Good Practice Guidelines for blood establishments and hospital blood banks

NOTE

This draft document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). The distribution of this draft document is intended to provide information on a proposed Guidelines Good Practice Guidelines for blood establishments and hospital blood banks to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the ECBS. Written comments proposing modifications to this text MUST be received in English by 18 September 2024 in the Comment Form available separately and should be addressed to the Department of Health Products Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland. Comments may also be submitted electronically to the Responsible Officer: Dr Yuyun Maryuningsih at: maryuningsihy@who.int

The outcome of the deliberations of the ECBS will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the second edition of the WHO style guide (KMS/WHP/13.1).
Good Practice Guidelines for blood establishments and hospital blood banks

Introduction

The World Health Organization (WHO) requirements for the collection, processing and quality control of blood, blood components including plasma for fractionation define a quality assurance system based on (i) the existence of a national structure that is independent of manufacturers, (ii) compliance with the process of quality assurance for biological products — i.e. control of starting material(s), production processes and final product(s) — and (iii) strict adherence to the principles of good manufacturing practice (GMP). The importance of establishing reliable quality assurance systems for the whole chain of blood collection, processing and distribution of blood components in blood establishments was also emphasized by the Sixty-third World Health Assembly in resolution WHA63.12 on the availability, safety and quality of blood products. In that resolution, quality assurance was seen as a necessary measure that would contribute to increased global availability of blood (including plasma) and blood products that meets internationally recognized standards. Resolution WHA63.12 recognized that a special effort is needed to strengthen globally the technical capacity of national regulatory authorities (NRAs) to assure the appropriate control of blood products. The resolution recalls earlier related resolutions which urged Member States to promote the full implementation of well organized, nationally coordinated and sustainable blood programs stressing the role of voluntary, non-remunerated blood donations from low-risk populations.

The WHO Expert Committee on Biological Standardization (ECBS) considered that the development of WHO guidelines on GMP for blood establishments is of highest priority in assisting Member States to meet their needs in this area, as requested by the International Conference of Drug Regulatory Authorities in 2008 (3). As a result, a first version of the WHO GMP Guidelines for Blood Establishments had been adopted by the ECBS in 2011. At that time the document PE 005 of the Pharmaceutical Inspection Cooperation Scheme (PIC/S) was used as reference document to the WHO Guidelines.

In 2018, PIC/S decided to update PE 005 by aligning it with the European Union/ European Directorate for the Quality of Medicines & Health care (EU/EDQM), Good Practice Guidelines (GPG) for the sake of harmonization globally for GMP requirements for collection, testing, processing, storage and distribution of blood and blood components, whatever their intended use. Although in most of the jurisdictions or in WHO guidelines, principles of GMP are applied to blood components, the GPG presented in this document are equivalent to GMP and the two terms can be used interchangeably, depending on national legislation.

In recent years, safety and quality in the transfusion chain has become an important topic in many countries and regions. In order to promote global implementation of measures to improve quality and safety of blood components, including plasma for further manufacturing, WHO adopted an Action Framework 2020-2023 to advance universal access to safe, effective and quality assured blood products, that aims as a strategic direction to global efforts to address present barriers to safe and high quality blood products.

One barrier identified through the WHO Global Database on Blood Safety, 2021, is deficiencies in safety, effectiveness and quality of blood products. The strategic objective stated in the action framework to address this barrier is to encourage member states to function and efficiently manage blood services. Updating the 2011 WHO Guidelines on Good Manufacturing Practice for Blood Establishment could assist the member states to implement this strategic objective.
Blood establishments should establish and maintain quality systems, based on GMP principles, involving all activities that determine quality policy objectives and responsibilities, and should implement them by such means as quality planning, quality control, quality assurance and quality improvement. A GMP approach to manufacturing safe blood components that consistently meet predefined specifications and customers’ expectations provides a model allowing for a documented system of incorporating quality into the entire process. When collecting and processing blood and plasma from human donors, GMP considerations should be addressed in a biological context due to the specific characteristics of materials of human origin.

The Good Practice Guidelines in this document consist of two parts:
— Part A represents the technical standards of Good Practice for blood establishments and hospital blood banks, covering GMP requirements adapted to the blood field, such as quality management, quality risk management, personnel, documentation, premises and equipment, qualification and validation, materials management, contract manufacturing, complaints and recalls, as well as specific Good Practice provisions related to collection, processing, testing, storage and distribution of blood components. This part A should be the relevant binding part within a blood regulatory system that needs to be implemented by blood establishments and hospital blood banks, and is used for inspections by the NRA.
— Part B includes additional guidance information that might be helpful to better understand and implement the Part A requirements. It has no binding character.

Part A addresses current and widely accepted GMP principles that are relevant to the consistent production of safe and quality assured blood components in blood establishments. The Good Practice Guidelines (GPG) described in Part A are fully aligned with other international Good Practice Guidelines for blood establishment, such as the document published by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM/CoE), the Commission of the European Union (EU) and the Pharmaceutical Inspection Cooperation Scheme (PIC/S). In order to facilitate global harmonization, these Good Practice Guidelines in Part A of this document should be the reference for any other national or regional standard for blood establishments.

If plasma collected in blood establishments is used as starting material for manufacturing of medicinal products, this activity must be performed in compliance with principles and guidelines of Good Manufacturing Practice. These Good Practice Guidelines (GPG) fully reflect the detailed principles and guidelines of GMP applied for pharmaceutical products as long as they are relevant for blood establishments and their quality systems. Accordingly, they are recognized as appropriate GMP standards also for the collection and testing of plasma for fractionation, as mentioned in Annex 14 of the EU or PIC/S GMP Guides, and any blood establishment that complies with the GPG Part A of this document, is considered to work in accordance with an appropriate quality system and is fulfilling the GMP requirements as supplier of the starting material for further manufacturing. Complementary guidance, especially with respect to the production of plasma for fractionation, is available in the WHO recommendations for the production, control and regulation of human plasma for fractionation (5).

The document is intended to serve as guidance for blood establishments and hospital blood banks and NRAs when implementing or enforcing these principles. It does not address the practice of transfusion medicine or management of emergencies or crises where specific policies defined by the NRA apply. Aspects of personnel and environmental protection are also not within the scope of this document.

The glossary as part of this document, uses terminology as referenced and defined in other WHO documents. Where possible, the terminology has been aligned as far as possible with the glossary used in the other international documents. Consistent with the approach used in codes of good manufacturing practice (GMP), the requirements in Part A of the GPG are defined using the term
‘should’. The intention is that the requirements identify what needs to be achieved but are not specific on how this is done.
Glossary and abbreviations

**Blood component**
Therapeutic components of blood (red cells, white cells, platelets, plasma, including plasma for fractionation) that can be prepared by centrifugation, filtration and freezing using conventional methodologies in blood establishments.

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

It encompasses the terms blood bank, blood centre, plasma collection centre, blood service, blood transfusion service and hospital-based blood services. Hospital-based blood services may additionally be engaged in storage, pretransfusion testing of patients and issuing of blood components, and function as both blood establishments and hospital blood banks.

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

**Calibration**
Set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument/system, or values represented by a material measure, and the corresponding known values of a reference standard.

**Change control/management**
A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure the system is maintained in a validated state.

**Closed system**
A system in which the contents are not exposed to air or outside elements during the collection, preparation and separation of components and during production of products.

**Computerised system**
A system comprising the input of data, electronic processing and the output of information to be used either for reporting, automatic control or documentation.

**Critical quality attribute**
A critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired component and product quality.

**Critical process parameter**
A critical process parameter (CPP) is a process parameter whose variability has an impact on a CQA and which therefore should be monitored or controlled to ensure the process produces the desired quality.

**Distribution**
Act of delivery of blood and blood components to other blood establishments, hospital blood banks, and manufacturers of blood- and plasma-derived products. It does not include issuing blood or blood components for transfusion.

**Donor**
A person in normal health with a good medical history who voluntarily gives blood or blood components, including plasma for fractionation.
Donor deferral
Suspension of the eligibility of an individual to donate blood or blood components; such suspension being either permanent or temporary.

Good Practices
All elements in established practice that collectively lead to final blood or blood components that consistently meet pre-defined specifications and compliance with defined regulations.

Good Manufacturing Practices
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.

Hospital blood bank
Hospital unit which stores and distributes and may perform compatibility tests on blood and blood components exclusively for use within the hospital facilities, including hospital-based transfusion activities.

Some hospital-based blood services may additionally be engaged in blood collection, processing and donation testing activities and thereby function as blood establishments.

Look-back (Trace-back)
The process of investigating a report of a suspected seroconversion of a donor, or a suspected transfusion-associated adverse reaction in a recipient, to identify a potentially implicated donor or donation.

Manufacture
All operations of purchase of materials and products, production, quality control, release, storage and distribution of finished products and the related controls.

Mobile site
A temporary or movable qualified place used for the collection of blood and blood components which is in a location outside of, but under the control of the blood establishment. There are vehicles, such as buses, that are enabled as mobile sites for blood collection.

Open system
A system in which a breach has occurred but every effort is made to prevent microbiological contamination by operating in a clean environment using sterilized materials and aseptic handling techniques.

Plasma collection center
Plasma collection centres: centres dedicated to the collection of plasmapheresis plasma (source plasma)

Plasma for fractionation
Plasma that is used as a starting material for plasma-derived medicinal products, which refers to both apheresis and recovered plasma (acc. Ph. Eu).

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

Preparation
Preparation of a blood component includes the steps of collection, processing, testing, release and storage.
Procedure

A procedure controls a distinct process or activity, including the associated inputs and outputs. A series of tasks usually performed by one person according to instructions.

A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the preparation of a blood component.

Process

A set of interrelated or interacting tasks that use input to deliver an intended result.

Processing

Any step in the preparation of a blood component that is carried out between the collection of blood and the issuing of a blood component.

Qualification

The actions for proving and documenting that any premises, systems or equipment are properly installed (IQ), work correctly and comply with specified requirements (OQ), and delivers the expected result (PQ).

Quality Assurance

A part of quality management focused on providing confidence that quality requirements will be met. All the activities from blood collection to distribution carried out with the objective of ensuring that blood and blood components are of the quality required for their intended use.

Quality control

Part of good practices that is concerned with sampling, specifications and testing, as well as with the organization, documentation and release procedures. The aim is to ensure that materials are not released for use during preparation, and blood and blood components are not released for distribution, until their quality has been judged to be met predefined specifications and that the necessary and relevant tests have been carried out.

Quality management

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

Quality monitoring

That part of a quality assurance programme concerned with maintenance and improvement of quality which deals with the identification and use of indicators to detect variations from standards or specifications.

Quality system

The organizational structure, responsibilities, policies, processes, procedures and resources established to implement and to verify quality requirements.

Quarantine

The physical isolation of blood components or incoming materials/reagents over a variable period of time while awaiting acceptance, issuance or rejection of the blood components or incoming materials/reagents. Note: Any system replacing the physical quarantine (e.g., computerised systems) should provide equivalent security.

Record

Written or electronically captured evidence that an event has occurred or an outcome has been achieved. A document that contains objective evidence which shows how well activities are being performed or what kind or results are being achieved.

Responsible person

The Responsible Person(s) should ensure that every unit of blood or blood component has been collected, tested, processed, stored, and distributed in compliance with the laws in force in that country and (if applicable) with the requirements of the Marketing Authorisation. The Responsible Person(s) shall meet the qualification requirements laid down in the national legislation, they shall be
permanently and continuously at the disposal of the blood establishment to carry out their responsibilities.

**Risk assessment**
A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

**Risk management**
The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

**Specification**
A document describing in detail the requirements with which the products or materials used or obtained during manufacture to conform. Specifications serve as a basis for quality evaluation of the criteria that must be fulfilled in order to achieve the required quality standard.

**Standard operating procedures (SOP)**
Written instructions that are adopted and implemented in the blood establishment for the performance of specific procedures in a standardized manner.

**Validation**
The establishment of documented and objective evidence that the predefined requirements for a specific procedure or process can be consistently fulfilled. It includes actions for proving that any operational procedure, process or system leads to the expected results in a consistent manner. Validation work is normally performed in advance of implementation according to a defined and approved protocol that describes tests and acceptance criteria.
Abbreviations

ACD-A anticoagulant citrate dextrose solution A
CAPA corrective actions and/or preventive action
CME continuing medical education
CPD continuing professional development
CPP critical control point
CQA critical quality attribute
DQ design qualification
EDQM/CoE the european directorate for the quality of medicines & healthcare of the council of europe
FAT factory acceptance test
FFP fresh frozen plasma
FMECA failure mode, effects and criticality analysis
FTA fault tree analysis
FMEA failure mode effects analysis
GMP good manufacturing practice
GPG good practice guidelines
HAV hepatitis A virus
HACCP hazard analysis and critical control points
HBsAg hepatitis B surface antigen
HBV hepatitis B virus
HAZOP hazard operability analysis
HCV hepatitis C virus
HCT haematocrit
HIV human immunodeficiency virus
HOA hazard operability analysis
HTLV1 and 2 human T lymphotropic virus 1 and 2
IOQ installation/operation qualification
IQ installation qualification
NAT nucleic acid amplification testing
NRA(S) national regulatory authority(ies)
OQ operational qualification
PIC/S the pharmaceutical inspection cooperation scheme
PHA preliminary hazard analysis
PQ performance qualification
PRBCS pathogen reduced blood components
RBC red blood cell
RhD rhesus D
SAT site acceptance testing
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>SAGM</td>
<td>saline-adenin-glucose-manitol</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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<td>TRALI</td>
<td>transfusion related acute lung injury</td>
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<tr>
<td>URS</td>
<td>user requirements specification</td>
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<tr>
<td>vCJD</td>
<td>variant creutzfeldt–jakob disease</td>
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<tr>
<td>VMP</td>
<td>validation master plan</td>
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<td>WNV</td>
<td>west nile virus</td>
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Part A: Good Practice Guidelines for Blood Establishments and Hospital Blood Banks (GPG)

1. Quality management

1.1. General requirements

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

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.

1.1.3. Quality should be recognised 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.

1.1.4. Attainment of this quality objective is the responsibility of senior management. It requires the participation and commitment both of staff in many different departments and at all levels within the organisation and of the organisation’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.

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.

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

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

1.2. Quality system

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.

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

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.
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, patient and staff safety and customer service, including full traceability. 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. The blood establishment should consider the development of appropriate contingency and emergency plans to maintain adequate supplies of blood and blood components.

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.

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.

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).

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.

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.

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.

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.

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.

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.

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

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.

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.

