and should be separate from storage areas.

6.4.6.7. If quarantine status is ensured by separate storage areas, these should be clearly marked and access limited to authorized personnel. Any alternative system (e.g., computerized) must provide equivalent security.

6.4.6.8. Segregated storage areas should be allocated for rejected, discarded, recalled, or returned materials, or blood and blood components.

6.4.6.9. Printed packaging materials, such as donation identifiers and irradiation labels, must be stored securely.

6.4.7. **Ancillary areas**

6.4.7.1. Staff rest and refreshment areas should be separate from other rooms.

6.4.7.2. Facilities for changing clothes, washing, and toilets should be accessible and adequate for the number of users. Toilets should not open directly into preparation areas.

6.4.7.3. Maintenance workshops should be separate from preparation areas. If tools and parts are stored in processing or laboratory areas, they must be kept in designated spaces.

6.4.8. **Waste Disposal Area**

6.4.8.1. A designated area should be established for waste storage with access restrictions. Waste should be segregated by type before disposal.

6.4.8.2. An area should be designated for the safe disposal of waste materials, disposable items used during collection, processing, and testing, as well as rejected blood and blood components.

6.4.8.3. Special procedures should be established for the disposal of potentially contaminated waste. .

6.4.8.4. There should be decontaminated area that should be for cleaning of equipment and work surfaces

6.4.8.5. Wastes should be segregated based on type of waste

6.5.Equipment and Materials

6.5.1. **General requirements (Equipment)**

6.5.1.1. All equipment should be identified, qualified, calibrated, and maintained to suit its intended purpose. Operating instructions should be available and appropriate records should be available.

6.5.1.2. Equipment should be selected to minimize hazards to donors, personnel, and blood components.

6.5.1.3. Validated processes should use qualified equipment. Qualification results, regular maintenance, and calibration should be documented.

6.5.1.4. Critical equipment must undergo regular maintenance to detect and prevent errors, ensuring optimal functionality.

6.5.1.5. Maintenance intervals and actions should be determined for each equipment item.

6.5.1.6. New or repaired equipment should meet qualification requirements before use.

6.5.1.7. Modifications or additions to validated systems and equipment should follow a change control procedure.

6.5.1.8. The impact of changes on quality and safety be assessed to determine revalidation needs.

6.5.1.9. Standard operating procedures for the use, maintenance, cleaning, and sanitation of equipment should be available.

6.5.1.10. Procedures should detail actions for equipment malfunctions or failures.

6.5.1.11. Equipment and material inventory records should facilitate traceability for recalls.

6.5.1.12. Repair and maintenance should not pose hazards to donors, staff, or quality of blood and blood components.

6.5.1.13. Equipment should be designed or chosen for thorough cleaning and decontamination.

6.5.1.14. Washing solutions and equipment should not contribute to contamination.

6.5.1.15. Equipment installation should prevent errors and contamination risks.

6.5.1.16. Contact materials should not react, add to, or absorb blood components.

6.5.1.17. Balances and measuring equipment of suitable range and precision should be available, calibrated, and checked at defined intervals.

6.5.1.18. Adequate calibration records, including pre-adjustment values, should be maintained.

6.5.1.19. Calibration reports should be reviewed, accepted, and signed. Failed calibrations shall be investigated.

6.5.1.20. Defective equipment should be labeled and removed from preparation areas. when possible.

6.5.2. **General Principle (Materials)**

6.5.2.1. Only reagents and materials from approved suppliers that meet the documented requirements and specifications should be used. Critical materials should be released by qualified personnel.

6.5.2.2. Manufacturers of sterile materials (e.g. blood bag systems, anticoagulant solutions) should provide a certificate of release for each batch.

6.5.2.3. The blood establishment should define acceptance criteria for such certificates in writing, and these criteria should include at a minimum, the material name, manufacturer, compliance with relevant requirements (e.g. pharmacopoeias or medical device regulations) and confirmation that the materials are sterile and pyrogen-free. Status of materials (quarantined, released, rejected) should be clearly indicated.

6.5.2.4. Materials and reagents should be stored under the conditions specified by the manufacturer and in an orderly manner that allows for batch/lot segregation and stock rotation.

6.5.2.5. Storage and use of materials should follow the 'first-expiring first-out' principle (i.e. the material that with the earliest expiration date should be used first).

6.6. Data Processing Systems

6.6.1. If computerized systems are used for data processing all associated software, hardware and back-up procedures should undergo regular checks to ensure reliability.

6.6.2. All software and hardware shall be validated prior to use and maintained in a validated state throughout their operational lifespan. Necessary measures shall be implemented to protect the hardware and software from unauthorized change and use.

6.6.3. A back-up procedure should be established to prevent loss of or damage to data during expected or unexpected down-times or system failures.

6.6.4. Systems should be properly maintained at all times, with documented maintenance plans for hardware and software. This strategy should include audits of quality assurance systems.

6.6.5. Changes to computerized systems should be validated, and any applicable documentation should be revised. Relevant personnel should be trained before changes are introduced into routine use.

6.6.6. Computerized systems should be maintained in a validated state, including user testing to demonstrate that the system performs all specified functions correctly both at initial installation and after any system modifications.

6.6.7. A hierarchy of user access should be established to regulate the ability to enter, amend, read or print data.

6.6.8. All necessary measures should be taken to ensure data protection. These measures include safeguards against unauthorized additions, deletions or modifications of data and transfer of data as well as mechanisms to resolve data discrepancies, and prevent unauthorized disclosure of such information.

6.6.9. Computer systems designed to control decisions related to inventories and blood component releases should prevent the release of unacceptable blood or blood components. Mechanisms should also prevent collection or release of components from deferred donors.

6.6.10. When data is transferred to another data format or system, validation should confirm that the value and meaning of data remain unchanged.

6.6.11. Computerized systems exchanging data electronically with other systems should include built-in checks to ensure correct and secure data entry and processing.

6.6.12. For manually entered critical data, accuracy should be verified either by a second operator or validated electronic means. Risk management should address the criticality and potential consequences of erroneous or incorrectly entered data..

6.6.13. Data should be secured against damage by physical and electronic means. Stored data should be checked periodically for accessibility, readability, and accuracy. Access to data should be ensured throughout the retention period.

6.6.14. Physical and/or logical controls should be in place to restrict access to computerized systems to authorized persons. Suitable methods of preventing unauthorized entry to the system include the use of keys, pass cards, personal codes with passwords, biometrics, and restricted access to computer systems or data storage areas.

6.6.15. Electronic records may be signed electronically. Electronic signatures should:

- have the same impact as hand written signatures of the blood establishment;
- be permanently linked to their respective record;
- include the time and date of application.

6.6.16. Electronic data must be archived and periodically checked for accessibility, readability, and integrity. Changes to the system (e.g., hardware or software updates) should ensure data retrievability and be tested.

6.7.Qualification and Validation

6.7.1. General Principles

6.7.1.1.Facilities and equipment should be qualified before implementation. Systems, processes, and tests should be validated.

6.7.1.2.Qualification and validation principles apply to all aspects of blood component collection, processing, preparation, testing, packing, storage, distribution, and issuance

6.7.1.3.Good Practice requires blood establishments to control the critical aspects of their operations throughout the lifecycle of blood components and associated processes. Planned changes to facilities, equipment, utilities, or processes should be formally documented, and their impact validated.

6.7.1.4.A quality risk management approach should assess, control, communicate, and review quality risks across the lifecycle of blood and blood components.

6.7.1.5.Qualification components and validation activities should be guided by documented risk assessments of facilities, equipment, utilities, and processes.

6.7.2. Organizing and Planning for Validation

6.7.2.1.Validation activities should consider the lifecycle of facilities, equipment, utilities, processes, and products.

6.7.2.2.Only trained personnel should perform validation activities following approved procedures, with appropriate quality oversight.

6.7.2.3.Key elements of the site validation program should be defined in a Validation Master Plan (VMP) or equivalent document.

6.7.3. Validation Master Plan (VMP)

6.7.3.1.Validation protocols should specify how qualification and validation will be performed, defining critical systems, attributes, parameters, and acceptance criteria.

6.7.3.2.All qualification and validation documents must be reviewed and approved by authorized personnel.

6.7.3.3.Deviations from approved protocols must be documented and scientifically justified.

6.7.4. Qualification

6.7.4.1.Qualification activities should address all stages, from user requirements specification (URS) development to the end-of-life of equipment, facilities, or systems.

6.7.4.2. Design Qualification (DQ): Demonstrates and documents that the design complies with Good Practice and is suitable for its intended purpose.

6.7.4.3. Installation Qualification (IQ): Ensures proper installation and compliance with engineering specifications.

6.7.4.4. Operational Qualification (OQ): Verifies system performance under operational conditions.

6.7.4.5. Performance Qualification (PQ): Confirms system performance under actual production conditions.

6.7.4.6. Equipment, facilities and systems should be evaluated periodically to confirm that they remain in a state of control.

6.7.4.7. The requalification interval should be justified and define the criteria for evaluation Potential changes over time should be assessed and addressed.

6.7.5. Process Validation

General Principles

6.7.5.1. The principles outlined in this section apply to the preparation, distribution, and issuance of blood components. They include initial validation of new processes, validation of modified processes, site transfers, and maintaining of the validated state (ongoing process verification). A robust product development process is essential to enable successful process validation.

6.7.5.2. Processes should ensure consistent blood component quality and undergo prospective validation wherever possible. Retrospective validation is no longer an acceptable approach.

6.7.5.3. Validation of new blood components should include all intended processes and manufacturing sites. A scientific and risk-based approach may be justified based on process knowledge and statistical process control from the development stage.

6.7.5.4. Validation activities should be representative of all intended process or product settings.

6.7.5.5. For validation of transferred processes (from one site to another or within the same site), the number of blood components required for validation may be reduced based on existing process knowledge and prior validation data are available.

6.7.5.6. The same approach may be used for different blood bag sizes or volumes, if justified.

6.7.5.7. The validation should demonstrate that critical quality attributes (CQAs) and critical process parameters (CPPs) are consistently met. The basis for identifying critical or non-critical attributes should be documented, incorporating risk assessment results. Critical processes include donor selection, suitability determination, component preparation, infectious disease testing, ABO RhD typing, antibody screening (if applicable), labelling, storage, and distribution.

6.7.5.8. Facilities, systems, and equipment should be qualified before use, and analytical methods should be validated. Regular evaluations should confirm that these remain in control.

6.7.5.9. Process knowledge from development studies or equivalent sources should be accessible to the blood establishment and be the basis of validation activities.

6.7.5.10. Suppliers of critical materials should be qualified before process validation begins. If this is not feasible, a justification based on quality risk management should be documented.

6.7.5.11. Blood components prepared during process validation may be released for clinical use only under predefined conditions, meeting good practice requirements, validation acceptance criteria, and continuous process verification criteria (if applicable).

6.7.6. **Concurrent Validation**

6.7.6.1. In exceptional circumstances, concurrent validation may be acceptable if it provides significant patient benefits and ensures systematic control of each unit for regulatory conformity. The validation protocol should be documented in the VMP and approved by authorized personnel.

6.7.6.2. Concurrent validation requires sufficient data to confirm that all units meet defined acceptance criteria. Results and conclusions should be formally documented and reviewed before clinical release.