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:

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

1.3. Good practice

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:

1.3.1.1. 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:
1.3.1.1. critical steps and significant changes to the process are validated;
1.3.1.1.2. all requirements are provided including:
  1.3.1.1.2.1. appropriately qualified and trained personnel;
  1.3.1.1.2.2. adequate premises and space;
  1.3.1.1.2.3. suitable equipment and services;
  1.3.1.1.2.4. correct materials, containers and labels;
  1.3.1.1.2.5. approved procedures and instructions;
  1.3.1.1.2.6. suitable storage and transport;
1.3.1.1.2. instructions and procedures are written in an instructional form in clear and
  unambiguous language, and are applicable specifically to the facilities;
1.3.1.1.3. operators are trained to carry out procedures correctly;
1.3.1.1.4. 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;
1.3.1.1.5. any significant deviations are fully recorded and investigated;
1.3.1.1.6. 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;
1.3.1.1.7. the distribution of the blood and blood components minimises any risk to their quality;
1.3.1.1.8. 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);
1.3.1.1.9. 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.
1.3.1.2. 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:
1.3.1.2.1. 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;
1.3.1.2.2. samples of starting materials, packaging materials, and intermediate and finished
  blood components are taken by approved personnel and methods;
1.3.1.2.3. test methods are validated;
1.3.1.2.4. 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;
1.3.1.2.5. the finished blood and blood components comply with the specifications and are
  correctly labelled;
1.3.1.2.6. 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;

1.3.1.2.7. no blood or blood components are released for distribution that do not comply with the requirements of the relevant authorisations.

1.3.1.3. 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.

1.4. Quality risk management

1.4.1. 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.

1.4.2. 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:

1.4.2.1. 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;

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

1.5. Change control

1.5.1. 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.

1.5.2. 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 and safety or reproducibility of the process.

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

1.5.4. 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.

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

1.5.6. Some changes may require notification to, or licence amendment from, a national regulatory authority.
1.6. Deviations

1.6.1. Blood components deviating from required standards should be released for transfusion only in exceptional circumstances and with the recorded agreement of the prescribing physician and the blood establishment/hospital blood bank physician.

1.6.2. 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 authorised by a designated person, and traceability should be ensured.

1.6.3. 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.

1.6.4. The corrective and preventive action (CAPA) system should ensure that existing component nonconformity or quality problems are corrected and that recurrence of the problem is prevented.

1.6.5. 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.

1.6.6. 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.

1.6.7. 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.).

1.6.8. 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.

1.6.9. 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.

1.7. Complaints

1.7.1. All complaints and other information, including serious adverse reactions and 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 Competent Authorities are notified, as appropriate, of serious adverse reactions or serious adverse events in accordance with regulatory requirements.

1.7.2. 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 the person is
not the Responsible Person, the latter should be made aware of any complaint, investigation or recall.

1.7.3. 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.

1.7.4. 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.

1.7.5. The competent authorities 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.

1.8. Recall

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

1.8.2. 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 Competent Authority.

1.8.3. 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.

1.8.4. Recall operations should be capable of being initiated promptly and at any time. 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.

1.8.5. The responsible person or other persons co-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.

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

1.8.7. 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.

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

1.9. Corrective and preventive actions

1.9.1. A system to ensure corrective and preventive actions (CAPA) for blood component nonconformity and quality problems should be in place.

1.9.2. Data should be routinely analysed to identify quality problems that may require corrective action or to identify unfavourable trends that may require preventive action.
All errors and accidents should be documented and investigated in order to identify problems for correction.

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.

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.

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.

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.

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.

**Self-inspection, audits and improvements**

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.

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

2.1. Personnel should be available in sufficient numbers to carry out the activities related to the collection, testing, processing, storage and distribution of blood and blood components and be trained and assessed to be competent to perform their tasks.

2.2. The organisation should have an adequate number of personnel with the necessary qualifications and experience. Management has the ultimate responsibility to determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the quality management system and continually improve its suitability and effectiveness through participation in management review. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.3. There should be an organisation chart in which the relationships between key personnel are clearly shown in the managerial hierarchy. Key personnel include the following functions and their substitutes:

- 2.3.1. a ‘Responsible Person’;
- 2.3.2. a processing manager, responsible for all processing activities;
- 2.3.3. a quality control manager, responsible for all quality control activities;
- 2.3.4. a quality assurance manager, responsible for ensuring that there are appropriate quality systems and protocols in place for the safe and secure release of all materials, reagents and blood and blood components;
- 2.3.5. a physician with the responsibility for ensuring the safety of donors (Responsible Physician).

2.4. All personnel should have up-to-date job descriptions, which clearly set out their tasks and responsibilities. Responsibility for processing management and quality assurance should be assigned to different individuals, and who function independently.

2.5. Personnel in responsible positions should have adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of good practice.

2.6. Individual responsibilities should be clearly defined and their correct understanding by individuals should be assessed and recorded. Personnel signature lists should be available.

2.7. All personnel should receive initial and continued training appropriate to their specific tasks. Training programs should be in place and should ensure that personnel have relevant knowledge in Good Practice. Training records should be maintained.

2.8. Training should be provided for all personnel whose duties take them into preparation areas or into laboratories (including technical, maintenance and cleaning personnel).

2.9. There should be written policies and procedures to describe the approach to training, including a record of training that has taken place, its contents and its effectiveness.

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

2.11. The training programme should be reassessed for any critical change in environment, equipment or processes. Training needs should be identified, planned, delivered and documented appropriately for the maintenance of validated systems and equipment.
Only persons who are authorised by defined procedures and documented as such may be involved in the collection, testing, processing and distribution processes, including quality control and quality assurance.

There should be written safety and hygiene instructions in place, adapted to the activities to be carried out, and in compliance to relevant national law.

Visitors or untrained personnel should, preferably, not be taken into the processing and laboratory areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

It is the organisation’s responsibility to provide instructions on hygiene and health conditions that can be of relevance to the quality and safety of blood components (e.g., during collection) and to ensure that staff report relevant health problems. These procedures should be understood and followed in a strict way by all staff members whose duties take them into the processing and laboratory areas. Personnel should be instructed when and how to wash their hands.

Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the preparation of blood components. Medical examinations should be carried out when necessary to assure fitness for work and personal health. There should be instructions ensuring that health conditions that can be of relevance to the quality and safety of blood and blood components are reported by the personnel.

There should be a written policy outlining the requirements for wearing of protective garments in the different areas. The requirements should be appropriate to the activities to be carried out.

Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the testing, processing and storage areas should be prohibited. In general, any unhygienic practice within the preparation areas or in any other area where the blood or blood components might be adversely affected should be forbidden.

3. Premises

3.1. General

Premises including mobile sites should be located, constructed, adapted and maintained to suit the activities to be carried out. They should enable work to proceed in a logical sequence so as to minimize the risk of errors, and should allow for effective cleaning and maintenance in order to minimize the risk of contamination.

Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect (directly or indirectly) blood components during their processing and storage, or the accurate functioning of equipment.

Premises should be designed and equipped so as to afford protection against the entry of insects or other (non-service) animals.

Steps should be taken to prevent the entry of unauthorised people. Areas for laboratory testing, processing, storage and quality control should not be used as a right of way by personnel who do not work in them.

Facilities should permit ease of maintenance and cleaning. Open drains should be avoided.
3.1.6. Requirements for the temperature and humidity of the preparation areas should be defined according to the operations undertaken within them and taking into account the external environment.

3.1.7. Preparation areas should be suitably lit, particularly where visual checks are carried out.

3.1.8. Component sampling may be carried out within the processing area provided it does not carry any risk for other components.

3.2. Blood donor area

3.2.1. There should be an area for confidential personal interviews with, and assessment of, individuals to assess their eligibility to donate. This area should be separated from all processing areas.

3.2.2. Premises should satisfy requirements for the health and safety of both the staff (including those of mobile teams) and the donors concerned with due regard to relevant legislation or regulations.

3.3. Blood collection area

3.3.1. Blood collection should be carried out in an area intended for the safe withdrawal of blood from donors that is appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation. This area should be organised in such a way as to ensure the safety of both donors and personnel as well as to avoid errors in the collection procedure.

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

3.3.2.1. sufficient size to allow proper operation and ensure donor privacy;

3.3.2.2. safety for staff and donors;

3.3.2.3. the presence of ventilation, electrical and water supply, lighting, ancillary facilities;

3.3.2.4. reliable communication, interim blood storage and transport.

3.3.3. The arrangement of the collection room and procedures should ensure that blood is collected in a safe and clean environment to minimise the risk of errors and microbial contamination.

3.3.4. Consideration should be given to the arrangement of donor beds and the handling of bags, samples and labels.

3.4. Blood testing and processing areas

3.4.1. There should be a dedicated laboratory area for testing that is separate from the blood-donor and blood-component processing area, with access restricted to authorised personnel, and should be used only for the intended purpose.

3.4.2. Laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.4.3. Special provisions may be necessary to protect sensitive instruments from vibration, electrical interference, humidity and extremes of temperature.
3.5. **Storage area**

3.5.1. Storage areas should provide for appropriately secure and segregated storage of different categories of blood and blood components and materials, including quarantine and released materials as well as units of blood or blood components collected under special criteria (e.g., autologous donation). Access should be restricted to authorised persons.

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

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

3.5.4. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and blood components, including packaging materials, intermediate and finished components, and materials in quarantine, released, rejected, returned or recalled.

3.5.5. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within predefined temperature limits. Where special storage conditions are required (e.g., temperature, humidity) these should be provided, checked and monitored. An alarm system should alert users in a timely manner to any excursion outside predefined limits.

3.5.6. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage. The reception area should be separate from the storage area.

3.5.7. If quarantine status is ensured by storage in separate areas, these areas should be marked clearly and their access restricted to authorised personnel. Any system replacing the physical quarantine (e.g., computerised system) should provide equivalent security.

3.5.8. Segregated areas should be allocated and identified appropriately for storage of rejected, discarded, recalled or returned materials, or blood and blood components.

3.5.9. Printed packaging materials (including sets of labels, e.g., donation identifier or irradiation labels) should be stored safely and in a secure manner.

3.6. **Ancillary areas**

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

3.6.2. Facilities for changing clothes and for washing and toilet purposes should be readily accessible and appropriate for the number of users. Toilets should not directly open to preparation areas.

3.6.3. Maintenance workshops should, as far as possible, be separated from preparation areas. If parts and tools are stored in processing and laboratory areas, they should be kept in a location reserved for that use.

3.7. **Waste disposal area**

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

3.7.2. Special procedures should be defined for potentially contaminated waste disposal.
4. Equipment and materials

4.1. General requirements

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

4.1.2. Equipment should be selected to minimise any hazard to donors, personnel or blood components.

4.1.3. All validated processes should use qualified equipment. Qualification results should be documented. Regular maintenance and calibration should be carried out and documented according to established procedures. The maintenance status of each item of equipment should be available.

4.1.4. All critical equipment should have regular, planned maintenance, taking into consideration manufacturer’s instructions, to detect or prevent avoidable errors and keep the equipment in its optimum functional state. The maintenance intervals and actions should be determined for each item of equipment.

4.1.5. New and repaired equipment should meet qualification requirements when installed and should be authorised before use.

4.1.6. All modifications, enhancements or additions to validated systems and equipment should be managed through the change control procedure of the blood establishment. The effect of each change to the system or equipment, as well as its impact on quality and safety, should be determined to identify the extent of revalidation required.

4.1.7. Instructions for use, maintenance, servicing, cleaning and sanitation should be available.

4.1.8. Procedures should be available for each type of equipment that detail the action to be taken if malfunctions or failures occur.

4.1.9. Only reagents and materials from approved suppliers that meet the documented requirements and specifications should be used. Critical materials should be released by a person qualified to perform this task.

4.1.10. Manufacturers of sterile materials (e.g., blood bag systems, anticoagulant solutions) should provide a certificate of release for each batch. The blood establishment should define acceptance criteria for such certificates in writing, and should include at least the name of the material, manufacturer, compliance with relevant requirements (e.g., pharmacopoeias or regulations for medical devices) and confirmation that the materials are sterile and pyrogen-free.

4.1.11. Status of materials (quarantined, released, rejected) should be indicated clearly.

4.1.12. Materials and reagents should be stored under the conditions established by the manufacturer and in an orderly manner that permits segregation by batch and lot as well as stock rotation.

4.1.13. Storage and use of materials should follow the ‘first-expiring first-out’ principle (i.e. the material that expires first should be used first).

4.1.14. Inventory records should be retained for a period acceptable to and agreed with the Competent Authority.

4.1.15. Equipment and material inventory records should be kept as a means to build up a history for a processed component to facilitate recalls.

4.1.16. Repair and maintenance operations should not present any hazard to the donor, staff or quality of the blood and blood components.
4.1.17. Equipment should be designed or selected so that it can be thoroughly cleaned (and where necessary decontaminated). This should be performed according to detailed and written procedures. It should be stored only in a clean and dry condition.

4.1.18. Washing/cleaning solutions and equipment should be chosen and used so that they are not sources of contamination.

4.1.19. Equipment should be installed in such a way as to prevent any risk of error or of contamination.

4.1.20. Parts of equipment and materials that come into contact with blood and blood components should not react with, add to or absorb from the blood or blood component to such an extent that they affect the quality of the component and thus present any hazard.

4.1.21. Balances and measuring equipment of an appropriate range and precision should be available. Equipment for measuring, weighing, recording and control should be calibrated and checked at defined intervals using appropriate methods. Adequate records of such tests should be maintained, including the values obtained prior to any adjustment. Calibration reports should include the accuracy of any testing equipment and traceability to a national or international standard. The report and/or calibration certificate should be reviewed and signed to show acceptance of the document. Any failed calibrations will require mention of non-conformance to allow investigation of the potential impact.

4.1.22. Defective equipment should be labelled clearly as such and, if possible, removed from preparation areas.

4.2. Data processing systems

4.2.1. If computerised systems are used, software, hardware and back-up procedures should be checked regularly to ensure reliability, be validated before use, and be maintained in a validated state. Hardware and software should be protected against unauthorised use or unauthorised changes. The back-up procedure should prevent loss of or damage to data at expected and unexpected down-times or function failures.

4.2.2. Risk management should be applied throughout the life cycle of the computerised system, taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the selection of the suppliers and the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.

4.2.3. The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

4.2.4. An up-to-date listing of all relevant systems and their functionality in meeting the requirements of good practice should be available. For critical systems, an up-to-date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

4.2.5. The validation documentation and reports should cover the relevant steps of the life cycle. The user should be able to justify the standards, protocols, acceptance criteria, procedures and records based on their risk assessment.
For the validation of bespoke or customised computerised systems, there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life cycle stages of the system.

Evidence of appropriate test methods and test scenarios should be demonstrated. In particular, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.

If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.

Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimise the risks.

For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.

Systems should be properly maintained at all times. Documented maintenance plans for hardware and software should be developed and implemented.

Regular back-ups of all relevant data should be carried out with an appropriate frequency. Integrity and accuracy of back-up data and the ability to restore the data should be checked during validation and monitored periodically.

Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GPG-relevant changes and deletions (a system-generated ‘audit trail’). For change or deletion of GPG-relevant data, the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

Changes in computerised systems should be validated; applicable documentation should be revised and relevant personnel trained appropriately before any change is introduced into routine use. Computerised systems should be maintained in a validated state. This should include user testing to demonstrate that the system is correctly performing all specified functions both at initial installation and after any system modifications.

All necessary measures should be taken to ensure protection of data. These measures ensure that safeguards against unauthorised additions, deletions or modifications of data and transfer of information are in place to resolve data discrepancies and to prevent unauthorised disclosure of such information.

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

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

There should be a hierarchy of permitted user access to enter, amend, read or print data.
4.2.19. Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data, and the date and time.