6.7.7. **Prospective Validation**

6.7.7.1. Prospective validation involves producing blood components under proposed new conditions. The number of runs, samples, and observations should be based on quality risk management and sufficient to establish process variability and trends.

6.7.7.2. Preparation of blood components during validation should reflect normal production volumes.

6.7.7.3. A process validation protocol should define CPPs, CQAs, and acceptance criteria, supported by development data or documented process knowledge.

6.7.7.4. Process validation protocols should include:

- Brief process description.
- Roles and responsibilities.
- Summary of CQAs and CPPs.
- Equipment/facilities with calibration status.
- Analytical methods and validation.
- In-process controls and acceptance criteria.
- Sampling plan and rationale.
- Methods for recording and evaluating results.
- Conditions for unit release and certification.

6.7.8. **Ongoing Process Verification and Maintenance**

6.7.8.1. Ongoing process verification and maintenance of the validated state should provide evidence, supported by statistical tools that the process remains controlled during routine preparation.

6.7.8.2. Critical processes should be monitored and periodically evaluated to ensure validity. If no significant changes occur, documented evidence of compliance may replace revalidation.

6.7.8.3. Blood establishments should use statistical process control to monitor and evaluate trends in blood and blood component quality control tests.

6.7.8.4. The extent and frequency of ongoing verification should be periodically reviewed and adjusted based on process performance and understanding.

6.7.8.5. Verification activities must follow an approved protocol, with results documented in a report. Statistical tools should assess process variability and ensure a state of control.

6.7.8.6. Maintaining the validated state requires:

- Calibration and monitoring.
- Preventive maintenance.
- Staff training and competency.
- Supplier requalification.
- Periodic review and performance monitoring.

- System retirement, if applicable.

6.7.8.7. Validation status and incremental changes should be documented in the Product Quality Review (PQR). Additional actions, such as enhanced sampling, should be assessed based on process performance.

6.7.8.8. Operational change control, document control, and quality control procedures are essential for maintaining validation.

7. preparation of blood components

7.1. General principles

7.1.1. The st**a**rting materials for blood component preparation are blood donations collected from suitable donors. The quality of these components is assured by control of all stages of production, including identification, labeling, storage conditions, packaging and dispatch.

7.1.2. The collection process itself is already crucial for the quality of blood components. Measures such as a reliable arm-cleaning and disinfection procedure, the use of closed and sterile collection systems, and appropriate microbiological controls should be implemented.

7.1.3. Time limits should be defined for the processing of blood components. There are detailed recommendations concerning the preparation and quality assurance of blood components

7.1.4. Quality monitoring of blood components should be consistent with the current specifications for in-process and finished components.

7.1.5. The processing of blood components must be carried out using appropriate and validated procedures, including measures to avoid the risk of contamination and microbial growth in the prepared blood components.

7.1.6. The use of closed systems is strongly recommended for all steps in component processing. Open systems may exceptionally be necessary due to local constraints and should be undertaken in an environment specifically designed to minimize the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures.

7.1.7. Sterile connecting devices must be used in accordance with a validated procedure. When validated, connections made using sterile connecting devices are regarded as closed system processing. The resulting weld must be checked for satisfactory alignment and its integrity must be confirmed.

7.1.8. Validation of freezing processes should consider worst-case scenarios that take into account minimum and maximum loads and positions in the freezer.

7.1.9. The standard operating procedures should describe the specifications for materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

7.1.10. The standard operating procedures for component preparation should be followed at all times using the validated methods.

7.1.11. Any deviations from these established procedures and processes may result in products not meeting specifications and such products should be considered as non-conforming products and must not be released for distribution.

7.2.**Preparation/Process record**

7.2.1. Each unit is considered to be a unique batch, but preparation records should provide sufficient information to build the history and traceability of a prepared component. Usually this information is captured in the computerized systems of the blood establishment. In general, the blood establishment should have access to the following processing records for each unit:

- The name and unique identifier of the component;
- The dates and times of commencement of significant intermediate stages and of completion of processing:
- The identification (initials) of the operator(s) who performed each critical step of the process (including the process controls) and, where appropriate, the name of any person who verified such steps;
- The batch number of any relevant consumables and/or analytical control number of each consumable;

- A record of the in-process controls and identity of the person(s) carrying them out, as well as the results obtained;
- The results of testing undertaken on the donation and/or the component (excluding quality monitoring);
- Notes on any deviation, including details of the procedures with signed authorization;
- Information on the processing of non-standard components with signed authorization.

7.2.2. Each activity that may affect the quality of blood and blood components should be documented and recorded at the time it takes place.

7.2.3. Critical activities should be double-checked, either by a second person or electronically.

7.2.4. There should be documentation to ensure that work is performed in a standardized manner according to standard operating procedures and that all critical steps in the process are traceable, especially those that have the potential to affect the quality of the product.

7.2.5. The documentation should allow all steps and all data to be confirmed by independent review.

7.2.6. All documentation should indicate the person performing the action, the date of the action and the equipment used in the action, where applicable.

7.2.7. Records should be legible, accurate, reliable and a true representation of the results and entries. The legibility of records is of great importance. Handwritten entry of data should be clear.

7.2.8. Corrections to any records should be made in a manner that permits the reading and review of the previous entry, the correction, the date of correction and the person responsible for the correction.

7.2.9. Critical manufacturing and laboratory testing records should be reviewed frequently for completeness, legibility and, when appropriate, accuracy by the manager or other designated person.

7.3.**Validation of test methods**

7.3.1. All analytical test methods used in qualification or validation exercises should be validated with an appropriate detection and quantification limit, where necessary.

7.3.2. Where microbial testing of blood components is carried out, the method should be validated to confirm that the product or residues, e.g. antibiotics, do not interfere with the analysis and influence the recovery of microorganisms.

7.3.3. Where microbial testing of surfaces is carried out, validation should be performed on the test method to confirm that sanitizing agents do not influence the recovery of microorganisms

7.3.4. In addition to the validation of the test system by the manufacturer, an onsite validation of the test system in the laboratory is required prior to its use in routine testing. This validation should demonstrate, that

- the performance specifications of the system established by the kit manufacturer are met by the laboratory;
- Laboratory personnel are thoroughly instructed, trained and competent to operate the test system.

7.3.5. Prior to first-time use, critical equipment, including related computer systems, should be thoroughly qualified. Installation qualification, operational qualification and performance qualification should be carried out and fully documented. This work may involve suppliers and/or third parties.

7.3.6. It is strongly recommended that any performance qualification should be performed by the end-user (and not by a third party) since this is intended to demonstrate that the process works as designed. In addition, a demonstration showing that the test system performance specifications are constantly met in routine donor testing is required. The means by which this may be achieved are:

- inclusion of internal and external quality control materials with every test series;
- previously tested samples collected for use as an internal panel for periodical in-process quality control;
- monitoring measurements of controls (for instance, graphically by using a Levi-Jennings diagram);
- statistically establishing the standard deviation of control measurements;

- implementation of deviation rules (warning range, control range, Westgard rules) to govern corrective actions;
- monitoring trends in control measurements on external standard or reference material;
- successful participation in external quality assessment schemes (proficiency testing) by all qualified members of staff.

7.4.**Preparation instructions**

7.4.1. Approved, written instructions for preparation should exist for each type of component that is produced. These should include:

- A process flow for each stage in the preparation of the component, including where it is undertaken and any critical equipment used;
- Methods (or reference to the methods) to be used for starting up and maintaining critical equipment (e.g. cleaning, assembly, calibration);
- The requirement to check that the equipment and work station are clear of previous blood components, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
- Detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, and critical process parameters such as time and temperature);
- The instructions for any in-process controls with their limits; o Requirements for storage of the components and any critical materials and consumables;
- Any special precautions to be observed

7.4.2. Blood components may be prepared by using a centrifugation step with subsequent separation, by using another validated preparation method, or by apheresis technology during collection.

7.4.3. Although the use of closed systems is strongly recommended for all steps in component processing, open systems may exceptionally be necessary due to local constraints in an environment specifically designed to minimize the risk of bacterial contamination.

7.4.4. When open systems are used, careful attention should be given to the use of aseptic procedures.

7.4.5. The critical equipment used for the preparation of blood components should be traceable to the corresponding manufacturing records.

7.5.**Processing and validation**

7.5.1. The quality of the components is assured by control of all stages of manufacture, including donor identification, collection, separation of components, labeling, storage, packaging and dispatch.

7.5.2. The standard operating procedures should describe the specifications for materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

7.5.3. The standard operating procedures for component preparation should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and such products should be considered as non-conforming products and must not be released for distribution.

7.6.**Handling of Starting material**

7.6.1. The starting materials for preparation of blood components are blood donations collected from suitable donors. Conditions of storage or transport, and the time prior to processing, are contributing factors to the quality of the product.

7.6.2. Delays in preparation or unsuitable conditions of storage or transport may adversely affect the quality of the final product. Blood and blood components should be placed in controlled and validated conditions as soon as possible after Venipuncture.

7.6.3. Donations and samples should be transported to the processing site in accordance with procedures that ensure both a constant approved temperature and secure confinement. This is especially important when blood is transported from distant collection sites.

7.6.4. Product transport or shipping at appropriate temperatures and temperature monitoring are important to ensure optimal quality. One way to ensure the temperature of products is to use packaging methods validated to keep the blood within the required temperature limits.

7.6.5. There should be validation data to demonstrate that the method of transport maintains the blood within the specified temperature range throughout the period of transportation. Alternatively, portable temperature loggers may be used to record the temperature during the transportation of blood to the processing site. Where the blood is not transported by the processing establishment itself, the responsibilities of the transport company should be clearly defined and periodic audits should be conducted to ensure compliance.

7.7.**Methods of production**

Blood components may be prepared by using a centrifugation step with subsequent separation, by using another validated preparation method, or by apheresis technology during collection.

7.7.1. **Centrifugation**

The centrifugation parameters (revolutions per minute, temperature, time, acceleration, and deceleration) are important for the composition and characteristics of the specific components. These critical parameters should be defined on the basis of validation data that demonstrate a process that consistently produces quality products. For each run, the centrifugation records should identify the operator and confirm that the centrifugation process was performed according to specifications.

7.7.2. **Separation**

After centrifugation, the bag system should be carefully removed from the centrifuge and placed into a plasma expressor or blood separation system. The different layers of the components (red cells, platelets, plasma) should be transferred to the satellite bags within the closed systems, in a manner designed to optimize the harvest of the intended component while minimizing the carry-over of other component fractions. Alternatively, blood components can be separated during collection by apheresis technology.

7.7.3. **Freezing**

Freezing is an important processing step that has an impact on quality, especially of plasma. The rate at which freezing proceeds and the core temperature are both considered to be important parameters. Rapid plasma freezing prevents or reduces the loss of critical constituents such as Factor VIII in frozen plasma that is either recovered or obtained by apheresis.

A system should be in place for ensuring that plasma is frozen to the specified core temperature within the time limit, keeping in mind that the freezing speed will be influenced by the type of

plasma container, the freezing equipment and the loading pattern, as well as by the volume of plasma.

The validation of the freezing process should consider worst-case scenarios that take into account both minimum and maximum loads and positions in the freezer.

Recording the temperature of plasma units and the freezing time during a freezing process allows one to evaluate the freezing capacity of the equipment and ensures a standardized freezing process. Validation studies should be available and should demonstrate that the temperature of a frozen pack reaches the proposed storage temperature following the specifications. As indicated above, the aim is to achieve rapid freezing and thereafter to minimize temperature changes to the frozen plasma. Freezing of cellular components such as red cells or cellular therapy should follow a well-defined, validated procedure that ensures the recovery and viability of the intended cellular product during thawing and final preparation steps.

7.7.4. **Leukocyte reduction**

Whole blood may be filtered for leukocyte reduction prior to centrifugation. Filtration of whole blood reduces the level of platelet and leukocyte contamination in plasma and red-cell concentrate preparations. Alternatively, components (e.g. red cells, platelets) may be filtered after separation.

The introduction of any leukocyte reduction process either by filtration or special centrifugation technique requires careful validation that takes national requirements into account. In addition to filter properties, the final result of filtration is influenced by several process parameters (e.g. flow rate, temperature, priming and rinsing) and by the properties of the component to be filtered (e.g. storage history of the component, number of leukocytes and number of platelets).

The filtration procedure should incorporate manufacturing specifications such as height and temperature. The method should be fully validated under the conditions to be used. Careful attention should be given to the rate of filtration. Rapid or slow filtration may indicate process failures.

Special centrifugation or filtration techniques of leukocyte reduction are used in several apheresis systems. When a standardized procedure is established on the apheresis system, the method should be validated under the conditions to be used.

An appropriate method should be used for leukocyte counting after leukocyte reduction. The method should be validated to ensure linearity, accuracy and reproducibility.

7.7.5. **Irradiation**

Regular dose-mapping of irradiation equipment should be performed. The exposure time should be set to ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose. The common recommended minimum dose is 25 Gy (2500 cGy).

Care should be taken regarding the increased potassium leakage from red cells after their irradiation, either by limiting the shelf-life of the red-cell concentrate or by further manufacturing steps such as washing.

For the radioactive source, allowance should be made at least annually for source decay. A second independent timing device should be used to monitor exposure time.

Radiation indicators should be used as aids to differentiating between irradiated and non-irradiated blood and blood components.

A defined procedure should ensure the separation of components that have not been irradiated from those that have been irradiated, and should ensure they have distinctive labeling.

8. Blood and blood components

- Blood components may be obtained using the methods described above. However, the sequence and the combination of the methods used in the production of blood components may vary from one product to another.
- The collection process itself is already crucial for the quality of blood components. Measures such as a reliable arm-cleaning and disinfection procedure, the use of closed and sterile collection systems, and appropriate microbiological controls should be implemented.
- Time limits should be defined for the processing of blood components.

8.1. Whole blood

8.1.1. Whole blood for transfusion is blood that is taken from a donor who has been assessed and found suitable as meeting the blood establishment and standards for Ethiopia blood transfusion services.

8.1.2. Whole blood is collected in sterile and pyrogen free containers with a suitable anticoagulant. It may be used without further processing. In some cases, whole blood for transfusion may also be used after leukocyte reduction.

8.1.3. The temperature of whole blood stored for transfusion should remain controlled between 2° and 6°C

8.1.4. The storage time depends on the anticoagulant/preservative solution used. Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the following critical parameters should be checked during the quality control assays:

- volume
- haemoglobin or haematocrit
- haemolysis at the end of storage.
- Visual changes including leakage

8.1.5. The primary use of whole blood is as a source material for the preparation of blood components.

8.1.6. Transportation and further manufacturing processes should be developed to maximize the number of components that may be produced from a whole blood donation.

8.1.7. After collection, whole blood should be kept at a controlled temperature appropriate to the intended component manufacture and should be delivered to the production site as quickly as possible.

8.1.8. If whole blood is collected away from the production site, the validated transport systems should ensure that correct temperatures are maintained throughout the process and that the product is delivered within 24 hours.

8.1.9. The period between collection and further processing depends on the product but should not exceed 24 hours.

8.1.10. The whole blood may also be filtrated to reduce leukocyte content prior to further processing.

8.1.11. Components should be manufactured by a method validated as meeting the predefined product specifications.

8.2.Red-cell concentrate

8.2.1. Red-cell concentrates are obtained from whole blood by centrifugation and removal of plasma with or without buffy coat, depending on the centrifugation parameters.

8.2.2. After subsequent addition of an appropriate nutrient solution, the red cells should be stored at 2–6°C as soon as possible. Alternatively, red-cell concentrates may be obtained using an apheresis system and likewise stored at 2–6°C.

8.2.3. Red-cell units that exceed 10°C after reaching the storage temperature should be discarded. The red-cell concentrate may be used for transfusion without further processing.

8.2.4. To obtain leukocyte-reduced red-cell concentrates, either whole blood filtration can be applied prior to separation or there can be a post-separation filtration of the red-cell concentrate.

8.2.5. A fully validated procedure should be established to determine optimum conditions for use of a leukocyte reduction method.

8.2.6. Red-cell concentrates are stored under the same storage conditions as whole blood. The storage time depends on the anticoagulant/preservative solution used. Further methods of preparation, such as irradiation or washing, are applied to obtain specific red-cell products, depending on the clinical indication. Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent.

8.2.7. Parameters measured depend on the type of red-cell concentrate product obtained. At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- haemoglobin or haematocrit;
- haemolysis at the end of storage;
- Residual leukocytes, if leukocyte reduction is performed.
- Visual changes including leakage

8.3.Platelet concentrate

8.3.1. Platelet concentrates are derived from whole blood or are obtained by apheresis.

8.3.2. After collection, whole blood can be kept for up to 24 hours in conditions that are consistent with the preparation of plasma and validated to maintain a temperature between 20°C and 24°C, following international or NRA recommendations.

8.3.3. The whole blood unit is centrifuged so that an optimal number of platelets remain in plasma (platelet-rich plasma (PRP)). Platelet concentrates are then obtained by hard-spin centrifugation of PRP and are then resuspend. However, if whole blood is centrifuged so that the blood platelets are primarily sedimented to the buffy coat layer, the buffy coat is separated and further processed to obtain a platelet concentrate. Either a single buffy coat or a pool of buffy coats is diluted with plasma or an appropriate nutrient solution, and platelets are concentrated by further centrifugation.

8.3.4. The platelet content per unit depends on the method of preparation. Similarly, the residual leukocyte content will vary according to the centrifugation parameters.

8.3.5. Platelet concentrates (both from whole blood and apheresis) should be stored in conditions that guarantee that viability and haemostatic activities are optimally preserved. The storage temperature should be 20–24°C.

8.3.6. Continuous gentle agitation of platelets during storage should be sufficient to guarantee the availability of oxygen to the platelets (but should be as gentle as possible).

8.3.7. A storage time should be defined in accordance with national regulations set by the NRA; it should normally not exceed five days in the absence of additional measures. In special circumstances, volume-reduced, split, washed or irradiated platelet concentrates can be prepared for specific treatments.

8.3.8. Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- platelet content;
- residual leukocytes, if leukocyte reduction is performed;
- pH, measured at the end of the recommended shelf-life;
- RBC contamination;
- Sterility test
- Visual changes including leakage

9. Plasma for transfusion and plasma for fractionation

9.1.Plasma for transfusion

9.1.1. Plasma for transfusion is prepared either from whole blood or from plasma collected by apheresis, and is frozen within a defined period of time to a temperature that should adequately maintain the labile coagulation factors in a functional state, consistent with the intended use of the plasma. In particular, Factor VIII content is critical both as a quality indicator and to assure the efficacy of cryoprecipitate.

9.1.2. If plasma is separated from a unit of whole blood that is refrigerated to 4°C, centrifugation should preferably take place within eight hours of collection.

9.1.3. If the whole blood unit is rapidly cooled to 20–24°C and maintained at this constant temperature after collection, separation can take place within 18–20 hours because such conditions have been found to protect Factor VIII.

9.1.4. If plasma is collected by apheresis, the freezing process should begin as soon as possible and ideally not later than six hours after the completion of the apheresis process. In compliance with EFDA requirements, consideration should be given to the time frames of processing with respect to the anticoagulant and device used and the product to be manufactured.

9.1.5. The freezing process should be validated and should take place in a system that will allow complete freezing to a predefined core temperature in a predefined time.

9.1.6. Product stability is dependent on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (more than one year) the optimal storage temperature is minus 25°C or colder.

9.1.7. Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the following critical parameters should be checked during the quality control assays:

- Volume;
- Factor VIII activity (especially if plasma is used to treat Factor VIII deficiencies);
- Residual leukocytes, if leukocyte reduction is performed;
- Fibrinogen
- Visual changes including leakage

9.1.8. Virus inactivation and/or quarantine of plasma for transfusion are applied in some countries. Further complementary guidance with respect to virus inactivation is available in WHO guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products, and in other publications.

9.1.9. Plasma for transfusion is suitable as source material for the production of fractionated products, and particularly Factor VIII concentrates or other labile factors. Plasma prepared in other ways should meet the specifications of the plasma fractionators and the requirements of the pharmacopoeia and NRA.

9.2.Plasma for fractionation

9.2.1. **Methods used to obtain plasma for fractionation**

9.2.1.1. Technically, human plasma for fractionation may be obtained by separation of plasma from whole blood, or by apheresis.

9.2.1.2. **Recovered plasma** Recovered plasma is plasma recovered by centrifugal separation from the cells and cellular debris of whole blood, following conditions described later

9.2.2. **Apheresis plasma (source plasma)**

Apheresis Plasma obtained by a procedure in which anticoagulated blood is removed from the donor, the plasma is separated from the formed elements, and at minimum the red cells are returned to the donor. The separation of cellular elements and plasma may be achieved either by centrifugation or filtration. The equipment used for the collection of plasma by automated methods is designed for such use. The manufacturers of the equipment provide operating manuals that include instructions for installation validation, routine preventive maintenance procedures, periodic performance checks (e.g., weight scale checks), alert mechanisms (e.g., haemoglobin detector) and troubleshooting. Annual preventive maintenance should be performed by a qualified person. Additionally, the manufacturers of the equipment usually provide support for the installation and train on-site technicians to maintain the equipment. Apheresis collection potentially increases the availability of plasma for fractionation, enabling higher donation frequency and larger volume per donation, independently from the collection of whole blood, and is the preferred approach for the regular collection of plasma from hyperimmune donors who have high antibody titres against specific disorders. In principle, the method of preparation should remove cells and cell debris as completely as possible and should be designed to prevent the introduction of micro-organisms. No antibacterial or antifungal agent

is added to the plasma. The residual blood cell content of the plasma, in the absence of dedicated leucoreduction filtration, may vary with the collection method

9.3.Characteristics of plasma for fractionation

9.3.1. Plasma frozen within 24 hours of collection

Subject to appropriate handling (storage and transport), plasma frozen, at -20°C or -30°C, within 24 hours of blood collection or apheresis will normally be suitable for optimal recovery of both labile factors (factor VIII and other coagulation factors and inhibitors) and stable plasma proteins (usually albumin and immunoglobulins) Table below sets out the main characteristics of plasma prepared either from whole blood (recovered plasma) or by apheresis. Both sources of plasma have been found by experience to be appropriate for the manufacture of the whole range of plasma products. That said, the method of collection and preparation has some impact on the characteristics and/or yield of the proteins fractionated from the plasma. Apheresis plasma collected from donors undergoing frequent plasmapheresis contains lower levels of IgG than plasma units produced by moderate serial plasmapheresis or from whole blood. The content of various coagulation factors is usually higher in apheresis plasma compared to recovered plasma due to a combination of reasons that include rapid separation of blood cells and plasma, differing ratios of anticoagulant added, and the possibility of freezing the plasma soon after completion of collection.