4.2.20. Creation, change and cancellation of access authorisations should be recorded.

4.2.21. Electronic records may be signed electronically. Electronic signatures are expected to:

4.2.21.1. have the same impact as handwritten signatures within the boundaries of the company;

4.2.21.2. be permanently linked to their respective record;

4.2.21.3. include the time and date that they were applied.

4.2.22. For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g., a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and be appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.

4.2.23. Data should be archived. These data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g., computer equipment or programs), then the ability to retrieve the data should be ensured and tested.

4.2.24. Computer systems designed to control decisions related to inventories and release of blood components should prevent the release of all blood or blood components considered not acceptable for release. Mechanisms should be in place to prevent collection and release of any components from a future donation from a deferred donor.

4.3. Qualification and validation

4.3.1. General principles

4.3.1.1. Facilities and equipment need to be qualified prior to implementation. Systems, processes and tests should be validated, which involves wider consideration beyond the facilities and equipment used. In this document, however, the term ‘validation’ is used in a generic sense, encompassing both qualification and validation activities.

4.3.1.2. The principles of qualification and validation are applicable to the preparation, distribution and issuance of blood components. It is a requirement of good practice that blood establishments and hospital blood banks control the critical aspects of their operations throughout the life cycle of the blood components and the associated processes. Any planned changes to the facilities, equipment, utilities and processes should be formally documented and the impact on the quality of blood components should be validated.

4.3.1.3. A quality risk management approach, consisting of a systematic process for the assessment, control, communication and review of risks to quality across the life cycle of the blood component, should be applied. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.

4.3.1.4. Data supporting qualification and/or validation studies which were obtained from sources outside of the blood establishment own quality system may be used provided
that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.

4.3.2. Organising and planning for validation

4.3.2.1. All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, processes and products into consideration.

4.3.2.2. Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures and report as defined in the blood establishment quality system. There should be appropriate quality oversight over the whole validation life cycle.

4.3.2.3. The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

4.3.2.4. The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

4.3.2.4.1. qualification and validation policy;

4.3.2.4.2. the organisational structure, including roles and responsibilities for qualification and validation activities;

4.3.2.4.3. summary of the facilities, equipment, systems, processes on-site and their qualification and validation status;

4.3.2.4.4. change control and deviation management for qualification and validation;

4.3.2.4.5. guidance on developing acceptance criteria;

4.3.2.4.6. references to existing documents;

4.3.2.4.7. the qualification and validation strategy, including requalification, where applicable.

4.3.2.5. For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity. These should be linked and traceable.

4.3.2.6. A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the qualification and validation phase, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

4.3.2.7. Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

4.3.3. Documentation including VMP

4.3.3.1. Good documentation practices are important to support knowledge management throughout the product life cycle. Validation protocols should be prepared which specify how qualification and validation should be performed and which define the critical systems, attributes and parameters and the associated acceptance criteria.

4.3.3.2. All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the quality system.

4.3.3.3. Qualification documents may be combined together, where appropriate, e.g., installation qualification (IQ) and operational qualification (OQ).

4.3.3.4. Any significant changes to the approved protocol during execution, e.g., acceptance criteria, operating parameters, should be documented as a deviation and be scientifically justified.

4.3.3.5. The relationship and links between documents in complex validation projects should be established.
4.3.3.6. Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the blood establishment should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

4.3.3.7. Results which fail to meet the predefined acceptance criteria should be recorded as a deviation and fully investigated according to local procedures. Any implications for the validation should be discussed in the report.

4.3.3.8. The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

4.3.3.9. A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel, either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

4.3.4. Qualification stages for equipment, facilities and systems

4.3.4.1. Qualification activities should consider all stages from initial development of the user requirements specification (URS) through to the end of use of the equipment, facility or system. The main stages and some suggested criteria (although these depend on individual project circumstances and may be different) which could be included in each stage are indicated below.

4.3.4.2. User requirements specification (URS). The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any good practice risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

4.3.4.3. Design qualification (DQ). The next element of the validation of new facilities, systems or equipment is DQ. This involves demonstration and documentation of the compliance of the design with good practice (i.e. the design is suitable for the intended purpose). The requirements of the URS should be verified during the DQ.

4.3.4.4. Factory acceptance testing (FAT)/site acceptance testing (SAT). Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, by the vendor prior to delivery. Prior to installation, equipment should be confirmed to comply with the URS/functional specification at the vendor site, if applicable. Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on-site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation. FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

4.3.4.5. Installation qualification (IQ). IQ should be performed on new or modified facilities, systems and equipment. IQ should include, but is not limited to, the following:

4.3.4.5.1. installation of components, equipment, piping, services and instrumentation, which are checked against up-to-date engineering drawings and specifications;

4.3.4.5.2. verification of the correct installation against predefined criteria;
4.3.4.5.3. collection and collation of supplier operating and working instructions and maintenance requirements;
4.3.4.5.4. calibration requirements;
4.3.4.5.5. verification of construction materials.

4.3.4.6. Operational qualification (OQ). The completion of a successful OQ should allow finalisation of calibration, operating and cleaning procedures, operator training and preventive maintenance requirements. OQ normally follows IQ, but depending on the complexity of the equipment, it may be performed as a combined CQA (IOQ). OQ should include, but is not limited to, the following:

- tests that have been developed from knowledge of processes, systems and equipment to ensure the system is operating as designed;
- tests to confirm upper and lower operating limits, and/or ‘worst-case’ conditions.

Performance qualification (PQ). Although PQ is described as a separate activity, in some cases it may be appropriate to perform it in conjunction with OQ or process validation. PQ should follow successful completion of IQ and OQ. PQ should include, but is not limited to, the following:

- tests, using production materials, qualified substitutes or simulated blood components proven to have equivalent behaviour, under normal and worst-case operating conditions. The frequency of sampling used to confirm process control should be justified;
- tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

4.3.5. Requalification

4.3.5.1. Equipment, facilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

4.3.5.2. Where requalification is necessary and performed over a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

4.4. Process validation

4.4.1. General

4.4.1.1. The requirements and principles outlined in this section are applicable to the preparation, distribution and issuance of blood components. They cover the initial validation of new processes and subsequent validation of modified processes or site transfers for maintaining the validated state (ongoing process verification). It is implicit in this section that a robust product development process is in place to enable successful process validation.

4.4.1.2. Processes should be shown to be robust and ensure consistent blood component quality prior to their distribution and routine clinical use. Processes should undergo a prospective validation programme, wherever possible. Retrospective validation is no longer an acceptable approach.

4.4.1.3. Process validation of new blood components should cover all intended processes and sites of preparation. A scientific and risk-based validation approach could be justified for new blood components based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing statistical process
control. The design assumes that the validation performed is representative for all process or product settings.

4.4.1.4. For validation of processes for preparation of blood components that are transferred from one site to another or within the same site, the number of blood components used for process validation could be reduced based on existing process knowledge, including the content of the previous validation that should be available. The same approach may be used for different blood bag sizes or volumes, if justified.

4.4.1.5. Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable blood component quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

4.4.1.6. The facilities, systems and equipment to be used should be qualified before use and analytical testing methods should be validated. Facilities, systems, equipment and processes should be periodically evaluated to ensure that they are still operating appropriately.

4.4.1.7. For all blood components, process knowledge from development studies or other sources should be accessible to the blood establishment, unless otherwise justified, and be the basis for validation activities.

4.4.1.8. During the validation of blood component preparation, a variety of personnel may be involved. It is expected that personnel routinely carrying out the activities are involved in the validation process.

4.4.1.9. The suppliers of critical materials should be qualified prior to their use for the preparation of blood components during process validation; otherwise, a justification based on the application of quality risk management principles should be documented.

4.4.1.10. Where blood components prepared during process validation are released for clinical use, this should be predefined. The conditions under which they are produced should fully comply with the requirements of good practice, with the validation acceptance criteria and with any continuous process verification criteria (if used).

4.4.2. Concurrent validation

4.4.2.1. In exceptional circumstances – justified on the basis of significant patient benefit, where there is a strong benefit-risk ratio for the patient and with systematic control of each blood component unit for their conformity to regulatory requirements – it may be acceptable to execute the validation protocol concurrently with distribution of the units produced during validations and not to complete a validation programme before routine production. However, the decision to carry out concurrent validation should be documented in the VMP for visibility and approved by authorised personnel.

4.4.2.2. Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given blood component meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Responsible Person prior to release for clinical use.

4.4.3. Prospective validation

4.4.3.1. Using this approach, a number of blood components may be prepared under the proposed new conditions. The number of process runs carried out, the number of samples taken and the number of observations made should be based on quality risk management principles and be sufficient to allow the normal range of variation and trends to be established and to provide sufficient data for evaluation. Each blood
establishment should determine and justify the number of blood component units necessary to demonstrate that the process is capable of consistently delivering quality blood components.

4.4.3.2. Preparation of blood components during the validation phase should reflect the numbers intended to be produced under normal production circumstances.

4.4.3.3. A process validation protocol should be prepared which defines the CPPs, CQAs and the associated acceptance criteria, which should be based on development data or documented process knowledge.

4.4.3.4. Process validation protocols should include, but are not limited to the following:

4.4.3.4.1. short description of the process;
4.4.3.4.2. functions and responsibilities;
4.4.3.4.3. summary of the CQAs to be investigated;
4.4.3.4.4. summary of CPPs and their associated limits;
4.4.3.4.5. summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
4.4.3.4.6. list of the equipment/facilities/personnel to be used (including measuring/monitoring/recording equipment) together with the calibration status;
4.4.3.4.7. list of analytical methods and method validation, as appropriate;
4.4.3.4.8. proposed in-process controls with acceptance criteria and the reason(s) for selecting each in-process control;
4.4.3.4.9. additional testing to be carried out with acceptance criteria;
4.4.3.4.10. sampling plan and the rationale behind it;
4.4.3.4.11. methods for recording and evaluating results;
4.4.3.4.12. process for release and certification of units (if applicable);
4.4.3.4.13. conclusion.

4.4.4. Ongoing process verification and maintenance of the validated state

4.4.4.1. Ongoing process verification should provide documented evidence, using statistical process control, that the process remains in a state of control during routine preparation.

4.4.4.2. All critical processes should be constantly monitored and periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that the process meets the prescribed requirements may be deemed acceptable in place of a full revalidation.

4.4.4.3. Blood establishments should monitor blood component quality using statistical process control to ensure that a state of control is maintained throughout the blood component life cycle with the relevant process trends evaluated.

4.4.4.4. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product life cycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

4.4.4.5. Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support
any conclusions with regard to the variability and capability of a given process and to
ensure a state of control.

4.4.4.6. The following items are essential to maintain a validated state:

4.4.4.6.1. calibration and monitoring;
4.4.4.6.2. preventive maintenance;
4.4.4.6.3. training and competency;
4.4.4.6.4. supplier requalification;
4.4.4.6.5. periodic review;
4.4.4.6.6. performance monitoring;
4.4.4.6.7. system retirement.

4.4.4.7. Maintenance of the validated status of the blood components should be documented in the product quality review. Incremental changes over time should also be considered and the need for any additional actions, e.g., enhanced sampling, should be assessed.

4.4.4.8. Operational change control, document control and quality control procedures support the maintenance of the validated state.

4.5. Validation of test methods

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

4.5.2. Where microbial testing of blood components is carried out, the method should be validated taking into consideration the eventual interference of residues with the analysis (e.g., antibiotics for the recovery of microorganisms).

4.6. Control of equipment and materials

4.6.1. General principles

4.6.1.1. Documented systems for purchasing equipment and materials should be available. These should identify the specific requirements for establishing and reviewing contracts for the supply of both equipment and materials.

4.6.1.2. The contracting process should include:

4.6.1.2.1. checks prior to awarding the contract to help ensure suppliers meet the organisation’s needs;
4.6.1.2.2. appropriate checks on received goods to confirm they meet specifications;
4.6.1.2.3. the requirement for manufacturers to provide a certificate of analysis for critical material;
4.6.1.2.4. checks to ensure that goods in use continue to meet specifications;
4.6.1.2.5. regular contact with suppliers to help understand and resolve problems;
4.6.1.2.6. performance of regular audits.

4.6.1.3. Qualification or requalification of equipment should occur in the following situations:

4.6.1.3.1. upon commissioning of new equipment, which should include design, installation, operational and performance qualifications, and full validation data from the manufacturer;
4.6.1.3.2. after any relocation, repairs or adjustments that might potentially alter equipment functioning;

4.6.1.3.3. if ever a doubt arises that the equipment is not functioning appropriately.

4.6.1.4. Where a fault or non-conformance with the potential to impact the quality, safety or efficacy of any blood components is identified, a risk assessment should be carried out to ascertain the impact on components already distributed or in storage that may have been affected by the fault or non-conformance. Decisions and actions should be taken in accordance with the outcome of the risk assessment and should be documented.

4.6.2. Calibration and monitoring of equipment

4.6.2.1. It is necessary to establish a mechanism to ensure the adequacy of the calibration and monitoring programmes, and that qualified personnel are available for their implementation. A calibration and monitoring plan should be used to define the requirements for establishing and implementing a calibration programme that includes the frequency of monitoring.

4.6.2.2. Trending and analyses of calibration and monitoring results should be a continuous process. Intervals of calibration and monitoring should be determined for each item of equipment to achieve and maintain a desired level of accuracy and quality. The calibration and monitoring procedure should be based on a recognised national or international standard. The calibration status of all equipment that requires calibration should be readily available.

4.6.2.3. To ensure appropriate performance of a system or equipment, a monitoring plan should be developed and implemented. The plan should take into account the criticality of the system or equipment, and should outline monitoring, user-notification and problem-resolution mechanisms. If an unusual event is observed, personnel should follow the standard response described in the monitoring plan. The standard response should involve notifying affected personnel and, possibly, initiation of a resolution response to the problem and risk assessment of the affected blood components. Depending on the severity of the problem and the criticality of the system or equipment, a back-up plan may need to be implemented to keep the process or system operating.

4.6.2.4. In addition to testing that evaluates the suitability of the implemented changes, sufficient validation should be conducted on the entire system to demonstrate that portions of the system not involved in the change are not adversely impacted.

4.6.2.5. The ability of a supplier to maintain its activities relating to a system or equipment should be requalified on a regular basis, notably to anticipate weaknesses in services or to manage changes in the system, equipment or supplier. The periodicity and detail of the requalification process depends on the level of risk of using the system or equipment, and should be planned for each supplier.

4.6.2.6. A periodic review process should be established to ensure that documentation for the system or equipment is complete, current and accurate. A report of the review process should be produced. When deviations or problems are found, actions should be identified, prioritised, planned and implemented.
5. **Documentation**

5.1. **General principles**

5.1.1. Good documentation constitutes an essential part of the quality system and is key to operating in compliance with good practice requirements. Various types of documents and media used should be defined fully in the quality management system of the organisation.

5.1.2. Documentation may exist in various forms: 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.

5.1.3. There are two primary types of documentation used to manage and record good practice compliance: 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.

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

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

5.2.2. Specifications describe in detail the requirements to which the blood and blood components or materials used or obtained during preparation and distribution should conform. They serve as a basis for quality evaluation (specifications set out in the Blood component monographs contained in the **EDQM Guide to the preparation, use and quality assurance of blood components** may be used).

5.2.2.2. Testing instructions detail all the starting materials, equipment and computerised 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.