Table 4: Characteristics of plasma for fractionation used in the manufacture of labile plasma products

Characteristic	Recovered plasma	Apheresis plasma
Volume, ml	100-260[24]	450-880[25]
Protein content, g/l (each donation)	≥50 [15] (but typically greater than in apheresis plasma)	≥50
Factor VIII, iu/ml (average)	≥0.7 [28] (but typically less than in apheresis plasma)	≥0.7
Anticoagulant concentration	Variable, according to donation size (volume of anticoagulant is fixed for a given pack type; the acceptable blood volume range should be specified)	Constant (metered into donation)
Acceptable donation frequency	Determined nationally, usually subject to a maximum of one donation every 2 months	Determined nationally

Preservation of factor VIII and other labile factors depends on the collection procedure and on the subsequent handling of the blood and plasma. With good practice, an average of 0.7 IU/ml

factor VIII can usually be achieved both with apheresis and recovered plasma. Units of plasma for fractionation with a lower activity may still be suitable for use in the production of coagulation factor concentrates, although the final product yield may be reduced. The implementation of good manufacturing practices in the preparation of plasma for fractionation should ensure that plasma bio burden is controlled, labile proteins are conserved as far as possible, and minimal proteolytic activity is generated.

9.3.2. **Plasma frozen after 24 hours of collection**

Plasma may be available that does not fulfill the above-defined criteria but still has value as a source of some plasma proteins. This would include: Plasma separated from whole blood and frozen more than 24h but usually less than 72hrs after collection Plasma, separated from whole blood stored at 4°C, and frozen within 72 hrs, of separation but within the assigned shelf-life of the blood) Plasma frozen within 24 hours but stored under conditions that preclude its use for the manufacture of coagulation factors. Provided the circumstances of manufacture and storage of such plasma does not result in increased bio burden, the plasma may be considered suitable for the manufacture of stable plasma proteins, but not coagulation factors.

Provided the circumstances of manufacture and storage of such plasma does not result in increased bio burden, the plasma may be considered suitable for the manufacture of stable plasma proteins, but not coagulation factors.

Plasma which is not frozen with 72 hrs of collection or separation from whole blood should not be used for fractionation.

9.3.3. **Plasma not meeting the requirement for fractionation**

Plasma obtained by therapeutic plasma exchange does not meet the criteria for fractionation to plasma products. Indeed, plasma from individuals subjected to therapeutic plasma exchange for the treatment of a disease state may present an enhanced risk of transmitting blood-borne diseases (due to infectious risks associated to plasma) and a high risk of irregular antibodies, and should not be offered for fractionation. In addition, such plasma cannot be classified as being obtained from a voluntary donor. Plasma from autologous blood donations is excluded from use as plasma for fractionation and may have higher prevalence of viral markers.

9.3.4. **Hyper-immune (antibody-specific) plasma**

The following are the three approaches for the preparation of plasma for the manufacture of specific immunoglobulins (antibody-specific immunoglobulins):

- Individuals selected from the normal population by screening of plasmas units for antibody titres. (Screening may be random, or may be informed by knowledge of history of recovery from an infectious disease – for example varicella).
- Individuals with a high titre of a specific antibody resulting from prophylactic immunization. Volunteers recruited to a panel for a targeted immunization programme. The clinical and ethical requirements for such a programme are considered in clinically relevant antibody specific immunoglobulins include anti-D (anti-Rho), and anti HAV, anti-HBs, anti-tetanus, anti-varicella/herpes zoster and anti-rabies immunoglobulins. For the most part, hyper immune globulins are prepared for intramuscular administration, but products for intravenous use are also available.

Note: Further complementary guidance with respect to the production of plasma for fractionation is available in;

i. Guidance on increasing supplies of plasma-derived medicinal products in low- and middle income countries through fractionation of domestic plasma: Geneva: World Health Organization;2021
ii. the WHO Recommendations for the production, control and regulation of human plasma for fractionation

9.3.5. **Cryoprecipitate and Cryo-poor plasma**

Cryoprecipitate is the cryoglobulin fraction of plasma and contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in plasma. Cryoprecipitate is obtained from fresh frozen plasma that is prepared in a way that protects Factor VIII stability.

Plasma is allowed to thaw either overnight at 2–6°C or by a rapid-thaw technique. Following thawing, the supernatant cryo-poor plasma and the cryoprecipitate are separated by hard-spin centrifugation.

The cryo-poor plasma is then expressed into a transfer bag. The two components are refrozen to the appropriate core temperature.

Stability during storage depends on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (for two years or longer) the optimal storage temperature is minus 25°C or colder.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the following critical parameters should be checked during the quality control assays of cryoprecipitate:

- volume;
- factor VIII activity;
- fibrinogen;
- von Willebrand factor activity (if applicable)
- Visual changes including leakage

Virus inactivation and/or quarantine can be applied. Under certain circumstances the use of small pool preparations of cryoprecipitate (by pooling single-donor cryoprecipitate units) may be desired.

10. Change control

10.1. A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality, traceability and availability of blood or blood components or that might have an impact on the safety of blood, blood components, donors or recipients.

10.2. The change control system should guarantee a formal approval of a change before it is implemented. Furthermore it should ensure that the impact of the proposed change is assessed and that all necessary measures such as qualification and validation, training of personnel, adoption of working instructions, revision of contracts, definition of maintenance tasks, information for third parties and authorities are defined and completed at the time the change is put into force.

10.3. The need for additional testing and validation should be determined on a scientific basis. A risk analysis may be appropriate as part of the QRM.

10.4. After the implementation of a change, a post-implementation evaluation should be carried out in order to determine whether the introduction of the change has been successful and effective. The introduction of new equipment, processes and methods should be treated as a change.

11. Packaging and Labeling

11.1. Packaging

11.1.1. Packaging should be of a sturdy construction so as to resist damage and to maintain acceptable storage conditions for the blood and blood components during transportation.

11.1.2. A standard operating procedure on packaging should be available stating how the contents should be packaged, the materials to be used, and the amount of any cooling elements and their storage conditions before use.

11.1.3. There should be appropriately authorized and dated specifications for starting and packaging materials, as well as finished blood and blood components. Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

- A description of the materials, including:
- The designated name and the internal code reference;
- The approved suppliers and, if reasonable, the original producer of the material;
- A sample of printed materials; Directions for sampling and testing;
- Qualitative and quantitative requirements with acceptance limits;
- Storage conditions and precautions;
- The maximum period of storage before re-examination.

11.1.4. Specifications for in-process and finished components should be available.

11.2. Labeling

11.2.1. The collected blood and intermediate and finished blood components should be labeled with relevant information of their identity and release status. The type of label to be used as well as the labeling methodology should be established in written procedures.

11.2.2. The label for a finished blood component should comply with the requirements by the ISBT 128 labeling system or contain at least the following information

- The unique donation number; there should be traceability through the use of this number to the donor and all records of the manufacturing steps to the final product;
- the product name;

- the required storage conditions;
- the expiry date and, where appropriate, time;
- the date of collection of the donation(s) from which the blood component was prepared and/or the production date and time (where appropriate);
- the ABO and RhD blood group (where appropriate); and
- the name or other identification of the component preparation site.
- Tested and negative for TTI (HIV 1& 2, HBsAg, HCVAb, SyphilisAb)

11.2.3. The blood establishment responsible for the preparation of the blood component should supply the person(s) using the blood component with information on its use, composition, and special conditions which do not appear on the label.

11.2.4. For autologous blood components, the label should additionally contain the name and unique identification of the patient as well as the statement “Autologous donation”.

11.2.5. The name of the blood component should be clearly stated on the label and should indicate any further processing such as leukocyte reduction or irradiation. In addition, the anticoagulant and/or any nutrient or preservative solution should be mentioned on the label.

11.2.6. Any final blood product should have its expiry date on its label. It should be also kept in mind that certain processing steps, such as irradiation, have an influence on the expiry date so that relabeling becomes necessary. The definition of an expiry date should be validated and based on scientific data according to the processing steps applied and the storage conditions, or should be the subject of stability studies.

12. Release of Blood and Blood Component

12.1. Each blood establishment should be able to demonstrate that a blood component has been evaluated and approved for release by an authorized person, preferably assisted by validated computerized systems.

12.2. The release criteria and specifications of blood components should be defined, validated, documented and approved.

12.3. There should be a standard operating procedure that details the actions and criteria that determine whether the blood or blood component can be released.

12.4. Before release, blood and blood components should be kept administratively and physically segregated from released blood and blood components.

12.5. In the absence of a validated computerized system for status control, the label of a unit of blood or blood component should indicate the release status.

12.6. The decision to release the blood components should be made by the responsible person of the establishment; it should be clearly documented and traceability should be ensured.

12.7. Electronic release of products should be fully validated.

12.8. The documented manufacturing processes should be followed at all times using validated methods and procedures.

12.9. Any deviations from these established procedures and processes may result in products not meeting specifications, in which case they should be considered non-conforming products and must not be released for distribution.

12.10. A review of the donor health record, collection and phlebotomy records, consent forms, records of production and test results should be performed and accepted (and should be recorded) prior to the release of the components.

12.11. The release of products should be arranged in such a way that each component from the donation has been evaluated to ensure conformance with product specifications such as platelet content in apheresis units, volume in plasma products or appearance for red blood cells prior to release for distribution.

12.12. The decision to release the component should not be made on the basis of a review of the collection processes alone. There should be a system of administrative and physical quarantine for blood and blood components to ensure that components cannot be released until all mandatory requirements have been met.

12.13. In the absence of a computerized system for product status control: the label of a blood component should identify the product status and should clearly distinguish released products from non-released (quarantined) ones;

12.14. records should demonstrate that, before a component is released, all current donor health records, collection and phlebotomy records, consent forms and test results have been verified and accepted by an authorized person.

12.15. If blood or blood components have been prepared from a donor who has donated on previous occasions, a comparison with previous records, specifically the ABO/RhD and infectious disease marker test results, should be made before final product release to ensure that current records accurately reflect the donor history.

12.16. Where release is subject to computer derived information, the following points should be checked:

12.17. Computer systems should be validated so that they are fully secure against the possibility of blood and blood components which do not fulfill all test or donor selection criteria being released.

12.18. The manual entry of critical data, such as laboratory test results, should require independent verification by a second authorized person.

12.19. There should be a hierarchy of permitted access to enter, amend, read or print data. Methods of preventing unauthorized entry should be in place, such as personal identity codes or passwords which are changed on a regular basis.

12.20. Computer systems should prevent the release of all blood or blood components considered not acceptable for release. It should be possible to prevent the release of any future donation from a donor.

12.21. In the event that the final product fails release due to noncompliance with the specified requirements and therefore due to potential impact on recipient safety, all other implicated components should be identified and appropriate action should be taken.

12.22. A check should be made to ensure that (if relevant) other components from the same donation(s) and components prepared from previous donations given by the donor(s) are identified. There should be an immediate updating of the donor record(s) to ensure that the donor(s) cannot make any further donation, if appropriate.