5.2.2.3. Procedures (otherwise known as standard operating procedures or SOPs) give directions for performing certain operations.

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

5.2.2.5. Technical agreements are agreed between contract givers and acceptors for outsourced activities.

5.2.3. Records/reports

5.2.3.1. Records 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 are used to generate other records. For electronic records, designated 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’.

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

5.2.3.3. Reports document the carrying out of particular exercises, projects or investigations, together with results, conclusions and recommendations.

5.3. Generation and control of documentation

5.3.1. 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 homogeneous systems.

5.3.2. A document control system, defined in a written procedure, should 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.

5.3.3. 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.

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

5.3.5. 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. SOPs, work instructions and methods should be written in an imperative mandatory style.

5.3.6. Documents within the quality management system should be regularly reviewed and kept up to date.

5.3.7. All significant changes to documents should be acted upon promptly, and should be reviewed, dated and signed by a person authorised to undertake this task.

5.3.8. Instructional documents should not be handwritten; however, where documents require the entry of data, sufficient space should be provided for such entries.

5.4. Good documentation practices

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

5.4.2. 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, testing, processing and distribution of blood and blood components are traceable.
5.4.3. The record system should ensure continuous documentation of the procedures performed from the blood donor to the recipient. That is, each significant step should 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.

5.4.4. 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.

5.5. Retention of documents

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

5.5.2. Specific retention requirements for certain documentation apply.

5.5.2.1. Records should be retained for a period according to local, national or other mandatory requirements, as appropriate.

5.5.2.2. Traceability data (that allow tracing from donor to recipient and vice versa) should be retained for 30 years if so required by local, national or regional regulatory requirements, as appropriate.

5.5.2.3. Documentation regarding investigations into serious adverse events and serious adverse reactions should be retained for a minimum of 15 years, if so required by local, national or regional regulatory requirements, as appropriate.

5.5.2.4. Quality system documentation and associated records should be retained for a minimum of 10 years.

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

5.6. Specifications

5.6.1. There should be appropriately authorised and dated specifications for starting and packaging materials, as well as finished blood and blood components.

5.6.2. Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

5.6.2.1. a description of the materials, including:

5.6.2.1.1. the designated name and the internal code reference;

5.6.2.1.2. the approved suppliers and, if reasonable, the original producer of the material;

5.6.2.1.3. a sample of printed materials;

5.6.2.2. directions for sampling and testing;

5.6.2.3. qualitative and quantitative requirements with acceptance limits;

5.6.2.4. storage conditions and precautions;

5.6.2.5. the maximum period of storage before re-examination.

5.6.3. Specifications for in-process and finished components should be available. Components should be labelled in accordance with legal requirements.
5.7. Preparation instructions

1474 5.7.1. Approved, written instructions for preparation should exist for each type of
1475 component that is produced. These should include:

1476 5.7.1.1. a process flow for each stage in the preparation of the component, including where it
1477 is undertaken and any critical equipment used;

1478 5.7.1.2. methods (or reference to the methods) to be used for starting up and maintaining
1479 critical equipment (e.g., cleaning, assembly, calibration);

1480 5.7.1.3. the requirement to check that the equipment and work station are clear of previous
1481 blood components, documents or materials not required for the planned process, and
1482 that equipment is clean and suitable for use;

1483 5.7.1.4. detailed stepwise processing instructions (e.g., checks on materials, pre-treatments,
1484 sequence for adding materials, and critical process parameters such as time and
1485 temperature);

1486 5.7.1.5. the instructions for any in-process controls with their limits;

1487 5.7.1.6. requirements for storage of the components and any critical materials and
1488 consumables;

1489 5.7.1.7. any special precautions to be observed.

5.8. Preparation records

1492 5.8.1. At all stages of the preparation, labelling should identify the individual components
1493 and their nature clearly. The label on an intermediate component should always allow
1494 the stage of processing to be determined and should always include:

1495 5.8.1.1. the name of the component;

1496 5.8.1.2. the unique numeric or alpha-numeric donation identification;

1497 5.8.1.3. the name of the producing blood establishment.

1498 5.8.2. Each unit is considered to be a unique batch, but preparation records should provide
1499 sufficient information to build the history and traceability of a prepared component. Usually this information is captured in the computerised systems of the blood
1500 establishment. In general, the blood establishment should have access to the following
1501 processing records for each unit:

1502 5.8.2.1. the name and unique identifier of the component;

1503 5.8.2.2. the dates and times of commencement of significant intermediate stages and of
1504 completion of processing:

1505 5.8.2.3. the identification (e.g., initials) of the operator(s) who performed each critical step of
1506 the process (including the process controls) and, where appropriate, the name of any
1507 person who verified such steps;

1508 5.8.2.4. the batch number of any relevant consumables and/or analytical control number of
1509 each consumable;

1510 5.8.2.5. a record of the in-process controls and identity of the person(s) carrying them out, as
1511 well as the results obtained;

1512 5.8.2.6. the results of testing undertaken on the donation and/or the component (excluding
1513 quality monitoring);

1514 5.8.2.7. notes on any deviation, including details of the procedures with signed authorisation;

1515 5.8.2.8. information on the processing of non-standard components with signed authorisation.
5.9. Procedures and records

5.9.1. Receipt

There should be written procedures and records for the receipt of each delivery of materials and reagents that can impact on the quality and safety of blood and blood components. Records of the receipts should include:

5.9.1.1. the name of the material on the delivery note and the containers;
5.9.1.2. the ‘in-house’ code (if any) of the material;
5.9.1.3. the date of receipt;
5.9.1.4. the names of the supplier and manufacturer;
5.9.1.5. the batch or reference number of the manufacturer;
5.9.1.6. the total quantity and number of items received;
5.9.1.7. the batch number assigned after receipt (as applicable);
5.9.1.8. the name/ID of the person who received the shipment;
5.9.1.9. any relevant comments.

5.9.1.2. There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

5.10. Sampling

5.10.1. There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

5.10.2. There should be written procedures for the testing of materials and blood components at different stages of processing, describing the methods and equipment to be used. The tests performed should be recorded.

5.11. Other

5.11.1. Written criteria and procedures for release and rejection should be available.

5.11.2. Records should be maintained of the distribution of blood components to assure traceability of any unit and to facilitate recall, if necessary.

5.11.3. There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached (if appropriate) for the following issues:

5.11.3.1. validation and qualification of processes, equipment and systems;
5.11.3.2. equipment assembly and calibration;
5.11.3.3. maintenance, cleaning and sanitation;
5.11.3.4. personnel matters, including signature lists, training in good practice and technical matters, clothing and hygiene, and verification of the effectiveness of training;
5.11.3.5. environmental monitoring;
5.11.3.6. pest control;
5.11.3.7. complaints;
5.11.3.8. recalls;
5.11.3.9. returns;
5.11.3.10. change control;
5.11.3.11. investigations of deviations and non-conformances;
5.11.3.12. audits of compliance with internal quality/good practice;
5.11.3.13. summaries of records, where appropriate (e.g., review of the quality of blood components);
5.11.3.14. supplier qualification and audits.

5.11.4. Records should be kept for major or critical analytical testing, processing equipment and areas where blood components have been processed. They should be used to record in chronological order (as appropriate) any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations (including the dates and identity of people who carried out these operations).

6. Blood collection, testing and processing

6.1. Donor eligibility

6.1.1. Procedures for safe identification of donors, suitability interview, and eligibility assessment should be implemented and maintained. They should take place immediately before each donation and comply with the legal requirements.

6.1.2. There should be secure and unique identification, as well as recording of the contact details, of donors. Robust mechanisms should link donors to each of their donations.

6.1.3. Upon arrival at the blood establishment, donors should provide evidence of their identity. All donors should undergo a systematic screening process to assess their suitability.

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

6.1.5. The selection process should include assessment of each donor carried out by a suitably qualified individual who has been trained to use accepted guidelines and who works under the responsibility of a physician. This assessment involves an interview, a questionnaire and further direct questions, if necessary.

6.1.6. The questionnaire should be designed to elicit information relevant to the medical history, general health and other known or probable risk factors related to the donor. It should be designed to be understandable by the donor and given to all donors each time they attend. On completion, it should be signed by the donor.

6.1.7. Relevant acceptance/deferral criteria should be in place at the blood establishment to control acceptance and deferral of donors.

6.1.8. The donor interview should be conducted in such a way as to ensure confidentiality.

6.1.9. The confidential interview should be conducted by staff specifically trained to ask further direct questions to supplement the information in the questionnaire. The person who carries out the assessment should certify that the relevant questions have been asked.

6.1.10. Records of suitability and final assessment of donors should be signed by a qualified healthcare professional.

6.1.11. Records should be kept for each activity associated with the selection of the donor. The record should reflect the decision to accept the donor by taking into consideration the medical history, history of deferral, donor interview and results of the physical
examination. Rejection of a donor and the reason for deferral should be recorded. A system should be in place to ensure that the donor is prevented from making future donations during a permanent or temporary deferral period.

6.1.12. Donors should be instructed to inform the blood establishment about any relevant information that was not previously disclosed or if signs or symptoms occur after a donation. This scenario indicates that the donation may have been infectious or that any other information not disclosed during the health screening may render prior donations unsuitable for transfusion.

6.1.13. Procedures should be in place to ensure that any abnormal findings arising from the donor selection process are properly reviewed by a qualified healthcare professional and that appropriate action is taken.

6.2. Collection of blood and blood components

6.2.1. The procedure for blood collection should be designed to ensure that the identity of the donor is verified and recorded securely, and that the link between the donor and blood, blood components and blood samples is established clearly.

6.2.2. Donor identity should be confirmed before each critical step in the process but, at the very least, before donor selection and immediately prior to venepuncture.

6.2.3. A system of unique donation numbers should be used to identify each donor and the related donation and all of its associated components, samples and records, as well as to link each one to each of the others.

6.2.4. 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.

6.2.5. Systems of sterile blood bags used for the collection of blood and blood components and their processing should be CE-marked or comply with equivalent standards if the blood and blood components are collected in another jurisdiction. The batch number of the bag should be traceable for each blood component.

6.2.6. 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.

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

6.2.8. The arrangement of the blood collection should ensure that blood is collected in a safe environment. Consideration should be given to the arrangement of donor beds and the handling of donations, samples and labels. Blood collection procedures should be designed to minimise errors and avoid any risk of microbial contamination of the donation as well as mix-up of samples.

6.2.8.1. Sterile blood collection and processing systems should be used for all blood components. Collection systems should be used in accordance with manufacturer’s instructions.

6.2.8.2. Before venepuncture, a check should be made to ensure that the collection system to be used is not damaged or contaminated, and that it is appropriate for the intended collection. Abnormal moisture or discoloration could suggest a defect.

6.2.8.3. Appropriate procedures for hand disinfection and personal hygiene should be in place, and should be performed by personnel before each donation.
6.2.8.4. The skin at the venepuncture site should be free from lesions, including eczema.

6.2.8.5. The venepuncture site should be prepared using a defined and validated disinfection procedure. The antiseptic solution should be allowed to dry completely before venepuncture. The prepared area should not be touched with fingers before needle insertion.

6.2.8.6. The effectiveness of the disinfection procedure should be monitored and corrective action taken where it is indicated to be defective.

6.2.8.7. The expiry date of the disinfectant should be checked. The date of manufacture and the date of opening of in-house disinfectants should be stated on their labels.

6.2.8.8. The blood container should be checked after donation for any defect. The integral blood bag collection tubing should be sealed off at the end as close as possible to the blood bag.

6.2.8.9. SOPs should be in place describing the actions to be taken following an unsuccessful donation. These should specify how to handle already-labelled material and the circumstances under which a repeat venepuncture might be possible.

6.2.9. Laboratory samples should be taken at the time of donation and be appropriately stored prior to testing. As specified by the NRAs, an aliquot of the original testing sample should be retained from each donation and stored for a defined time that would permit retesting if indicated.

6.2.10. The procedure used for the labelling of records, blood bags, and laboratory samples with donation numbers should be designed to avoid any risk of identification error and mix-up.

6.2.11. After blood collection, blood bags should be handled in a way that maintains the quality of the blood and at a storage temperature and transport temperature appropriate to the requirements for further processing.

6.2.12. Blood and blood components should be placed in controlled and validated conditions as soon as possible after venepuncture. Donations and samples should be transported to the processing site in accordance with procedures that ensure a constant approved temperature and secure confinement. 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 transportation of blood to the processing site.

6.2.13. If a deviation occurs, its investigation and the defined CAPAs should be approved in writing by a competent person.

6.2.14. 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.

6.2.15. There should 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.

6.3. Laboratory testing

6.3.1. All blood donations should be tested to ensure that they meet specifications and to ensure a high level of safety for the recipient.

6.3.2. All laboratory testing procedures should be validated before use.
6.3.3. In addition to the validation of the test system by the manufacturer, an on-site verification of the test system in the laboratory is required prior to its use in routine testing. This validation should demonstrate that:

6.3.3.1. the performance specifications of the system established by the kit manufacturer are met by the laboratory;

6.3.3.2. laboratory personnel are thoroughly instructed, trained and competent to operate the test system.

6.3.4. All donation testing activities, handling of donor specimens, sampling, analysis and data processing should be undertaken independently of diagnostic testing of patients.

6.3.5. Each step of the handling and processing of samples should be described, as should the conditions of pre-analytical treatment of specimens (e.g., centrifugation), storage and transportation (duration, temperature, type of container, storage after testing).

6.3.6. Upon receipt of samples at the laboratory, positive identification of the samples received against those expected should be carried out.

6.3.7. There should be data confirming the suitability of any laboratory reagents used in testing of donor samples and blood-component samples.

6.3.8. Testing of blood components should be carried out in accordance with the recommendations of the manufacturers of reagents and test kits (unless an alternative method has been validated before their use) before release of the blood component.

6.3.9. Pre-acceptance testing should be performed on samples before purchasing batches of commercial reagents. Prospective purchasers should require potential suppliers to provide them with a certificate of analysis or evidence that individual lots meet defined acceptance criteria for the intended purpose. Each lot of reagent should be qualified by the purchaser to demonstrate suitability for its intended purpose within the system used for testing.

6.3.10. There should be a reliable process in place for transcribing, collating and interpreting results.

6.3.11. The quality of the laboratory testing should be assessed regularly by participation in a formal system of proficiency testing, such as an external quality-assurance programme.

6.4. Screening for infectious markers

6.4.1. Testing of donations for infectious agents is a key factor in ensuring that the risk of transmission of infectious agents is minimised and that blood components are suitable for their intended purpose.

6.4.2. Each donation should be tested in conformity with legal requirements. As a minimum blood donors should be tested at each donation for antibodies to HIV-1/HIV-2, for antibodies to HCV, and for HBsAg.(6)

6.4.3. Additional testing for other agents or markers may be required depending on the type of product, taking into account the epidemiological situation in any given region or country and the individual risk of transmitting infectious agents, in accordance with national legal requirements, where applicable.

6.4.4. Serological testing should be performed on samples transferred directly into the analyser from the original sample tube or aliquoted in a fully automated environment. Secondary aliquot samples may be used for nucleic acid amplification technique (NAT) testing of mini-pools of individual samples.
6.4.5. If NAT testing is performed by assembling various samples in mini-pools, a thoroughly validated system of labelling/identification of samples, a validated strategy and pooling process, and a validated algorithm to reassign pool results to individual donations should be in place.

6.4.6. There should be clearly defined procedures to resolve discrepant results.

6.4.7. Where blood and blood components have had a single reactive screening test, the original sample should be retested in duplicate according to the Competent Authority requirements. Blood and blood components that have a repeatedly reactive result in a serological screening test for infection with the viruses HIV-1/2, HCV or HBV should be excluded from therapeutic use. They should be labelled as reactive and should be stored separately in a dedicated environment or destroyed.

6.4.8. Appropriate confirmatory testing should take place. In the case of confirmed positive results, appropriate donor management should take place, including the provision of information to the donor and follow-up procedures.

6.4.9. Screening algorithms should be defined precisely in writing (i.e., SOPs) to deal with initially reactive specimens, and to resolve discrepancies in results after retesting.

6.5. Blood group serological testing of donors and donations

6.5.1. Blood group serology testing should include procedures for testing specific groups of donors (e.g., first-time donors, donors with a history of transfusion).

6.5.2. Each donation should 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. This should not normally apply to plasma for fractionation.

6.5.3. ABO and RhD blood groups should be verified on each subsequent donation.

6.5.4. Comparison should be made with the historically determined blood group. If a discrepancy is found, the applicable blood components should not be released until the discrepancy has unequivocally been resolved.

6.5.5. Donors with a history of transfusions or pregnancy since their last donation should be tested for clinically significant irregular red cell antibodies. If clinically significant red cell antibodies are detected, if applicable, the blood or blood component should be labelled accordingly.

6.5.6. Only test reagents that have been licensed or evaluated and considered to be suitable by a responsible national authority/competent authority should be used. In the EU, these reagents are considered as in vitro diagnostic devices and should be CE-marked.

6.5.7. Quality control procedures should be implemented for the equipment, reagents and techniques used for ABO and RhD blood grouping and other blood group antigen typing as well as detection and identification of alloantibodies. The frequency of the control is dependent on the method used.

6.6. Processing and validation

6.6.1. All equipment and technical devices should be used in accordance with validated procedures.

6.6.2. The processing of blood components should be carried out using appropriate and validated procedures, including measures to avoid the risk of contamination and microbial growth in the prepared blood components. Depending on the type of processing and based on a risk assessment, the microbial contamination load on critical
equipment, surfaces and the environment of the preparation areas should be monitored.

6.6.3. 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 used in an environment specifically designed to minimise the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures and the premises used should preferably be a grade A environment with a grade B background. A less stringent background may be acceptable if combined with additional safety measures such as preparing the blood component just in time for transfusion as predefined in the specifications, or immediately after preparation applying storage conditions which are unfavourable to microbial growth.

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

6.6.5. Sterile connecting devices should 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 should be checked for satisfactory alignment and its integrity should be confirmed.

6.7. Labelling

6.7.1. At all stages, all containers should be labelled with relevant information on their identity. In the absence of a validated computerised system for status control, the labelling should clearly distinguish released from non-released units of blood and blood components.

6.7.2. The type of label to be used, as well as the labelling methodology, should be defined and established in written SOPs.

6.7.3. Labels applied to containers, equipment or premises should be clear, unambiguous and in the agreed format of the blood establishment.

6.7.4. Labelling system for collected blood, intermediate and finished blood components, and samples should unmistakably identify the type of content, and comply with the labelling and traceability legal requirements.

6.7.5. The label for a finished blood component should comply with the local, national or regional regulatory requirements and contain at least the following information:

6.7.5.1. the unique donation number; there should be traceability through the use of this number to the donor and all records of the processing steps to the final product

6.7.5.2. the product name;

6.7.5.3. the required storage conditions;

6.7.5.4. the expiry date and, where appropriate, time;

6.7.5.5. the date of collection of the donation(s) from which the blood component was prepared and/or the production date and time (where appropriate);

6.7.5.6. the ABO and RhD blood group (where appropriate); and

6.7.5.7. the name or other identification of the component preparation site

6.7.6. Blood establishments responsible for the preparation of blood components should provide clinical users of blood components with information on their use, composition, and any special conditions that do not appear on the component label.
6.7. For autologous blood and blood components, the label should also comply with additional requirements for autologous donations and should contain also the name and unique identification of the patient as well as the statement “Autologous Donation”.

6.8. Release of blood and blood components

6.8.1. There should be a safe and secure system to prevent any single blood sample and blood component from being released before all mandatory requirements have been fulfilled. Each blood establishment should be able to demonstrate that each blood or blood component has been formally approved for release by an authorised person. Records should demonstrate that before a blood component has been released, all current declaration forms, relevant medical records, and test results have met all acceptance criteria. If a computerised system is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.

6.8.2. There should be SOPs that detail the actions and criteria that determine whether the blood or blood component can be released. The release criteria and specifications of blood components should be defined, validated, documented and approved.

6.8.3. There should be a defined procedure for exceptional release of non-standard blood and blood components under a planned non-conformance system. The decision to allow such release should be documented clearly and traceability should be ensured.

6.8.4. Before release, blood and blood components should be kept administratively and physically segregated from released blood and blood components. In the absence of a validated computerised system for status control, the label of a unit of blood or blood component should identify the release status.

6.8.5. 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.

6.8.6. In the event that the final blood component fails to be released due to a confirmed positive test result for infection for an agent, a check should be made to ensure that other components from the same donation and components prepared from previous donations given by the donor have been identified. An immediate update should be made to the donor record.

6.8.7. In the event that a final component fails release due to a potential impact on patient safety, the donor record should be immediately updated to ensure, where appropriate, that the donor(s) cannot make a further donation.

6.9. Quality monitoring and control

6.9.1. Quality monitoring

6.9.1.1. Acceptance criteria should be based on a defined specification for each blood donation and blood component (specifications set out in Chapter 5, Blood component monographs contained in this Guide may be used).

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

6.9.2. Quality control

6.9.2.1. All quality control procedures should be validated before use.
6.9.2.2. Results of quality control testing should be evaluated continuously and steps taken to correct defective procedures or equipment.

6.9.2.3. Standard procedures for the quality control of blood components should be in place. The suitability of each analytical method to provide the intended information should be validated.

6.9.2.4. Quality control of blood and blood components should be carried out according to a sampling plan designed to provide the intended information.

6.9.2.5. Testing should be done in accordance with the instructions recommended by the manufacturer of the reagents and/or test kits.

6.9.2.6. The performance of the testing procedures should be regularly assessed by participation in a formal system of proficiency testing.

6.9.2.7. Records of quality control procedures should include identification of the person(s) undertaking the tests or procedures. Any corrective action taken should also be recorded. If corrections in records are necessary, the original recording should not be obliterated, but should remain legible.

7. Storage and distribution

7.1. The Quality System of the blood establishment should ensure that, for blood and blood components intended for the manufacture of medicinal products, the requirements for storage and distribution should comply with legal and technical requirements.

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

7.3. Storage conditions should be controlled, monitored and checked. Appropriate alarms should be present and checked regularly; all checks should be recorded. Appropriate actions on alarms should be defined.

7.4. 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.

7.5. Before distribution, blood components should be visually inspected.

7.6. Autologous blood and blood components, as well as blood components collected and prepared for specific purposes, should be stored separately.

7.7. Appropriate records of inventory and distribution should be kept.

7.8. Records should be kept of the distribution of blood components between blood establishments, between blood establishments and hospital blood banks. 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 or consignee.

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

7.10. Verification of transportation

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

7.10.2. It is recognised 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 transport.

7.10.3. A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g., delays during transportation, failure of cooling and/or monitoring devices, blood component susceptibility and any other relevant factors.

7.10.4. Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the blood component may be subjected should be performed, unless otherwise justified.

7.11. Return of blood and blood components into inventories for subsequent reissue should be allowed only if all requirements and procedures relating to quality as laid down by the blood establishment to ensure the integrity of blood components are fulfilled.

7.12. Blood components should not be returned to the blood establishment for subsequent distribution unless there is a procedure for the return of blood components that is regulated by a contract, and if there is, documented evidence for each returned blood component that the agreed storage conditions have been met. Before subsequent distribution, records should identify that the blood component has been inspected before reissue.

8. Outsourced activity management

8.1. General principles

8.1.1. Tasks that are performed externally should be defined in a specific written contract.

8.1.2. 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. 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.

8.1.3. 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.

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

8.1.5. 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.

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

8.2. The contract giver

8.2.1. 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.
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. 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.

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 authorised person.

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

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

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. 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.

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

A contract should be drawn up between the contract giver and the contract acceptor that specifies their respective responsibilities relating to the contracted operations. All arrangements for blood collection, testing and processing should be in compliance with the requirements of good practice and regulatory requirements and agreed by both parties.

The contract should specify the procedure, including the necessary requirements to be provided by the contract acceptor, by which the Responsible Person or other authorised 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.

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

2017  8.4.5. The contract should permit the contract giver to audit the facilities of the contract acceptor.

2019  8.4.6. 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.
Part B: Further guidance for interpretation and implementation of GPG

1. Quality management

1.1. General requirements

Each blood establishment should develop and maintain a Quality System that is based on Good Manufacturing Practices. Attainment of this quality objective is the responsibility of senior management. It requires the participation and commitment both of staff in all departments and at all levels within the organisation. Quality should be recognised as being the responsibility of all persons involved in the processes of the blood establishment. The basic concepts of quality management, good practice and quality risk management are interrelated and they are described in this document in order to emphasise their relationships and fundamental importance to the preparation of blood and blood components. The requirements for implementing a quality system also apply to hospital blood banks.

When blood and blood components are imported from another country, the importing country should have regulations in place that ensure that the imported products were collected and manufactured in compliance with equivalent requirements. While an import of blood components for transfusion is a relatively rare case, more important could this question be with regard to the import of plasma to be further manufactured. Reference is made to the WHO document on Improving access to safe blood products through local production and technology transfer in blood establishment. (7)

It is clarified in the document that some basic concepts of quality management, good practice and quality risk management are partially overlapping and cannot strictly be separated.

A product quality review is one of the instruments for surveying the overall quality status of a blood component and its preparation processes. Such a review is done annually and should include a review of various elements of the quality system, as well as materials used and the status of the facility and equipment. This should help the blood establishment to learn from the experience of preparing the products as part of the continuous improvement.

1.2. Quality risk management

Introducing the concept of quality risk management has largely contributed to facilitate the implementation of Good Manufacturing Practice in the area of pharmaceutical products. The same concept can be applied also to blood establishments. Using quality risk management does however not mean, that it is used to ignore or overrule the requirements of good practice standards. It however facilitates to take appropriate measures in order to mitigate the identified risks and thereby better controlling possible risk situations that might have an impact on the quality and safety of a product. In newer editions of internationals QRM guidelines, the term risks is sometimes going to be replaced by the term harm.

In the context of quality risk management, the following definitions are used:

- Quality risk management: a systematic process for the assessment, control, communication and review of risks to the quality and safety of the product across its lifecycle.
- Hazard: the potential source of harm.
- Risk: the combination of the probability of occurrence of harm and the severity of that harm.
- Severity: A measure of the possible consequences of a hazard.
• Stakeholders: Any individual, group or organization that can affect, be affected by a risk.

Quality risk management activities are usually undertaken by interdisciplinary teams, include experts from the appropriate areas in addition to individuals who are knowledgeable about the quality risk management process. The personnel appointed should be able to:

- Conduct a risk analysis;
- Identify and analyze potential risks;
- Evaluate risks and determine which ones should be controlled and which ones can be accepted;
- Recommend and implement adequate risk control measures;
- Devise procedures for risk review, monitoring and verification;
- Consider the impact of risk findings on related or similar products and/or processes.

The following figure show an overview of a typical quality risk management process:

Initiation of a quality risk management process include the following steps:

- Define the problem and /or risk question & identifying the potential for risk;
- Assemble data on the potential hazard impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

Risk assessment can be applied by following three steps with three fundamental questions:

<table>
<thead>
<tr>
<th>Step</th>
<th>Question</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>Risk identification</td>
<td>What might go wrong?</td>
<td>Identifying hazards referring to the risk question or problem description, including identifying the possible consequences. Information can include historical data (deviations, audit non-conformance, ..) theoretical analysis, informed opinions, and the concerns of stakeholders.</td>
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Risk analysis

What is the probability it will go wrong?
What are the consequences (severity)?

Linking the probability of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation

Compares the identified and analyzed risk (risk number) against given risk criteria.

Risk evaluations consider the strength of evidence for all three of the fundamental questions.

Basic risk management facilitation methods, such as flowcharts, check sheets, process mapping, cause and effect diagrams are available. In general, one or more of the following risk management methodologies are used for risk assessment. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

A. Failure Mode Effects Analysis (FMEA):
- FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.
- Potential Areas of Use(s): FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities. FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

B. Failure Mode, Effects and Criticality Analysis (FMECA):
- FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis. In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.
- Potential Areas of Use(s): FMECA application in blood establishments can be utilized for failures and risks associated with the preparation or testing processes; however, it is not limited to this application. The output of an FMECA is a relative risk “score” for each failure mode, which is used to rank the modes on a relative risk basis.

C. Fault Tree Analysis (FTA)
- The FTA tool is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts’ process understanding to identify causal factors.
- Potential Areas of Use(s): FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e., solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

D. Hazard Analysis and Critical Control Points (HACCP):
HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:
1. conduct a hazard analysis and identify preventive measures for each step of the process;
2. determine the critical control points;
3. establish critical limits;
4. establish a system to monitor the critical control points;
5. establish the corrective action to be taken when monitoring;
6. indicates that the critical control points are not in a state of control;
7. establish system to verify that the HACCP system is working effectively;
8. establish a record-keeping system.

Potential Areas of Use(s): HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

E. Hazard Operability Analysis (HAZOP):

HAZOP is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called “guide-words”. “Guide-words” (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s): HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

F. Preliminary Hazard Analysis (PHA):

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential Areas of Use(s): PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other
risk management tools such as those in this section.

G. Risk ranking and filtering:

- Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. “Filters,” in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

If the identified risk number is above an acceptable level, it is necessary to assess, if there are risk reduction measures necessary and/or what level of risk can be accepted. The following questions may help:

- What can be done to reduce or eliminate risks? create a risk control strategy to mitigate the severity, probability of harm, and improve the detectability of hazards.
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?
- Is the residual risk after applying risk control strategy accepted?

Risk communication include sharing of information about risk and risk management between the decision makers and other parties. The output/results of the quality risk management process should be appropriately communicated and documented.

Quality risk management is an ongoing part of the quality management process and takes into account new knowledge and experience which is reviewed if it might have an impact on the original quality risk management decision. The frequency of any review should be based upon the level of risk and might include reconsideration of risk acceptance decisions.

1.3. Change control

Any change should be carefully assessed and its impact on the process, equipment, document and product systematically evaluated. Any change may alter the well-established processes in an unknown way. A change should therefore only be implemented and used for routine production if all work has been done, including e.g., modification of documentation (SOPs) and training of personnel.