12.23. When computerized systems are in use, aspects such as access and privileges, data integrity, audit trail, and back-up systems should be considered during risk assessment, with appropriate controls identified and implemented.

12.24. Products that cannot be released should be destroyed and the record of destruction should be retained.

13. Storage, Distribution, Transportation and Return

13.1. Storage

13.1.1. The receipt, handling and storage of material for blood and blood components should be described on Standard operating procedures.

13.1.2. There should be a system in place to maintain and control storage conditions.

13.1.3. Storage areas for blood components to be dispatched should be located near an entrance or exit to facilitate dispatch.

13.1.4. Only authorized persons should have access to storage areas. Procedures for storage should be validated to ensure the quality of blood and blood components during the entire storage period, and to exclude mix-ups of blood components.

13.1.5. Storage conditions should be controlled, monitored and checked within the defined period of time.

13.1.6. The personnel authorized should be trained to be aware of the correct storage temperature ranges and alarm settings. Temperature records should be available to demonstrate that the blood components are stored at the required temperature throughout the storage area.

13.1.7. A temperature monitoring and recording system that is independent from the temperature regulating system should be in place.

13.1.8. Appropriate alarms should be present, with upper and lower limits and regularly checked and records should be maintained. Depending on the method of measuring the temperature, a delay of the alarm may be acceptable in order to avoid an alarm being triggered by opening a door or taking out a product, but any such delay should be reasonably justified.

13.1.9. If the temperature sensor is placed in a reference solution, no delay of the alarm should be accepted. Appropriate actions on alarms should be defined, and a person should be authorized to decide on the use or rejection of affected products.

13.1.10. Temperature excursions may occur and each event should be evaluated using the deviation management system

13.1.11. An alternative storage area with appropriate temperature is recommended for recovery in case of temperature control failure of the available system.

13.1.12. Areas for storage should be secured against the entry of unauthorized persons and should be used only for the intended purpose. Storage areas should provide effective segregation of quarantined and released materials or components.

13.1.13. There should be a separate and controlled area for rejected components and materials. If a temporary mechanical or electrical failure affects control of storage temperatures, an

examination of the records should be made to evaluate the impact on quality of the plasma or blood components.

13.1.14. For the main blood components, the common storage temperatures should be for:

a) **Red cell concentrate** Storage in 2°C -6°C, Expiry Date
   - With CPD/ACD CP2D- 21 days
   - With CPDA-1 -35 Days
   - With additive solution SAGM -42 Days

b) **Whole Blood-**Storage in 2°C -6°C Expiry date With CPD/ACD/ CP2D- 21 days, With CPDA-1 -35 Days

c) **Platelet** Storage 20°C -24°C with continuous gentle agitation Expiry date 24 hours to 5 days depending on collection system or manufacturing of blood bag.

d) **Fresh Frozen Plasma** Storage -18 °C or colder**,** Expiry date 12 Months

e) **Cryoprecipitate** Storage -18 °C or colder**,** Expiry date 12 Months

13.1.15. Besides the temperature, continuous agitation is very important (for platelets). Based on the manufacturer's instructions, the moving velocity should be set in a way that obtains an optimal quality of the product. The moving velocity should be part of the qualification of the equipment.

13.1.16. During the whole blood collection and manufacturing process it should be ensured that blood or blood components are never placed in direct sunlight or near a heating source.

13.1.17. All storage equipment should be subject to qualification, cleaning and preventive maintenance. Thermometers or temperature sensors should be calibrated every year.

13.1.18. There should be a system to ensure stock rotation involving regular and frequent checks that the system is operating correctly. Blood and blood components beyond their expiry date or shelf-life should be separated from usable stock

13.1.19. Provisions should be in place in the event of equipment failure or power failure in the main storage facility.

13.1.20. Appropriate alarms should be present and checked regularly. All checks should be recorded. Appropriate actions on alarms should be defined

13.2. **Distribution**

13.2.1. Blood components should be visually inspected before distribution. There should be a record that identifies the person distributing and the customer receiving the components. Dispatch of blood components should be made by authorized personnel.

13.2.2. At the time of dispatch, there should be a procedure in place to ensure that all blood components being issued have been formally released for use.

13.2.3. SOP for packaging should be available and state how the contents should be packaged, the materials to be used, and the amount of any cooling elements and their storage conditions before use.

13.2.4. Distribution should take place in a safe and controlled way in order to assure product quality during transport.

13.3. **Transportation**

13.3.1. Blood components should be transported in accordance with the defined conditions.

13.3.2. All transportation and storage actions, including receipt and distribution, should be defined by written procedures and specifications.

13.3.3. Storage conditions should be controlled, monitored and checked during transportation of blood and blood components.

13.3.4. All transportation and intermediate storage actions, including receipt and distribution, should be defined by written SOPs and specifications.

13.3.5. The transportation containers should be of sturdy construction in order to resist damage and should be validated to maintain acceptable storage conditions for the blood and blood components (e.g. by using appropriate cooling elements or insulation during transport).

13.3.6. The transportation and storage conditions for blood components, the packaging format and the responsibilities of the persons involved should be in accordance with agreed procedures between the sites in question.

13.3.7. Appropriate records of inventory and distribution should be kept between blood establishments and health facilities. These records should show the date of supply, unique component identifier and name of the blood component, the quantity received or supplied and the name and address of the supplier and receiver.

13.3.8. Packaging should maintain the integrity and storage temperature of blood and blood components during distribution and transportation.

13.3.9. Any transportation mechanism for blood and blood components should be validated

13.3.10. Verification methods for storage conditions during transportation should be in place. It is recognized that verification of transportation may be challenging due to the variable factors involved. However the different modes of transportation should be clearly defined. Seasonal and other variations should also be considered during verification of transportation of blood components.

13.4. **Returns**

13.4.1. Blood components should not be returned to stock for subsequent distribution, unless:

- the procedure for return of a blood component is regulated by contract agreement
- the storage conditions have consistently been met for each return of blood component
- the integrity of the container has been maintained (i.e. unopened)
- Sufficient materials available for compatibility testing.

13.4.2. Return of blood and blood components into inventories for subsequent reissue should be allowed only if all requirements and procedures relating to quality management system as laid down by the blood establishments.

13.4.3. In case of medical urgency, components may be returned and subsequently distributed using a defined procedure. The records should indicate that the blood component has been inspected and found to be acceptable before re-issue.

14. Contract manufacturing/ Outsourcing activities

14.1. **General principle**

14.1.1. Tasks that are performed externally should be defined in a specific written contract. Outsourced activities that may impact on the quality, safety or efficacy of the blood components should be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a blood component or work of unsatisfactory quality.

14.1.2. There should be a written contract covering these activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

14.1.3. Outsourced arrangements made for collection, processing and testing, storage and distribution, including any proposed changes, should be made in accordance with a written contract, with reference to the specification for the blood or blood component(s) concerned.

14.1.4. The responsibilities of each party should be documented to ensure that good practice principles are maintained.

14.1.5. The contract giver is the establishment or institution that subcontracts particular work or services to a different institution and is responsible for setting up a contract defining the duties and responsibilities of each side.

14.1.6. The contract acceptor is the establishment or institution that performs particular work or services under a contract for a different institution.

14.1.7. In blood establishments, all tasks that have an influence on the quality of collected blood and the manufacture of blood components such as;

- Component processing, testing or information technology support which is performed externally by another party should be subject to a specific written contract.
- The contract should ensure that the contract acceptor meets GMP requirements in all disciplines relevant to the contract giver's activities.

14.1.8. The contract giver is ultimately responsible for ensuring that processes are in place to assure the control of outsourced activities and the quality of purchased materials. These processes should incorporate QRM and should include:

- assessing (prior to outsourcing operations or selecting material suppliers) the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g. audits, material evaluations, qualification)
- Defining the responsibilities and communication processes for quality related activities of the parties concerned.
- Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and identification and implementation of any improvements needed.

- Monitoring of incoming ingredients and materials to ensure that they are from approved sources using the agreed supply chain.

14.1.9. Details should be specified in a technical quality agreement or contract. The contract or agreement should:

- clearly establish the duties of each party
- state the responsibilities of each party
- mention any technical arrangements
- define the flow of information, especially regarding deviations and changes
- define the handling and archiving of documents, samples and other relevant materials and information
- state that any of the duties given to the contract acceptor should not be passed to a third party without evaluation and approval of the contract giver
- permit the contract giver and competent authorities to visit and inspect the facilities of the contract acceptor

14.1.10. The contract giver should provide the contract acceptor with all necessary information to enable compliance with expectations regarding services or goods. This assures that the work or service is performed in compliance with existing regulations. The overall responsibility for the work and duties carried out externally lies always with the contracting company.

14.1.11. The contract should be agreed and signed by quality assurance representatives from both parties and should be kept up to date.

14.2. **The Contract giver**

14.2.1. The contract giver is responsible for assessing the competence of the contract acceptor to successfully carry out the work being outsourced and for ensuring, by means of the contract, that the principles and guidelines of good practice are followed.

14.2.2. The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly and in accordance with the specification and any other legal requirements.

14.2.3. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the materials, samples or the contracted operations that

might pose a hazard to the premises, equipment, personnel, other materials or other blood components of the contract acceptor.

14.2.4. The contract giver should ensure that all blood and blood components, analytical results and materials delivered by the contract acceptor comply with their specifications and that they have been released under a quality system approved by the Responsible Person or other authorized person.

14.3. **The contract acceptor**

14.3.1. The contract acceptor should have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work requested by the contract giver.

14.3.2. The contract acceptor should ensure that all products, materials or test results delivered by the contract giver are suitable for their intended purpose.

14.3.3. The contract acceptor should not pass to a third party any of the work entrusted under the contract without the contract giver's prior evaluation and approval of the arrangements.

14.3.4. Arrangements made between the contract acceptor and any third party should ensure that the relevant blood collection, processing and testing information is made available in the same way as between the original contract giver and contract acceptor.

14.3.5. The contract acceptor should refrain from any activity that may adversely affect the quality of the blood and blood components prepared and/or analyzed for the contract giver.

14.4. **The Contract**

14.4.1. A contract should be drawn up between the contract giver and the contract acceptor that specifies their respective responsibilities relating to the contracted operations.

14.4.2. All arrangements for blood collection, processing and testing should be in compliance with the requirements of good practice and regulatory requirements and agreed by both parties.

14.4.3. The contract should specify the procedure, including the necessary requirements to be provided by the contract acceptor by which the responsible Person or other authorized person releasing the blood and blood components for sale or supply can ensure that

each component has been prepared and/or distributed in compliance with the requirements of good practice and regulatory requirements.

14.4.4. The contract should clearly describe who is responsible for purchasing materials, testing and releasing materials, undertaking blood collection, and processing and testing (including in-process controls).

14.4.5. In the case of subcontracted analyses, the contract should state the arrangements for the collection of samples and the contract acceptor should understand that they may be subject to inspections by the competent authorities. Preparation and distribution records, including reference samples if relevant, should be kept by, or be available to, the contract giver.

14.4.6. Any records relevant to assessment of the quality of the blood or a blood component in the event of complaints or a suspected defect should be accessible and specified in the defect/recall procedures of the contract giver.

14.4.7. The contract should permit the contract giver to audit the facilities of the contract acceptor. Where contracts are defined at a level higher than the blood establishment (e.g. Regional or national level) a system should be in place that permits an appropriate evaluation of the suitability (in terms of quality and safety) and the availability of the materials and equipment concerned.