1.4. Deviations

Non-conformity is a process or activity which does not fulfil its intended purpose. A nonconformity occurs when a requirement is not fulfilled. This could be because there has been a failure to follow the procedures in the management system, or a defective material or equipment failure, or the documented procedures are not fit for purpose. The result of a nonconformity, is a failure to meet product specifications, carry out a task as required, or meet customer or stakeholder requirements. In principle, each deviation should be investigated to find out possible root causes for the failure, and should identify appropriate measures to correct the deviation and to define and implement appropriate corrective and preventive measures that should ensure the the same issue does not re-occur in future.

In principle, blood components that do not fulfil the specifications, should not be release. Only in very exceptional and justified cases (e.g., if there is no treatment option using another product) it is at the discretion of the physician that is treating the patient to make a risk – benefit assessment to identify if the risk of not using the product to treat the patient is higher than the risk resulting
from the deviation. This procedure should be pre-defined and clarify, how the treating physician is informed about the observed deviation and its impact on the quality and safety of the product.

Accepting and using a non-conforming product for treating a patient is then a purely medical decision and the physician accepts responsibility for transfusion the concerned product.

For example: A manufactured product that does not conform to specifications and is identified during the quality control process as a nonconforming product. An equipment that has not been validated and produces imperfect product is a nonconforming process. The manufacturing unit should have a process in place for controlling nonconforming product. This process should include the following steps:

- Control the nonconformance.
- Review the nonconformance.
- Determine the disposition of nonconformance.
- Perform root cause analysis.
- Take appropriate corrective action.
- Monitor the effectiveness of CA.
- Document the entire process.

Any nonconformance should be investigated to identify actions that would prevent the nonconformance event from recurring. If the nonconformance is highly critical to the product, impacts multiple processes, or indicates a systemic issue, then CAPA process should be initiated. The manufacturing unit should have procedures to “identify existing and potential causes of nonconforming product, or other quality problems.”

1.5. Complaints

A complaint is an expression of discontent or concern associated with any aspect of the service provided and or results delivered. The approach to handling complaints is similar to the approach to handle a deviation or non-conformity.

1.6. Recall

The blood establishments should have procedures for the recall of non-conforming blood or blood components that are determined after release not to meet specified requirements. Different types of recalls can be differentiated:

- Recall: The removal from further distribution, or use, of a product (blood component) that violates regulatory requirement or does not comply with specifications.
- Withdrawal: The voluntary removal by the manufacturer (blood establishment) of a product (blood component) that does not violate regulatory requirement.

There should be personnel authorised within the blood establishment to assess the need for blood and blood component recalls and to initiate and co-ordinate the necessary actions. 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 NRAS. The need for recipient notification depends on the assessment why a recall or a withdrawal of a blood component has occurred. 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 if they might have been put at risk. Recall operations should be capable of being initiated promptly and at any time. 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.

The person authorised to initiate and co-ordinate the recall actions should normally be the responsible person that can take such decisions independent from the management within the organisation.
Recalled blood components or products should be identified and stored separately in a secure area while awaiting a decision on their use/disposal. 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. The effectiveness of the arrangements for recalls should be regularly evaluated.

Some of the examples for recall are described below. These errors should in principle have been detected during the release and a proper release procedure should have prevented the release of these products. If, however, some information only becomes available after the products have been released, a recall of the products may need to be considered.:

- **Post donation information:**
  It might occur that a donor informs the blood establishment after donation about an important element. If this information would have been available already on the day of donation, the donor would have been deferred this day. This post donation information therefore leads to a product that has been collected from a donor that would not have fulfilled the donor selection criteria. Therefore, the product does not comply with the requirements and is therefore recalled.

- **Documentation errors – errors in donor screening and component production:**
  Documentation errors on the records of donation or during component manufacturing are most often due to incomplete information, such as missing documentation of collection, production, storage time. These are errors of Good Manufacturing Process (GMP) and may have an impact on the quality and safety of the product, or on the traceability, and may trigger the need for a recall of the products.

- **Component production error:**
  Error in processing, storage or processing times or improper storage conditions, unacceptable volume, inadequate SAGM added to RBCs. These errors lead to product that has not been prepared using the validated process and should therefore be recalled.

- **Labelling errors:**
  Errors may occur in the product labelling, the volume of the component, or any other product attribute listed on the label. These are errors that may lead to the wrong product and therefore the product is recalled. There may be a recipient risk; an example would be the transfusion of an incorrect ABO group.

- **Breach in sterility:**
  Incidents such as incomplete seals may lead to an increased risk of bacterial contamination of the component. Although the risk depends on the component involved and the exact problem that occurred, any contamination must be prevented at any rate.

- **Errors in infectious disease testing:**
  For recalls associated with infectious disease markers, recipient notification should be in accordance with lookback procedures.

- **Rh D or red cell antigen phenotyping errors or discrepancies:**
  These errors may be of importance for the recipient and a (delayed) haemolytic transfusion reaction may occur. A recipient receiving units erroneously typed as antigen negative to prevent alloimmunization may develop an antibody. Discrepancies may be related to weak subgroups of A or B, or weak or partial D antigens.

- **Unacceptable Quality Control of blood components**

- **Increased risk of TRALI:**
  Components may be recalled for increased Transfusion Related Acute Lung Injury (TRALI) risk if a companion blood component from the same donation or a component from a later donation from the same donor has been associated with a TRALI reaction.

### 1.7. Corrective and preventive actions
An effective CAPA process is critical for eliminating systemic issues during manufacturing. It is to be noted that not every nonconformance will end up triggering a CAPA. The CAPA process is initiated when a nonconformance is critical or systemic in nature.

In summary, best practices when implementing both corrective and preventive actions include assessing the non-conformance and understand the details. Each action, result and conclusion should be documented allowing to demonstrate that the issue had been investigated carefully and the duty of diligence has been fulfilled. Documentation is essential for this. The right person(s) have to be assigned to deal with the issue. Individuals having the responsibility of overseeing the organization’s quality management systems should be closely involved and able to communicate easily on actions needed and taken to handle non-conformities. The steps taken to deal with non-conformances should be very clear and straightforward. Enabling tracking, reviewing and traceability of the entire process helps the organization to analyse and understand if the measures implemented in the workflow are correct and whether actions are performed and effectively working. By using a systematic approach and standard monitoring and evaluation mechanisms, the organization can mitigate risks that similar non-conformances may occurrence in future. The whole process should be under close oversight by quality assurance people and the responsible person.

Implementing corrective actions to non-conformance involves e.g., the following steps.

- Step 1 - Initiate a deviation. The following questions should be asked:
  - What did happen? By whom has it been detected? When did it happen? This helps us to know when non-conformances happened and to better understand the kind of impact it has caused for a defined period.
  - Inform the supervisor and quality assurance person (if necessary)
  - Where did it happen? This is aimed at identifying where the actual problem could happen. If it affects a specific segment of the organization, then such crucial details could be determined for necessary actions and interventions by the responsible persons.
  - Why did the problem occur? This could involve going through the entire organization’s operational workflows to understand the root cause of the problem and how to deal with it. To get to the bottom of the matter, the auditing team should go through and identify elements that could have played a role for the occurrence of non-conformances. This could also involve evaluating the organization’s Quality Management framework to see if there are some gaps that could be leading to nonconformity within the organization’s workflow.

- Step 2 – The organisation should understand the extent of problem. Is it a minor or major problem? Is the nonconformity an indication of a more systemic problem, or is it likely to reoccur? If so, then a corrective action should be initiated to identify the root cause.
  - Which part of the workflow and which products are affected?
  - Does it happen persistently, or did it happen once and did not recur?
  - Is there a risk for staff, donor or patient?
  - Are there any regulatory requirements that need to be taken into consideration? Is there a need to inform thee relevant regulatory authorities?

- Step 3: Document the problem and define the actions to be taken (planning)
  - It is necessary to document the findings. This is done in a non-conformance report. The documentation of findings serves two purposes.
    - It helps to deal with similar non-conformance in the future.
    - It provides evidence that could be used as a reference point when trying to hold individuals accountable for their actions.
o All the findings should be captured accurately and stored such that they can be retrieved easily when needed. This is typically done in a non-conformance tracking system.

- Step 4: Contain the non-conformance immediately (action)
  o After the problem has been identified, immediate action should be taken to contain the problem, while the efforts are made to understand the nature of the problem. This step is crucial for temporary mitigation of the problem but does not necessarily offer the final intervention needed to eliminate the problem.

- Step 5: Broadly study the root cause (analysis)
  o Root cause analysis is necessary to correct complex non-conformances. This helps to separate the perceived problem and the actual cause and so, it helps decision-makers in the organization to understand the core of the issue.
  o In the following, examples of questions that may be helpful when investigating a non-conformance are mentioned:
    - SOP
      - Is the SOP up to date?
      - Does the SOP lack detail or clarity?
      - Is the SOP too complicated? Could flow charts be used?
    - Training
      - Was the member of staff properly trained? Check training and competency records.
      - Was the member of staff inexperienced?
      - Was the member of staff performing an unfamiliar task?
    - Personnel
      - Was there an inappropriate staff mix e.g., lack of senior staff, trained staff, and use of locums?
      - Did the operators know and understand what they have to do?
      - Were working conditions appropriate or were other factors leading to distractions?
    - Equipment
      - Was the equipment unreliable?
      - Was maintenance programme adhered to?
      - Was there insufficient equipment/ emergency backup?
      - Is the equipment designed to make detection of problems obvious?
      - Were there calibration problems?
  o Reagent/Kit/Assay
    - Was the reagent / kit / assay in date?
    - Was the reagent / kit / assay correctly stored?
    - Was reagent reconstituted correctly?
  - Communication
    - Was there lack of effective communication to clinical team?
    - Was there lack of effective communication between lab staff?
• Step 6: Planning and implementing the corrective action plan (action)
  o Once the non-conformance is fully understood the decision-makers can create an understanding and strategy to solve the problem. This step includes designing and implementing a well-detailed corrective action. Their purpose is to ensure, through testing or observation, that a process or a specific task within a process works as designed.
  o The plan should be communicated by setting up actions and assigning them to the responsible individuals.
  o A follow-up on the actions taken ensuring that all stakeholders are kept in the loop about the corrective action being taken to solve the problem is necessary.

• Step 7: Evaluation and tracking (analysis)
  o Evaluation is important to understand if the adopted corrective action really provided the solution to deal with the non-conformances. The organization should design a monitoring and evaluation framework to help in following the efficiency of the corrective action that was implemented.
  o Tracking if the non-conformance was solved is another important step in this process. A non-conformance tracking system can help. It is important to assign responsibility to certain individuals so they can be held accountable if the problem persists.

• Step 8: In addition to implementing corrective actions, it is necessary to consider implementing also preventive actions. Preventive action involves a series of measures that could be employed to avoid the reoccurrence of the same non-conformance.

1.8. Self-inspection, audits and improvements

The self-inspection (or self-audit) process should cover verification of compliance with the standards but also with national regulations and relevant international guidelines to ensure that all the activities are complying to the applicable standards and take into consideration the current state of science. They should be carried out regularly by trained and competent persons, in an independent way, and according to approved procedures. All results should be documented and appropriate corrective and preventive actions should be taken in a timely and effective manner. Self-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. External audits may be helpful to allow an external person to look from outside. All audit results should be documented and reported to the management. Appropriate corrective and preventive actions should be taken in a timely and effective manner and should be assessed for effectiveness after implementation. The quality assurance department should not audit itself but should be subject to an independent audit. These audits are not a substitute for official inspections performed by the competent national authorities who check compliance with national regulations.

2. Personnel and organisation

The number of personnel as well as necessary qualifications and experience are dependent on the function of the organization whether the organization fully function for the collection, testing, processing, storage, release or distribution of blood or only function for the collection, storage, and release or distribution. The quality assurance manager and the head of organization should be a different personnel and function independently. The quality assurance manager is responsible for ensuring the appropriate quality system and protocols are in place for the safety and to make sure that all materials, equipment, reagents as well as blood and blood components are only released if they comply with the pre-defined specifications. A nurse or blood service technician may be assigned to help doctors/physician assess donors and follow-up activities. They report to the head of blood collection unit, but doctors should be present or can be contacted to provide advice and, if necessary,
medical assistance in case of a severe donor reaction. In addition, defining a responsible person also for the lab activities could be considered, depending on the size and type of the organisation.

Approved training programs should be available, including:

- principles of transfusion medicine;
- Good Manufacturing Practice;
- equipment maintenance and infrastructure hygiene;
- Continuing professional development (CPD) or continuing medical education (CME) related to transfusion field.

Programs for initial training of newly recruited personnel or personnel taking over new functions should take into account all appropriate tasks and procedures, including general topics such as quality management, GMP and computerized systems. The same topics and principles are applied to trainings aimed at reintroducing to personnel after a long absence at work. The timeframe should have been set. The training record should contain the trainer's name, all specific tasks (including the corresponding Standard Operating Procedures) and the training finish date, signed by both the trainee and the trainer. Upon completion of training, personnel should be assessed to be competent in duties at the place of assignment. The training profile of each personnel is supposed to be updated annually.

In case of personnel limitations, staff who have worked for many years may not have a training record to demonstrate competence. In such cases, the use of a written "recognition of prior learning" device, can help to provide documented evidence of competence. For example, a properly trained senior manager may declare his staff as competent based on experience, observation and other relevant factors. Continuous training programs (theoretical and/or practical training, internal and/or external training) should be in place to ensure that personnel retain skills in carrying out assigned tasks. The training program should include technical development and related sciences. Training should also include changes about Standard Operating Procedures and personnel needs. Training can be face-to-face or documented online meetings, or self-training.

The competence of personnel should be evaluated and documented after completion of the initial training and periodically afterwards. Once the initial competencies are determined, a competency assessment and training program should be conducted. The effectiveness of training is reviewed and assessed periodically. For the requirements in this section applying quality risk management approaches could be beneficial at all steps, such as resources allocation, training and competency assessment means definition, frequencies, etc.

It is the organisation's responsibility to provide instructions on hygiene and health conditions that can be of relevance to the quality and safety of blood components and to ensure that staff report relevant health problems. It is important to consider that there are biological risks in blood establishments, so it is necessary to apply biosafety measures. One of them is the monitoring of the health condition of workers, who work directly with blood, as well as considering the possibility of their vaccination (for example, with Hepatitis A and Hepatitis B vaccines). Furthermore, compliance with data protection regulations is important, but this aspect is outside the scope of the Good Practices.

3. Premises

Premises including mobile sites should be suitable for the activities to be carried out. They should enable work flow to proceed in a logical sequence so as to minimize the risk of errors, and should allow for effective cleaning and maintenance in order to minimize the risk of contamination. Considerations should also be given to protect the health and safety of donors, if necessary. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect (directly or indirectly) blood components during their processing and storage, or the accurate functioning of equipment. This may include the availability of appropriate infrastructure, including supply of water and electricity and a mean to deal with any rupture. In order to avoid open drains, these should be of adequate size and equipped with traps to prevent back siphoning. Not all blood establishments are constructed in a way to easily facilitate compliance with this requirement, and space may be limited.
or arrangement of premises may be difficult to allow a logic flow of persons/materials. Reference is made to using a risk-based approach and implement risk mitigation measures whenever necessary if the premises do not facilitate compliance with the requirements. Implementing organisational measures, such as e.g., allowing only a limited number of donors entering the facility and use of signs and barriers may contribute to implement some logic flow of persons. Temporary material storage areas should be clearly identified and protected (if necessary) in case of limited appropriate storage rooms. As the refreshment areas for donors pre- and post-donation should be assigned and separated from other working areas. Post-donation areas should be located within the same facility near the blood donation area and but supervision of donors may be delegated to other trained staff if appropriate procedures are in place to ensure donor safety.