15. Documentation

15.1. General principles

15.1.1. Good documentation constitutes an essential part of the quality system and is key to operating in compliance with good practice requirements. It ensures that work performed is standardized, and that there is a traceability of all steps in the preparation of blood and blood components; i.e., donor selection, collection, processing, testing, storage, dispatch, quality control and quality assurance. Various types of documents and media used should be defined fully in the quality management system of the organization.

15.1.2. Documentation may exist in various forms such as paper-based, electronic or photographic. The main objective of the system of documentation used should be to establish, control, monitor and record all activities that directly or indirectly impact on all aspects of the quality and safety of blood and blood components as well as any

derived medicinal products. The Quality Management System should include sufficient instructional detail to facilitate common understanding of the requirements, in addition to providing for adequate recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

15.1.3. There are two primary types of documentation used to manage and record good practice compliance namely instructions (directions, requirements) and records/reports. Appropriate practices should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded or documented on media from which data may be rendered in a readable form for humans.

15.2. **Required good practice documentation (by type)**

15.2.1. Documents setting out specifications, procedures and records covering each activity undertaken by a blood establishment should be in place and kept up-to-date.

15.3. Instructions (directions or requirements)

15.3.1. Specifications should describe in detail the requirements to which the blood and blood components or materials used or obtained during preparation and distribution. They serve as a basis for quality evaluation.

15.3.2. Testing instructions should detail all the starting materials, equipment and computerized systems (if any) to be used and specify all sampling and testing instructions. If applied, in-process controls should be specified, together with their acceptance criteria.

15.3.3. Procedures (i.e. Standard Operating Procedures or SOPs) should give directions for performing certain operations.

15.3.4. Protocols should give instructions for performing certain discreet operations, and may record the outcome (e.g., qualification and validation protocols).

15.3.5. Technical agreements should be agreed between contract givers and acceptors for outsourced activities.

15.4. **Records/Reports**

15.4.1. Records should provide evidence of various actions taken to demonstrate compliance with instructions, e.g., activities, events, investigations and, in the case of processed blood and blood components, a history of each unit (including its distribution). Records include the raw data that is used to generate other records. For electronic records, regulated users should define which data are to be used as raw data. All data on which quality decisions are based should be defined as 'raw data'.

15.4.2. Certificates of analysis should provide a summary of testing results on samples of reagents, products or materials, together with the evaluation for compliance with a stated specification.

15.4.3. Reports are critical components of a Quality Management System, serving as formal records of specific activities, projects, or investigations, together with results, conclusions and recommendations

15.5. **Generation and control of documentation**

15.5.1. All types of documents should be defined and adhered to. Requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented and validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms (i.e., some elements are electronic and others are paper- based). Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems.

15.5.2. A document control system, defined in a written procedure, must be established for the review, revision history and archiving of documents, including SOPs. Appropriate controls for electronic documents, such as templates, forms and master documents, should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

15.5.3. Documents should be designed, prepared, reviewed, and distributed with care. Reproduction of working documents from master documents should not allow errors to be introduced through the reproduction process.

15.5.4. Documents containing instructions should be approved, signed and dated by appropriate and authorized persons. This may also be undertaken electronically.

Documents should have unambiguous content and be uniquely identifiable. The effective date should be defined.

15.5.5. Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

15.5.6. Documents within the Quality Management System should be regularly reviewed and kept up-to-date.

15.5.7. All significant changes to documents must be acted upon promptly, and must be reviewed, dated and signed by a person authorized to undertake this task.

15.5.8. Instructional documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

15.6. **Good Documentation Practice**

15.6.1. Records should be legible and may be handwritten, transferred to another medium such as microfilm, or documented in a computerized system.

15.6.2. Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the donation, collection, processing, testing and distribution of blood and blood components are traceable.

15.6.3. The record system must ensure continuous documentation of the procedures performed from the blood donor to the recipient. That is, each significant step must be recorded in a manner that permits a component or procedure to be traced, in either direction, from the first step to final use/disposal.

15.6.4. Any alteration made to the entry on a document should be signed and dated; the alteration should permit reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.7. **Standard Operating Procedures**

15.7.1. All activities and critical procedures should be specified in written instructions (SOPs) including but not limited:

- Donor eligibility
- Collection and preparation of blood components
- Laboratory testing, quality control testing

- Labeling requirements
- Storage, release, dispatch, transportation
- Processes of recall of the blood products components
- Testing materials purchase and receipt
- Sampling, which include the methods and equipment to be used, the amounts to be taken
- Quality assurance procedures (complaint investigations, deviation management)
- Recall of non-conforming products
- Change control and document control
- Validation and qualification of processes, equipment and systems;
- Equipment calibration;
- Maintenance, cleaning and sanitation;
- Environmental monitoring;
- Investigations of deviations and non-conformances;
- Audits of compliance with internal quality/Good Practice;
- Summaries of records, where appropriate (e.g., review of the quality of blood components);

15.7.2. All activities should be carried out according to the standard operating procedures. The standard operating procedures and the processes should be regularly reviewed and updated as necessary in order to improve the quality of products and services delivered. The document review process should itself be documented.

15.8. **Retention of documents**

15.8.1. It should be clearly defined which record is related to each activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period. Those controls must be validated if appropriate.

15.8.2. Specific retention requirements for certain documentation apply.

15.8.3. Records must be retained for the required period to allow traceability.

15.8.4. Documentation regarding investigations into Serious Adverse Events should be retained.

15.8.5. Quality System documentation and associated records should be retained.

15.8.6. For other types of documentation, the retention period must be defined on the basis of the business activity that the documentation supports. These retention periods should be specified.

16. Blood Collection, Testing, and Processing

16.1. Donor Eligibility

16.1.1. Blood establishments shall implement and maintain procedures for the safe identification of donors, suitability interviews, and eligibility assessments.

16.1.2. Each donor shall have a secure and unique identification.

16.1.3. Blood establishments shall record and securely store the contact details of all donors, ensuring that robust mechanisms are in place to link donors with each of their donations.

16.1.4. Upon arrival at the blood establishment, donors shall provide their identity and undergo a systematic screening process to determine their suitability for donation.

16.1.5. Only healthy individuals with an acceptable medical history can be accepted as donors of blood or blood components.

16.1.6. The donor selection process shall be conducted by suitably qualified individuals who are trained to use accepted blood donor medical assessment guidelines.

16.1.7. The donor questionnaire shall be designed to gather relevant information about the donor's medical history, general health, and any known or probable risk factors.

16.1.8. The questionnaire shall be written in a manner that is understandable to the donor and shall be provided to every donor at each visit. Once completed, the donor shall sign the questionnaire to confirm its accuracy.

16.1.9. Blood establishments shall establish and enforce clear acceptance and deferral criteria to determine donor eligibility.

16.1.10. The following minimum criteria shall be strictly followed for donor selection:

a) Age limits for donors shall be clearly defined.
b) The maximum allowable volume to be collected at each donation shall be specified.
c) Time intervals between donations shall be strictly regulated.
d) A comprehensive medical assessment shall be conducted prior to donation.
e) Donors' medical history, including infectious disease history and regional epidemiology, shall be evaluated.

f) Any factors in the donor's history or behavior that increase the risk of infection shall be assessed.
g) Clear criteria shall be established for temporary deferral, including the duration before the donor is eligible again.
h) Criteria for permanent exclusion from future donations shall be clearly defined.
i) Medication use by the donor shall be carefully considered.
j) Apheresis donors shall meet the general blood donation acceptance criteria unless otherwise specified.

16.1.11. Donor interviews shall be conducted in a manner that ensures the confidentiality of the donor's responses.

16.1.12. Confidential interviews shall be carried out by trained personnel who can ask further direct questions to supplement the questionnaire. The individual conducting the assessment shall certify that all necessary questions have been asked.

16.1.13. All records regarding the suitability and final assessment of donors shall be signed by a qualified healthcare professional.

16.1.14. Blood establishments shall maintain detailed records for each activity related to the selection of donors, and these records shall document every step in the donor selection process.

16.1.15. The record shall reflect the decision to accept the donor, taking into account the medical history, deferral history, donor interview, and results of the physical examination. If a donor is rejected, the reason for deferral shall be recorded. A system shall be in place to prevent the donor from making further donations during any temporary or permanent deferral period.

16.1.16. Donors shall be instructed to inform the blood establishment if they become aware of any relevant information not previously disclosed, or if they experience signs or symptoms after a donation. If such information suggests that the donation may have been infectious or unsuitable for transfusion, the blood establishment shall take appropriate action.

16.1.17. Procedures shall be established to ensure that any abnormal findings from the donor selection process are promptly reviewed by a qualified healthcare professional and appropriate actions shall be taken based on these findings.

16.2. **Collection of Blood and Blood Components**

16.2.1. The donor's identity shall be verified and securely recorded before blood collection to ensure a clear link between the donor, their blood, blood components, and samples.

16.2.2. Donor identity should be confirmed before key steps, but, at the very least, before donor selection and immediately prior to venipuncture.

16.2.3. A system of unique donation numbers shall be used to identify each donor, donation, and its components, samples, and records, ensuring traceability.

16.2.4. During or following the donation, all records, blood bags and laboratory samples should be checked for the issued donation number. Donation number labels that have not been used should be discarded using a controlled procedure.

16.2.5. Systems of Sterile blood bags used for collection and processing shall meet regulatory requirements or equivalent standards. The batch number of the bag should be traceable for each blood component.

16.2.6. All handling of materials and reagents, such as receipt and quarantine, sampling, storage, labelling, processing, packaging and transport, should be done in accordance with written procedures or instructions and, if necessary, recorded.

16.2.7. Only reagents and materials from approved suppliers that meet documented requirements and specifications should be used.

16.2.8. Blood collection shall be conducted in a safe environment, minimizing errors and risks of microbial contamination or sample mix-up.

16.2.9. Only Sterile blood collection and processing systems shall be used for blood and blood components, following manufacturer instructions.

16.2.10. Appropriate procedures for hand disinfection and personal hygiene should be in place, and should be performed by personnel before each donation.

16.2.11. The skin at the venipuncture site should be free from lesions, including eczema.

16.2.12. Effectiveness of disinfection shall be monitored, with corrective actions taken if necessary. Expiry dates on disinfectants shall be checked.

16.2.13. Blood containers shall be inspected for defects before and after donation, and blood bag tubing sealed close to the bag.

16.2.14. Blood establishment shall have Standard operating procedures that address actions for unsuccessful donations, including handling of labeled materials.

16.2.15. Samples shall be taken at donation time and stored appropriately before testing.

16.2.16. The labeling process for blood bags, samples, and records shall prevent errors or mix-ups.

16.2.17. Blood and components shall be stored and transported under controlled, validated conditions that maintain specified temperatures.

16.2.18. Any deviations from standard procedures shall be approved in writing by a qualified person.

16.2.19. Where the blood is not transported by the processing establishment itself, the responsibilities of the transport company shall be clearly defined and periodic audits shall be conducted to ensure compliance.

16.2.20. There shall be a system in place to ensure that each donation can be linked to the collection and processing system into which it was collected and/or processed.

16.3. **Laboratory Testing**

16.3.1. All blood donations shall be tested to ensure they meet safety specifications and provide a high level of safety for recipients.