The following figures summarizes some of the main requirements for the different areas within a blood establishment. An area does not necessarily have to be a completely separate room. It may be acceptable to have different areas within the same big room if appropriate segregation measures are implemented in order to avoid mix-ups and ensure a controlled way of working.

While it is recognized that areas that are temporarily used as mobile collection sites may not fulfil the same requirements as the blood collection area of a blood establishment, these areas should be carefully selected and assessed prior to their use to ensure their suitability for blood collection. This may include ensuring also acceptable temperature conditions in case the mobile collections are held outside.

Special considerations may also be given to ensure proper waste management and segregated areas for handling waste, following other local or national regulations. In general such regulations are applicable to protect blood establishment staff and environment from a risk of spreading infectious agents in the environment. These aspects are not necessarily covered by the Good Practice aiming to ensure the quality and safety of the products.

4. Equipment and materials

All equipment should be identified, qualified, calibrated and maintained to suit its intended purpose. All critical equipment should have regular, planned maintenance, taking into consideration manufacturer’s instructions, to detect or prevent avoidable errors and keep the equipment in its optimum functional state. New and repaired equipment should meet qualification requirements when installed and should be authorised before use. All modifications, enhancements or additions to validated systems and equipment should be managed through the change control procedure of the blood establishment. The effect of each change to the system or equipment, as well as its impact on quality and safety, should be determined to identify the extent of revalidation required. Instructions for use, maintenance, servicing, cleaning and sanitation should be available. Equipment should be selected so that it can be thoroughly cleaned according to written procedures and using cleaning solutions that not represent sources of a new contamination. In order to avoid that operators continue to use defective equipment they should be labelled clearly as such and, if possible, removed from preparation areas. Critical materials should be released by a person qualified to perform this task and necessary quality controls should be documented.

Facilities and equipment need to be qualified prior to implementation. The principles of qualification and validation are applicable to the preparation, distribution and issuance of blood components. It is a requirement of good practice that blood establishments and hospital blood banks control the critical aspects of their operations throughout the life cycle of the blood components and the associated processes. Any planned changes to the facilities, equipment, utilities and processes should be managed under the change control process, formally documented and the impact on the quality and safety of blood components should be assessed. As part of a quality risk management system, decisions on the
scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.

The qualification of equipment in general is done stepwise, as indicated in the following table, beginning with IQ followed by OQ and PQ. At regular intervals it is necessary to requalify the equipment.

Processes should be shown to be robust and ensure consistent blood component quality prior to their distribution and routine clinical use. Processes should undergo a prospective validation programme, wherever possible. Retrospective validation is no longer an acceptable approach.

Process validation of new blood components should cover all intended processes and sites of preparation. A scientific and risk-based validation approach could be justified for new blood components based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing statistical process control. The design assumes that the validation performed is representative for all process or product settings.

In conclusion, the following items are essential to maintain a validated state:

- calibration and requalification of equipment;
- preventive maintenance;
- training and competency;
- supplier and material requalification;
- continued process verification;
- performance monitoring;
- system retirement.

Maintenance of the validated status of the blood components should be documented in the product quality review. Incremental changes over time should also be considered and the need for any additional actions, e.g., enhanced sampling, should be assessed. Operational change control, document control and quality control procedures support the maintenance of the validated state.

A periodic review process should be established to ensure that documentation for the system or equipment is complete, current and accurate. A report of the review process should be produced. When deviations or problems are found, actions should be identified, prioritised, planned and implemented.
**General requirements**

All validated processes should use qualified equipment. Qualification results should be documented. Regular maintenance and calibration should be carried out and documented. New and repaired equipment should meet qualification requirements when installed and should be authorised before use. For each equipment a specific file including all instructions should be available (at same place of or nearby) equipment. Defective equipment should be labelled clearly as such and, if possible, removed from preparation areas.

**Qualification and Validation**

Facilities and equipment need to be qualified prior to their use in routine and:
- Installation qualification (IQ)
- Operational qualification (OQ).
- Performance qualification (PQ).
- Requalification

Systems, processes, and tests should be validated prior to use in routine.

**Process validation**

Protocols should include:
1. short description of the process
2. functions and responsibilities.
3. summary of the CQAs to be investigated.
4. summary of CPPs and their associated limits.
5. summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
6. list of the equipment/facilities/personnel to be used (including measuring/monitoring/recording equipment) together with the calibration status;
7. list of analytical methods and method validation, as appropriate;
8. proposed in-process controls with acceptance criteria and the reason(s) for selecting each in-process control;
9. additional testing to be carried out with acceptance criteria;
10. sampling plan and the rationale behind it;
11. methods for recording and evaluating results;
12. process for release and certification of units (if applicable)

Process validation of new blood components should cover all intended processes and sites of preparation. The design assumes that the validation performed is representative for all process or product settings, and using this approach, a minimum number of units to be included in the process validation should be determined.

Any validation should be documented in a report, including an evaluation of results, with all relevant evidence, and a clear conclusion on the outcome and validity of the process validation study should be included.

Due to the fact that blood donations are a rare starting material, validation protocol often are written to forsee a concurrent process validation. This should be justified and the potential risks for patients assessed to demonstrate a significant patient benefit. This decision to carry out concurrent validation should be documented in the validation protocol and be approved by authorised personnel and the treating physicians. Where a concurrent validation approach has been adopted, based on risk
assessment, there should be sufficient data to support a conclusion that any given blood component
meets the defined acceptance criteria.

5. Documentation

5.1 General principles

Documents setting out specifications, procedures and records covering each activity undertaken by a
blood establishment should be in place and kept up-to-date. Records should be legible and may be
handwritten, transferred to another medium or documented in a computerised system. 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, testing, processing, storage and distribution of blood and
blood components are traceable. The record system should ensure continuous documentation of the
procedures performed from the blood donor to the recipient. That is, each significant step should 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. 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.

5.2 Generation and control of documentation

A document control system, defined in a written procedure, should 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.
Documents should be designed, prepared, reviewed, and distributed with care. Replication of working
documents from master documents should not allow errors to be introduced through the process of
replication. Documents containing instructions should be approved, signed and dated by appropriate
and authorised persons. This may also be undertaken electronically. Documents should have
unambiguous content and be uniquely identifiable. The effective date should be defined. 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. Documents within the
Quality Management System should be regularly reviewed and kept up-to-date. All significant changes
to documents should be acted upon promptly, and should be reviewed, dated and signed by a person
authorised to undertake this task.

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 to
improve the quality of products and services delivered. The document review process should itself be
documented.

All types of documents should be defined and adhered to. Requirements apply equally to all forms of
document 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.

It should be clearly defined which record is related to each activity and where this record is located.
Secure controls should be in place to ensure the integrity of the record throughout the retention
period. These controls should be validated if appropriate. Specific retention requirements for certain
documentation apply. Records should be retained for a period according to local, national regulatory
requirements, as appropriate.
Specifications describe in detail the requirements to which the blood and blood components or materials used or obtained during preparation and distribution should conform. They serve as a basis for quality evaluation.

Testing instructions should include details of all the starting materials, equipment to be used and all sampling and testing instructions. If applied, in-process controls should be specified, together with their acceptance criteria.

Standard Operating Procedures or SOPs give directions for performing certain operations. Protocols give instructions for performing certain discrete operations, and may record the outcome (e.g., qualification and validation protocols).

Records provide evidence of various actions taken to demonstrate compliance with instructions, e.g., activities, 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’.

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

All activities and critical procedures should be specified in written instructions (SOPs) including:

- Donor eligibility
- Collection and preparation of blood and blood components
- Laboratory testing, quality control testing
- Labelling 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,
- Quality assurance procedures (complaint investigations, deviation management)
- Recall of non-conforming products
- Change control and document control

6. Blood collection, testing and processing

An important topic that is not within the scope of the Good Practice are the elements regarding blood donor mobilization in the community. Reference is made to other WHO documents such as Towards 100% voluntary blood donation: a global framework for action.(8)

6.1. Donor eligibility

Donor registration

Upon presentation at the blood establishment, donors should positively identify themselves by stating their full name, address and date of birth. Each donor should also provide proof of a permanent place of residence, including a telephone number where appropriate, so that they can be contacted after donation, if necessary. Proof of identity with a photograph — such as an identity card, passport or
Epidemiological surveillance of the donor population

To ensure optimal long-term safety of blood components, blood establishments should maintain continuous epidemiological surveillance of the donor population. The objective of this surveillance is to know, as precisely as possible, the prevalence and incidence, and their respective trends, of infectious markers that are relevant to the safety of blood components. This enables countermeasures to be taken in a timely manner. The system should be able to gather epidemiological data not only at national/regional levels but also among donor populations that provide blood at individual blood establishments within a country or region. Consideration should be given to the travelling patterns of the donor population with respect to possible transmission of infectious diseases (i.e. malaria, Chagas disease, vCJD, etc.). The information from epidemiological surveillance can furthermore be used:

- to detect, among donor populations of various collection centres, differences that may be associated with objective differences in viral markers within donor populations;
- to detect differences in the donor selection and screening processes at collection centres;
- to monitor trends in infectious markers which may reflect either a change in the rate of viral
markers in the population or a possible deviation in the donor selection or screening process at specific collection sites;

- to assess the relevance of any preventive measures such as a strengthened donor selection process, additional deferral criteria, or implementation of additional screening tests to avoid contamination of blood components.

When donations from first-time donors are used to prepare blood components, epidemiological data on this specific donor group should be included in the estimate of the risk for infectious diseases transmitted by blood. It has been shown that first-time donors, who may occasionally include test-seeking persons, constitute a group that in some situations is more likely to have bloodborne viral markers than regular donors who have already gone through a selection/deferral process. It is currently advisable to collect and analyse epidemiological data at the collection sites for human immunodeficiency virus (HIV1/HIV2), hepatitis C virus (HCV) and hepatitis B virus (HBV) since they historically represent the major pathogenic risks associated with blood components. It is the responsibility of the NRAS to define whether this list should be modified or should include additional criteria such as emerging infectious agents, on the basis of local or regional epidemiology. All tests performed should be recorded to ensure traceability. Only confirmed positive tests (i.e. tests which are repeatedly reactive in a screening test and positive in at least one confirmatory test) should be reported and analysed.

Information to donors

Potential donors should be informed on the whole blood or plasma donation process (ideally both verbally and in writing) and that it is necessary to respond to questions about their medical history and personal behaviour so that it can be determined whether they are eligible for blood or plasma donation. Written information can be a leaflet explaining infectious risks associated with blood products, and the impact of social behaviour on infectious risks or infectious risk factors. This information is usually provided by a licensed and specifically trained physician, or by a designated qualified person under the direct supervision of a licensed physician. The information should clearly explain the deferral criteria that exclude a donor from donating blood or plasma. It is important to ensure that the reasons for deferral are well understood by the potential donor. The candidate donor should be asked to sign a form of informed consent to give blood in which he/she acknowledges understanding the moral and legal responsibilities and possible risks associated with donating blood, as well as the occasional complications that may occur. The declaration of consent should also include a statement that the donor understand that each donation is tested for the presence of infectious disease markers and authorizes the release of his/her blood and blood components for transfusion, further manufacturing or other beneficial purposes (e.g., as reagent for proficiency testing). Donors should be informed to contact the blood establishment if there is an unexpected event after the donation, such as illness or the discovery of new information not disclosed during the health screening.

Questionnaire and interview

The interview assessment of each donor should be carried out by a qualified person who is trained in the use of donor selection criteria using a validated written questionnaire with direct questions if necessary. In order to obtain relevant and consistent information about the donor’s medical history (concerning illnesses and drug use) and general health, the donor should review, complete and sign a predefined questionnaire that is adapted to the type of donor (e.g., first-time donor or repeat donor). The questionnaire should cover questions about the medical history of the donor, his/her travel habits, risk behaviours, use of medication, and other medical treatment. A list of countries may be provided to assist the donor to complete the questionnaire with regard to earlier residency or travel. Similarly, a list of drugs that may pose a threat to the recipient or may be an indication of poor donor health may also be provided. The CA may provide requirements for such lists. The questions should be drafted in
such a way that donors may easily identify whether they are in good health. The questionnaire may be administered in several ways and may be in several languages, such as:

- by a person reading questions to the donor and recording the responses;
- by the donor reading the questions and recording the responses;
- by computerized written questions presented to the donor with the donor recording the responses;
- by the computer reading the questions to the donor and the donor recording the responses;
- by other validated methods that ensure that the donor understands the question, how to completely answer the question and how to record the response to the question.

There should be a link between the donor, the donor questionnaire and the collected products. After the donor’s history has been reviewed, the collected components should be identified in a way that links the products to the history records but maintains the confidentiality of the donor. The product should be identified by a unique donation number linked to the donor name but the product information should not include the donor name except as required by the NA in cases such as autologous donations. After reading the donor information and/or answering the questionnaire, donors who are at risk of carrying a disease transmissible by blood should be able to exclude themselves voluntarily and confidentially. Such confidential self-exclusion should also be possible after the donation (e.g., by phone). Donor identification and information, the donor selection interview and the donor assessment should all take place before each donation. The premises and layout of the blood establishment (or the mobile collection unit) should allow for adequate confidentiality during the donor interview and selection process so as not to discourage the candidate donor from answering questions about personal or private behaviour; otherwise, the safety of the blood donation could be compromised. The minimum intervals between two donations should be defined and should then be audited or reviewed for compliance with the waiting period prior to each donation. WHO Donor Selection and WHO Blood Donor Counselling: implementation guidelines provide further information on implementing the best practices at local and national level.

**Deferral policy and deferral criteria**

As part of the blood establishment’s deferral policy, a list of permanent or temporary deferral criteria used for potential donors should be clearly defined, and incorporated in the educational material for donors and the establishment’s procedures. It should also be determined whether the donor has previously been deferred, and reasons for any deferral should be reviewed so that a decision may be made on whether to accept the donor for current donation. A donor who is deferred should be informed of the reason for deferral, encouraged not to donate at other facilities while deferred and informed that the reason for the deferral may be shared with other health professionals or government agencies according to legal requirements. Both acceptance and deferral criteria for the donation of blood should be formulated by the NRAS and should be national requirements that are applied nationwide. WHO Blood donor selection: guidelines on assessing donor suitability for blood donation, deferral criteria include:

- clinical or laboratory evidence of bloodborne infectious diseases such as acute or chronic infection with HIV, HCV or HBV (in certain jurisdictions donors with elevated titres of anti-HBs may be acceptable);
- past or present recreational drug use (both injection and not injection);
- persistent bacterial or protozoal infections.