16.3.2. All laboratory testing procedures shall be validated prior to use to ensure accuracy and reliability.

16.3.3. In addition to the manufacturer's system validation, the laboratory shall perform on-site verification of the test system, ensuring:

a) The test system meets the performance specifications established by the manufacturer.
b) Laboratory personnel are properly trained and competent to operate the test system.
c) Donation testing is conducted independently of patient diagnostic testing.

16.3.4. Clear procedures shall be established for handling, processing, and storing samples, including pre-analytical treatment, storage, and transportation.

16.3.5. Upon receipt, laboratories shall verify the positive identification of samples against those expected.

16.3.6. Data confirming the suitability of laboratory reagents used in testing donor samples shall be available, and all testing should follow the manufacturer's guidelines unless an alternative, validated method is used.

16.3.7. Blood establishments shall ensure the quality of commercial reagents. All reagents are required to undergo pre-acceptance testing, with suppliers providing certificates of analysis to confirm compliance with acceptance criteria.

16.3.8. A reliable system shall be in place for transcribing, collating, and interpreting test results.

16.3.9. Laboratories shall regularly participate in proficiency testing programs, such as external quality assurance, to assess the quality of their testing procedures.

16.4. **Testing for Infectious Markers**

16.4.1. All blood donations shall be tested for infectious agents to minimize the risk of disease transmission and ensure the suitability of blood components for their intended use.

16.4.2. Each donation shall be tested at least for HIV-1, HIV-2, HCV, Syphilis and HBV, in accordance with legal requirements as applicable.

16.4.3. Based on the regional or national epidemiological situation, additional tests for other infectious markers may be required as per national legal requirements.

16.4.4. Serological testing should be performed on samples transferred directly into the analyser from the original sample tube or aliquoted in a fully automated environment for HIV-1, HIV-2, HCV and HBV, syphilis as applicable.

16.4.5. Nucleic acid amplification technique (NAT) testing may be performed on mini-pools of individual samples using secondary aliquots, with proper validation of the pooling process.

16.4.6. If NAT testing is done in mini-pools, a validated system for labelling, identification, and result reassignment to individual donations shall be in place.

16.4.7. Clear procedures shall be established to resolve discrepancies in test results.

16.4.8. Donations with a single reactive screening test shall be retested in duplicate.

16.4.9. Blood and blood components that are once reactive for HIV-1/2, HCV, HBV, or syphilis shall be excluded from therapeutic use, labelled as reactive, and stored or destroyed in a dedicated environment. In cases of confirmed positive results, appropriate donor management shall be implemented, including informing the donor and conducting follow-up procedures.

16.4.10. Written standard operating procedures (SOPs) shall define screening algorithms to address initially reactive specimens and resolve discrepancies in retesting results.

16.5. **Blood Group Serological Testing of Donors and Donations**

16.5.1. A blood establishment shall have established Blood group serology testing procedures for specific groups of donors, such as first-time donors and those with a history of transfusion.

16.5.2. Each donation shall be tested for ABO and RhD blood groups and at least all first-time donors should be tested for clinically significant irregular red cell antibodies.

16.5.3. ABO and RhD blood groups shall be verified for every subsequent donation, and compared with the historically determined blood group. Any discrepancies shall be resolved before releasing the blood components.

16.5.4. Donors with a history of transfusions or pregnancy shall be tested for clinically significant irregular red cell antibodies. If such antibodies are detected, the blood or blood component shall be labelled accordingly.

16.5.5. Only test reagents that are approved or deemed suitable by the authority shall be used.

16.5.6. Quality control procedures shall be in place for the equipment, reagents, and techniques used for blood grouping and antibody detection.

17. Quality and Risk management system

17.1. **Quality management**

17.1.1. **General requirements**

17.1.1.1. Each blood establishment should develop and maintain a Quality System that is based on Good Manufacturing Practices.

17.1.1.2. For blood and blood components imported from another jurisdiction and intended for use or distribution, there should be a Quality System for blood establishments in the stages preceding importation equivalent to the Quality System in practice in the country of import.

17.1.1.3. Quality should be recognized as being the responsibility of all persons involved in the processes of the blood establishment, with management ensuring a systematic approach towards quality and the implementation and maintenance of a Quality System.

17.1.1.4. Attainment of this quality objective is the responsibility of senior management. It requires the participation and commitment of both staff in many different departments

and at all levels within the organization and of the organization's suppliers and distributors. To achieve this quality objective reliably there should be a comprehensively designed and correctly implemented quality system incorporating good practice and quality risk management.

17.1.1.5. Each actor in the supply chain should establish, document and fully implement a comprehensively designed quality system to deliver quality assurance based on the principles of quality risk management by incorporating good practice and quality control.

17.1.1.6. The basic concepts of quality management, good practice and quality risk management are interrelated. They are described here in order to emphasize their relationships and fundamental importance to the preparation of blood and blood components.

17.1.1.7. The requirements for implementing a quality system also apply to hospital blood banks.

17.1.2. **Quality system**

17.1.2.1. Quality management is a wide-ranging concept covering all matters that individually or collectively influence the quality of blood and blood components. It is the sum total of the organised arrangements made with the objective of ensuring that blood components are of the quality required for their intended use. Quality management therefore incorporates good practice.

17.1.2.2. The Quality System encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, collection, processing and testing, storage, distribution, quality control, blood component recall, and external auditing, contract management, non-conformance and self-inspection.

17.1.2.3. The Quality System should ensure that all critical processes are specified in appropriate instructions and are carried out in accordance with the standards and specifications of Good Practice and comply with appropriate regulations.

17.1.2.4. The quality system should be designed to assure the quality and safety of prepared blood and blood components, as well as ensure donor and staff safety and customer service. This strategy requires the development of clear policies, objectives and responsibilities. It also requires implementation by means of quality planning, quality

control, quality assurance and quality improvement to ensure the quality and safety of blood and blood components, and to provide customer satisfaction.

17.1.2.5. Senior management has the ultimate responsibility to ensure that an effective quality system is in place and resourced adequately, and that roles and responsibilities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the quality system is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the quality system.

17.1.2.6. Senior management should establish a quality policy that describes the overall intentions and direction of the blood establishment and/or hospital blood bank (hereinafter referred to as 'organisation') related to quality. They should also ensure quality system management and good practice governance through management review to ensure its continuing suitability and effectiveness.

17.1.2.7. The quality system should be defined and documented. A quality manual or equivalent document should be established and contain a description of the quality system (including management responsibilities).

17.1.2.8. All blood establishments and hospital blood banks should be supported by a quality assurance function (whether internal or related) for fulfilling quality assurance. That function should be involved in all quality-related matters, and should review and approve all appropriate quality-related documents.

17.1.2.9. An independent function with responsibility for quality assurance should be established. This quality assurance function will be responsible for the oversight of all quality processes but need not necessarily be responsible for carrying out the activities. The Quality assurance:

- It is part of quality management that ensures that all critical processes are appropriately described in written instructions, are performed in accordance with the principles of GMP and comply with the appropriate regulations. The quality assurance system should be fully documented, distributed and explained to everyone involved in the manufacturing processes.
- All parts of the quality assurance system should be adequately resourced with competent personnel, suitable premises, and suitable and sufficient equipment

and facilities to enable the manufacturing steps to be completed in a safe and quality compliant manner.

17.1.2.10. All procedures, premises and equipment that have an influence on the quality and safety of blood and blood components should be validated and qualified before introduction and should be re-validated and re-qualified at regular intervals, as determined as a result of these activities.

17.1.2.11. A general policy regarding qualification of facilities and equipment as well as validation of processes, automated systems and laboratory tests should be in place. The formal objective of validation is to ensure compliance with the intended use and regulatory requirements.

17.1.2.12. A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality, traceability, availability or effect of components, or the safety of components, donors or patients. The potential impact of the proposed change should be evaluated, and the degree of revalidation or additional testing, qualification and validation needed should be determined.

17.1.2.13. A formal system for the handling of deviations and non-conformances should be in place. An appropriate level of root-cause analysis should be applied during the investigation of deviations, suspected product defects, and other problems. This strategy can be determined using quality risk management principles. If the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing them. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed in accordance with quality risk management principles.

17.1.2.14. Management should review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary.

17.1.2.15. There should be periodic management review to monitor the quality system effectiveness and its operations, with the involvement of senior management, and to

identify opportunities for continual improvement of blood and blood component processes.

17.1.2.16. Product quality reviews should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify component and process improvements.

17.1.2.17. A product quality review may also be considered as an instrument for surveying the overall quality status of a blood component and its preparation processes, including the collection. Such a review should normally be conducted annually and should be documented. It may include:

- review of starting materials;
- review of critical in-process controls;
- review of results of quality control and quality monitoring;
- review of all changes;
- review of the qualification status of equipment;
- review of technical agreements and contracts;
- review of all significant deviations and non-conformances, and the effectiveness of the corrective actions implemented;
- review of the findings of internal and external audits and inspections, and the effectiveness of the corrective actions implemented;
- review of complaints and recalls;
- review of donor acceptance criteria;
- review of donor deferrals;
- review of look-back cases.

17.1.3. **Good practice**

17.1.3.1. Good practice is the part of quality management that ensures that blood and blood components are produced and controlled consistently to the quality standards appropriate to their intended use. Good practice is concerned with collection, processing, testing, release and storage (hereinafter included in the generic term ‘preparation’) and quality control. The basic requirements are:

17.1.3.2. All processes are defined clearly and reviewed systematically in the light of experience and shown to be capable of consistently delivering blood and blood

components of the required quality and complying with their specifications. This strategy includes ensuring that:

- critical steps and significant changes to the process are validated;
- all requirements are provided including:
  - ✔ appropriately qualified and trained personnel;
  - ✔ adequate premises and space;
  - ✔ suitable equipment and services;
  - ✔ correct materials, containers and labels;
  - ✔ approved procedures and instructions;
  - ✔ suitable storage and transport;
- instructions and procedures are written in an instructional form in clear and unambiguous language, and are applicable specifically to the facilities;
- operators are trained to carry out procedures correctly;
- records are made, manually and/or by recording instruments, during preparation which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the blood or blood component was as expected;
- any significant deviations are fully recorded and investigated;
- records of preparation (including distribution) that enable the complete history of the blood or blood component to be traced are retained in a comprehensible and accessible form;
- the distribution of the blood and blood components minimizes any risk to their quality;
- a system is available to recall any blood or blood component (including those prepared using a batch of critical materials that have been distributed or issued);
- Complaints about blood and blood components are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective blood components to prevent reoccurrence.

17.1.3.3. Quality control is the part of good practice that is concerned with sampling, specifications and testing, as well as with the organisation, documentation and release

procedures which ensure that materials are not released for use in preparation, and blood and blood components are not released for distribution, until their quality has been judged to be satisfactory and that the necessary and relevant tests have been carried out. The basic requirements are:

- adequate facilities, trained personnel and approved procedures are available for sampling, inspecting/testing starting materials, packaging materials, intermediate components and finished blood and blood components and, if appropriate, for monitoring environmental conditions;
- samples of starting materials, packaging materials, and intermediate and finished blood components are taken by approved personnel and methods;
- test methods are validated;
- records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are recorded and investigated fully;
- the finished blood and blood components comply with the specifications and are correctly labelled;
- records are made of the results of inspection, and that testing of materials, intermediate and finished blood and blood components are formally assessed against specifications;
- no blood or blood components are released for distribution that do not comply with the requirements of the relevant authorizations.

17.1.3.4. Quality reviews of all blood and blood components (including export-only blood components) should be conducted with the objective of continuously verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished blood components to highlight any trends and to identify product and process improvements.

17.2. **Quality risk management (QRM)**

17.2.1. Quality risk management is the part of the quality system that ensures that the process performance and quality monitoring and review systems are based on risk.
Appropriate statistical tools should be used (where appropriate) in the assessment of ongoing process capability.

17.2.2. The quality system should ensure that processes are in place to ensure the control of outsourced activities and quality of purchased materials. These processes should incorporate the principles of quality risk management and systematically ensure that:

17.2.3. the evaluation of the risk to quality is based on scientific knowledge, experience with the process and, ultimately, is connected to protection of the donor and patient;

17.2.4. The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

17.2.5. An effective QRM approach can ensure the quality of a product by providing proactive means to identify and control potential quality issues. It can also facilitate and improve the decision-making process in cases when quality problems or deviations from standard processes and specifications have to be assessed or planned changes need to be evaluated.

Note: Details of QRM processes and applications can be found in QRM guidelines such as the Q9 guideline of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This describes processes and offers a selection of methods and tools for applying the QRM principles.

17.3. **Change control**

17.3.1. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process results in a blood component of the desired quality, consistent with the approved specifications. Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.

17.3.2. Written procedures should be in place to describe the actions to be taken if a planned change is proposed for a starting material, blood component specification, process, item of equipment, environment (or site), product range, method of production or testing or any other change that may affect donor safety, blood component quality or reproducibility of the process.

17.3.3. Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the blood establishment’s quality system.

17.3.4. Quality risk management should be used to evaluate planned changes to determine the potential impact on blood component quality, the blood establishment’s quality

systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.

17.3.5. Following implementation, where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

17.3.6. The introduction of new equipment, processes and methods should be treated as a change.

17.4. **Deviations management**

17.4.1. The handling of deviations and non-conformances should be defined in writing. Actions should be taken within a reasonable time frame in order to avoid any impact on other products manufactured within the same establishment.

17.4.2. There should be a defined procedure for the release of non-standard blood and blood components under a planned non-conformance system. The decision for such release should be clearly documented and authorized by a designated person, and traceability should be ensured.

17.4.3. Any deviation from standard operating procedures, validated processes, or non-conformances with specifications or other quality-related requirements should be recorded and investigated. The potential impact on the quality of the product in question, or on other products, should be evaluated.

17.4.4. There should be systems in place to ensure that deviations, adverse events, adverse reactions and non-conformances are documented, carefully investigated for causative factors of any defect and, where necessary, followed up by the implementation of corrective actions to prevent recurrence.

17.4.5. The CAPA system should ensure that existing component nonconformity or quality problems are corrected and that recurrence of the problem is prevented.

17.4.6. Deviations from established procedures should be avoided as much as possible and should be documented and explained. Any errors, accidents or significant deviations that may affect the quality or safety of blood and blood components should be fully recorded and investigated in order to identify systematic problems that require corrective action. Appropriate CAPAs should be defined and implemented.

17.4.7. Investigations relating to serious deficiencies, significant deviations and serious component defects should include an assessment of component impact, including a review and evaluation of relevant operational documentation and an assessment of deviations from specified procedures.

17.4.8. There should be procedures for notifying responsible management in a timely manner of deficiencies, deviations or non-compliance with regulatory commitments (e.g. in submissions and responses to regulatory inspections), component or product defects, or testing errors and related actions (quality-related complaints, recalls, regulatory actions, etc.).

17.4.9. Senior management and the Responsible Person should be notified in a timely manner of serious deficiencies, significant deviations and serious component or product defects, and adequate resources should be made available for their timely resolution.

17.4.10. A regular review of all significant deviations or non-conformances should be conducted, including their related investigations, to verify the effectiveness of the CAPAs taken.

17.5. **Complaint and recall**

17.5.1. **Complaint**

17.5.1.1. There should be a system in place to ensure that all complaints are handled according to written and approved standard operating procedures.

17.5.1.2. All complaints and other information, including serious adverse events that may suggest that defective blood components have been issued, should be documented, carefully investigated for causative factors of the defect and, where necessary, followed up by recall and the implementation of corrective actions to prevent recurrence. Procedures should be in place to ensure that the Authority is notified, as appropriate, of serious adverse reactions or serious adverse events in accordance with regulatory requirements.

17.5.1.3. Complaints, adverse events or reactions, as well as any information concerning potentially defective products, should be carefully reviewed and thoroughly investigated in order to find the root cause of the problem. Consideration should be given to determining whether other products are also affected. All investigations and actions should be carried out in a timely manner to ensure that the safety of the

recipient is not compromised and that other products manufactured within the same establishment are not affected.

17.5.1.4. A person should be designated as responsible for handling complaints and deciding the measures to be taken. This person should have sufficient support staff. If this person is not the Responsible Person, the latter should be made aware of any complaint, investigation or recall.

17.5.1.5. If a blood or blood component defect or testing error is discovered or suspected, consideration should be given to checking related blood and blood components in order to determine whether they are also affected.

17.5.1.6. All the decisions and measures taken as a result of a complaint should be recorded. Complaint records should be reviewed regularly for any indication of specific or recurring problems requiring attention and the possible recall of distributed blood and blood components. When requested, the blood establishment should disclose this information to the Authority for review.

17.5.1.7. The Authority should be informed in cases of complaints resulting from possible faulty processing, component deterioration or any other serious quality problems, including the detection of falsification.

17.5.2. **Recall**

17.5.2.1. There should be personnel authorized within the blood establishment to assess the need for blood and blood component recalls and to initiate and co-ordinate the necessary actions.

17.5.2.2. An effective recall procedure should be in place, including a description of the responsibilities and actions to be taken. This should include notification of the Authority.

17.5.2.3. A recall should always be initiated whenever it is discovered that a product does not meet the release criteria of the blood establishment and the authority.

17.5.2.4. Actions should be taken within pre-defined periods of time and should include tracing all relevant blood components and, where applicable, should include trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the transfusion reaction and to retrieve available blood components from that donor, as well as to notify consignees and recipients of

components collected from the same donor in the event that they might have been put at risk.

17.5.2.5. Recall operations should be capable of being initiated promptly and at any time. Therefore, the standard operating procedures should include emergency and "out of hours" contact details. Depending on the type of recall; the authority should be informed as per timeline indicated on the recall directive and guideline of EFDA. In certain cases recall operations may need to be initiated to protect public health prior to establishing the root cause(s) and full extent of the quality defect.

17.5.2.6. The persons authorised to initiate and co-ordinate the recall actions should normally be independent of the commercial management within the organisation. If they do not include the senior management and the responsible Person (blood establishment), the latter should be made aware of any recall operation.

17.5.2.7. Recalled blood components or products should be identified and stored separately in a secure area while awaiting a decision on their fate.

17.5.2.8. The progress of the recall process should be recorded and a final report issued, including reconciliation of the delivered and recovered quantities of the blood and blood components or products.

17.5.2.9. The effectiveness of the arrangements for recalls should be regularly evaluated.

17.5.2.10. Once the decision is made, recalled products should be destroyed as per the authority disposal directive. If recalled products are not destroyed, they should be clearly identified and stored separately in a secure area.

17.6. **Corrective and preventive actions**

17.6.1. A system to ensure corrective and preventive actions for blood component nonconformity and quality problems should be in place. The system should include the management of deviations and non-conformances, complaints, events and findings of the quality system management review, inspections and audits, and should ensure the proper recording of all corrective and preventive actions taken.

17.6.2. Data should be routinely analysed to identify quality problems that may require corrective action or to identify unfavourable trends that may require preventive action.

17.6.3. All errors and accidents should be documented and investigated in order to identify problems for correction.

17.6.4. Deviations with the potential to affect quality should be investigated and the investigation and its conclusions should be documented, including all the original details. The validity and extent of all reported quality defects should be assessed in accordance with quality risk management principles in order to support decisions regarding the degree of investigation and action taken. Where appropriate, corrective actions should be taken prior to distribution of blood and blood components or reporting of a test result. The potential impact of the source of the deviation on other components or results should also be considered and preventive action should be taken to eliminate the root cause of the deviation and thereby avoid recurrences.

17.6.5. Investigations should include a review of previous reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action. Processes and relevant data should be monitored with a view to taking preventive action to avoid potential deviations occurring in the future. Where appropriate, statistical or other tools should be used to assess and monitor process capabilities. As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations.

17.6.6. An appropriate level of root-cause analysis work should be applied during the investigation of deviations. In cases where the true root cause(s) cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause of the deviation, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

17.6.7. The decisions that are made during and following investigations should reflect the level of risk that is presented by the deviation as well as the seriousness of any non-compliance with respect to the requirements of the blood component specifications or good practice. Such decisions should be timely to ensure that patient safety is maintained in a way that is commensurate with the level of risk that is presented by those issues.

17.6.8. As part of periodic quality system reviews, an assessment should be made of whether CAPAs or any revalidation should be undertaken. The reasons for such corrective actions should be documented. Agreed CAPAs should be completed in a timely and effective manner. There should be procedures for the ongoing management and review of these actions and the effectiveness of these procedures should be verified during self-inspection.

17.7. **Self-inspection and Process Improvements**

17.7.1. **Internal Audit (self-Inspection)**

17.7.1.1. Self-inspection or audit systems should be in place for all elements of operations to verify compliance with the standards. They should be carried out regularly by trained and competent persons, in an independent way, and according to approved procedures.

17.7.1.2. Internal audits should be arranged according to a schedule and should cover all parts of the operations, including data processing systems. Each audit should be carried out according to an approved audit plan that assesses compliance with internal requirements and applicable national and/or international regulations.

17.7.1.3. All results should be documented and appropriate corrective and preventive actions should be taken in a timely and effective manner.

17.7.1.4. The quality assurance department, where the internal audit function resides, should not audit itself but should be subject to an independent audit. Internal audits are not a substitute for official inspections performed by the competent national authorities who check compliance with national regulations.

17.7.2. **Process improvement**

17.7.2.1. Ideas for potential improvements to any of the systems may come from research, development, brainstorming, or from the management of non-conformances, events and complaints, from internal or external audit or inspection findings, and from deviations detected during quality monitoring activities.

17.7.2.2. The process should track corrective or preventive actions that are developed and implemented. An effectiveness check should be in place to determine the impact or effectiveness of any changes. These activities should be documented and reported at least annually to the executive management (in the quality management review report).

18. Annex-1

- Guidance on increasing supplies of plasma-derived medicinal products in low- and middle income countries through fractionation of domestic plasma: Geneva: World Health Organization; 2021

https://iris.who.int/bitstream/handle/10665/340171/9789240021815-eng.pdf?sequence=1

19. References

1. WHO Technical Report Series, No. 1060, 2025
2. PIC/S Good Practice Guidelines for Blood Establishments and Hospital Blood Banks, June, 2021
3. Recommendation for the production control and regulation of human plasma for fractionation-(WHO TRS No 941 Annex 4, 2007)
4. EFDA Good Manufacturing Practices Guideline for Pharmaceutical Products: Main Principles 4th Edition