Other deferral criteria, either permanent or temporary, may include:

- High-risk sexual behaviours include having multiple sex partners, receiving or paying money or drugs for sex, including sex workers and their clients, men having sex with men (MSM);
- sexual partners of any of the above or of someone the donor suspects may carry the above risk factors;
- jaundice within the 12 months prior to donation, since this may be a clinical sign of hepatitis A, B or C;
transfusion with blood, blood components, cellular therapy products or vascularized tissue transplant in the 12 months prior to donation, as blood transfusion and transplantations are risk factors for all bloodborne infections. Each NRA should decide a deferral period, such as
12 months, depending on each country’s situation.

- exposure to someone else’s blood, including an accidental needle stick in the 12 months prior to donation;
- tattooing, scarification, ear-piercing or acupuncture in the 12 months prior to donation (since these practices may be vehicles for transmission of viral diseases) unless clear evidence is provided that it was carried out under sterile conditions;
- risk factors for Human T-cell lymphotropic virus (HTLV) infection;
- risk factors for malaria infection (e.g., travel in countries where the prevalence is high);
- a confirmed family history of CJD;
- Inmates of prisons and penal institutions.

When temporary deferral criteria are used, a specific procedure involving trained personnel should be in place for the reinstatement of donors. There are deferral criteria that are temporary (as long as a risk factor has been identified) but that can be waived after additional controls have been carried out on the donor or the period of deferral has passed. NAs may recommend or define different deferral criteria and timelines, e.g., when implementing NAT testing for the relevant viruses.

**Physical examination, donor health criteria and donor acceptance**

A targeted physical examination should be carried out by a licensed and specifically trained physician according to an established procedure prior to the first donation and thereafter before subsequent blood donations, and in case of special apheresis programmes at regular intervals. Depending on national regulations established by the NRASs, the physical examination may be performed by a suitably educated and trained physician substitute under the supervision of a licensed physician. NRASs should, usually after consultation with the blood establishment, determine the health criteria and the acceptable limits taken into account during the physical examination — such as measurement of haemoglobin, blood pressure, weight, age, pulse rate and temperature, or any other criteria considered to be of concern for the safety of blood components or donors. A written standard operating procedure based on the relevant acceptance/deferral criteria should be in place at the blood establishment to control donor acceptance and deferral criteria, in compliance with the national requirement. Abnormal donor findings should be referred to the physician who has the responsibility of making the final decision about the donor’s eligibility on the basis of current medical knowledge and national regulations. If the physician has any doubt about the donor’s eligibility, the donor should be deferred. An appropriate computerized record system (or, if that is not available, a manual system) should be in place for donor records (including their medical history and health status), and for the purpose of ensuring traceability of all donations. Such information provides historical perspective of the health status of donors, including previous temporary deferrals, and contributes to reinforcing the judgement about whether the donation would create a risk to the quality and safety of the blood components. Records should be kept for each activity associated with the selection of the donor. The record should reflect the decision to accept the donor, taking into consideration the medical history, donor deferral history, the donation interval, the answers given in the interview or questionnaire, and the results of the physical examination. The rejection of a donor and the reason for the deferral should be recorded. An authorized interviewer should sign the donor selection records and the final assessment of the donor’s suitability. As with all other manufacturing steps under GMP, donor selection and acceptability procedures should be followed at all times using the validated methods. Any deviations from established procedures and processes may result in products not meeting specifications so such products should be considered as non-conforming products and should not be released for distribution.

### 6.2. Collection of blood and blood components
Donors should confirm their identity (by a method such as stating name and date of birth) immediately prior to venepuncture. Also prior to venepuncture, a check should be made to ensure that the collection system to be used has not expired, is not damaged or contaminated, and that it is appropriate for the intended collection. Any abnormal moisture or discoloration suggests a defect and in such a case the collection system should be discarded. An investigation should be conducted to evaluate the extent of the problem and appropriate corrective actions should be taken. The collection systems should be used in accordance with the instructions of the manufacturer.

All personnel involved in collection of blood from blood donor should undergo appropriate training and pass a practical competency test before they are allowed to perform unsupervised venepuncture. A standardized and validated procedure for the preparation of the phlebotomy site should be followed using a suitable disinfection solution which should be allowed to dry depending on the type of disinfectant. The expiry date of the disinfectant should be checked before use. If refillable bottles are used, they should be cleaned before being refilled. The date of manufacture and the date of opening of in-house disinfectants should be stated on the label. The prepared skin area should not be touched after the disinfection and before the needle has been inserted. Care should be taken not to lean over or speak over the disinfected skin.

Systems of sterile blood bags used for the collection of blood and blood components and their processing should be of assured quality. In western countries, in general this is achieved using CE-marked collection bags. Compliance with other equivalent standards or approval by regulatory authorities may also be acceptable. The batch number of the bag should be traceable for each blood component.

For blood donations, laboratory samples should be taken at the time of donation. Procedures should be designed to minimize the risk of microbial contamination to the unit, such as diverting at least the first 10 ml collected in the tubing into test tubes for testing. Methods should be implemented to minimize the deterioration of the sample, such as refrigeration of the sample if required by the manufacturer’s instructions for the sample tube or test kit. The sample labelling process should include steps (such as labelling the tubes immediately at the chair side) to prevent the misidentification of samples. The test samples should be labelled immediately in a manner that links the donor, the samples and the blood donation without breaching the confidentiality of the donor.

The mixing can be done by using a continuously running automatic mixing balance or by periodic manual mixing. If manual mixer is used, the blood bags should be inverted every 30-45 seconds. Collection of one standard unit of whole blood should be achieved within 12–15 minutes (depending on the component to be prepared later on), as longer durations may result in activation of the coagulation factors and cellular components. Records should be kept for each activity associated with the donation, including identification of the person who performed the venepuncture. Records should also show any unsuccessful donation, adverse reactions or adverse events. The maximum collection time for acceptance of the donation for component processing should be specified and controlled. Donations that exceed the maximum time period should be recorded and further decision to be made on the fate of the donation. A system of unique donation numbers should be used to identify each donor and the related donation, all associated components, samples and records, and to link each one to the others. When the donation is completed, all records, blood bags and laboratory samples should be checked for the donation number issued. Donation number labels that have not been used should be discarded using a controlled procedure. Procedures to exclude misidentification should be in place. After blood collection, the blood bags should be handled in a way that maintains the quality of the blood. The donation samples should not be obtained by squeezing the blood out from the blood bag. The collection and labelling of the blood samples should be carried out at the bedside. The blood collection bag and the corresponding donation samples should not be removed from the donor.
bedside until all of the sample tubes or collection bags have been duly checked and verified against the donor's identification.

As with other GMP manufacturing steps, the donor product collection process 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 therefore such products should be considered non-conforming products and should not be released for distribution.

6.2.1 Collection by apheresis

In apheresis procedures, whole blood is collected from the donor, mixed with anticoagulant, and passed through an automated apheresis device. The blood component of choice is separated from the other blood components which are returned to the donor in a series of collection/separation and return cycles. The operational parameters of the apheresis system should be implemented in compliance with the instructions of the equipment manufacturer and in compliance with any specified safety requirements of the NRAS. In general, the anticoagulant — often 4% sodium citrate or anticoagulant citrate dextrose solution A (ACD-A) — is delivered at a rate that will yield a specified ratio of anticoagulant to blood. The volume of the component collected from the donor during one procedure and over a period of time should be regulated by internal policies based on current medical knowledge and on national regulations set by the NRAS. The number of collection/separation and return cycles for each donor depends on the total volume of the component that is to be harvested. To determine the number of cycles to be employed, the equipment requires programming with data inputs such as donor weight, height and haemoglobin values, and the pre-donation platelet count if platelets are to be collected. The amount of time required for the donation procedure depends on the number of cycles. An adequately trained physician should be available during apheresis sessions. The donor apheresis collection process should be followed at all times using validated methods. Any deviations from the established procedures and processes may result in products not meeting specifications and therefore they should be considered non-conforming products and should not be released for distribution.

6.2.2 Safety of donors

Donors should be managed with high standards of care to assure their safety during blood donation process. Despite this, adverse donor reactions/ events do occur. All measures should be taken to avoid anything that could adversely affect the donor before, during and after the donation. Special attention should be drawn to the potential risk of transmission of diseases or infections during the collection and sampling processes. Donors should be given post-donation instructions regarding a period of recovery, such as refraining from certain activities for a while, drinking more fluids than usual and making sure to eat appropriately after the donation. Donors should be advised to refrain from activities such as heavy lifting, operating large items of equipment and other strenuous activities for a period of time until their blood volume has recovered. Donors should also be provided with information on how to obtain medical advice if they experience an adverse donor reaction after leaving the blood establishment. Throughout the procedure of withdrawal of blood or blood components, the donor should be monitored. Personnel should be educated to provide appropriate aid in case of any adverse reaction. Donors should be kept under post-donation observation (e.g., for 15 minutes or more) prior to leaving the blood establishment and should be offered refreshment to replace fluid loss. Drinks may be provided to donors during donation process. In these circumstances, a suitable container for the drink is required. Donors should remain under observation for anticipated reactions to donation until they are able to articulate that they feel well enough to leave and be unattended. Immediate care should be given to the donor if there is a adverse donor reaction and documented. Following recovery, explanation should be provided to blood donors regarding the adverse reaction and reassurance should be given. Appropriate preventive and corrective measures should be implemented. Information regarding donor reactions and a process to track and trend reactions should be in place as part of
Haemovigilance monitoring in order to evaluate the number, type and severity of reactions. This information should be used to improve donor safety.

6.3. Laboratory testing

6.3.1. Testing for infectious markers

All tests for the infectious disease markers have to be negative. It is recommended that national algorithms should be developed and used to enable consistent resolution of discordant/indeterminate or unconfirmed results. (6) In addition to testing for immunoassays (serological) for infectious disease markers, NAT testing of blood donations for the virus genomes has been introduced in some countries to increase the chance of identifying infected donors.

During the natural course of infection, viraemia usually occurs significantly at a point earlier than that at which immunochemical markers (antibodies) can be detected in the infected serum. Thus, infection may be detected by NAT up to 50–60 days before seroconversion (i.e. to HCV) occurs. Testing for the presence of nucleic acid may be performed for viruses such as HCV, HBV, HIV, HAV, WNV (where appropriate) and/or Parvovirus B19, and the application of this technology may be extended to other transmissible microbes. There are window periods that cannot be detected using NAT tests (e.g., 35-76 days for HBV ID-NAT, 41-90days for HBV mini-pool NAT), and transfer from pooled plasma to individual NAT is underway worldwide, and NRAs should determine an appropriate pool size in light of the epidemiological situation and other factors. NATs require a specifically designed laboratory environment, special equipment and specially trained laboratory personnel. Mainly because of an extraordinary risk of false-positive results due to the so-called “carry-over” (inadvertent transfer of the amplification product DNA to neat donor samples), very stringent handling and logistics are mandatory. Hence, a specific logistics system may have to be established not only in the laboratory but also at the blood establishment in order to collect and suitably label samples. Contiguously tracing samples through the whole process from the donor, through pooling (if applicable), testing and release of the donation may present a particularly demanding challenge. A system should exist in the country or region for approval of test systems, such as an official approval system by the Competent Authority or a delegated laboratory. The required minimal sensitivity of tests for the different antigens/antibodies or nucleic acids should be defined by the NRASs. WHO Guidelines on Donation Testing provides further detailed information on testing.

6.3.2 Handling of samples and data

Multiple specimens may be collected from a donor in order to meet all testing requirements (i.e. ABO & RhD typing, test for transfusion transmissible infections markers and NAT testing). There should be written standard operating procedures that clearly describe the collection, transportation and labelling of donor samples (i.e., whole blood, sera, anticoagulant, container tubes etc.) and which define the sampling procedure performed on material for analysis (e.g., how and by whom it is done, transfer of samples, accountability of samples, volume of sample according to test instructions of the test manufacturer). Sample labelling at the site of collection and identification during all subsequent processing is critical and should be under control at all times. The following practical points should be considered in order to ensure the traceability and integrity of samples and data:

- The integrity of the sample should be checked for compliance with the recommendations made by the manufacturer of the test kit.
- Aliquot samples for analysis should be withdrawn from the donor sample preferably by automated pipetting equipment.
- To provide for positive identification of all aspects (donation, donor specimen, aliquot samples etc.) it may be advisable to use a barcode system. Hence, starting with the donation, barcodes that is also eye-readable should be used for labelling. To cope with system failures and disasters, barcode data management should be operated by a main server and a backup server. In case of failure of the automatic barcode reader system and/or data processors, an appropriate system
should be available for manual entry and tracing of data throughout the whole process until release of donations for transfusion. Manual handling of data should include independent repeat entry into the database; the data format should include a check-digit algorithm or an automated test for identity of the two sets of data.

- Pipetting devices and machines should be validated before routine use, and validation reports should be available.
- Calibration of the pipetting devices should be performed periodically and should be documented.

6.3.3 Testing and post-analytical procedures

Where required, prior approval of the Competent Authority should be obtained before the modified method is used for release of a blood component. Laboratory reagents intended for prolonged use should be marked with the preparation date, expiry date, specific storage conditions and signature of the person who prepared them. Instructions for use and storage should be followed. All unscreened blood components should be placed in a secured physical segregation/quarantine until all the required tests have been completed. Screening algorithms should be precisely defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens and to resolve discrepancies in results after retesting. A collection batch should be quarantined if there is any discrepancy between the results. The quarantine should be lifted only after thorough investigations, and resolution of the discrepancies. Appropriate corrective and preventive actions should be taken. Records of the events, the findings of the investigations, and the corrective and preventive actions taken should be maintained. All available measures should be taken to ensure that blood and blood components that are repeat reactive upon screening for an infectious disease marker are excluded from therapeutic use. Repeat reactive material should be stored away from all other blood components in a separate dedicated storage area. Such material should eventually be destroyed to prevent inadvertent re-entry into the transfusion chain.

Test algorithms should provide details for appropriate confirmatory testing. In the case of repeatedly reactive results, clearly defined follow-up instructions should be followed. Actions include:

- notification and deferral of the donor;
- disposal of the indicated donation and of concurrent products;
- tracing and destruction of products which have not yet expired.

If products from the donor have been processed for further manufacture, there should be a procedure in place to assess both the safety of the manufactured products and whether a recall is needed. Procedures for donor- and/or recipient-initiated look-backs should also be defined. Look-backs should be designed in such a way that the transfusion chain of donor–blood (or blood product)–recipient can be unequivocally reconstructed. The procedure should comprise notification and counselling action where indicated.

The following practical points should be considered in order to ensure that the equipment used for virology testing performs appropriately:

- There should be a mechanism to ensure positive sample identification and linkage to the donor. The preferred method is by sample tubes with barcodes.
- Ideally, the addition of reagent and samples and the testing process should be automated, in order to minimize risk of human errors and to ensure full traceability of the testing process.
- If addition of reagents and samples or preparation of test plates are done manually, full documentation of each addition step should be kept, ensuring identification of the test plate and the location of the reaction well.

6.3.4 Test interpretation and follow-up of reactive results

The transfer and interpretation of raw data is a critical step and should therefore be documented and reviewed by a responsible person, as should the test parameters. Traceability and archiving of raw data
should be guaranteed. The data should be examined by the supervisor, or by another person authorized to do so, before being officially accepted. If computerized systems are used, accepted data should be downloaded directly to the server, or there should be a secure system for manual download which ensures positive release. Manual transcription of results is discouraged as mistakes may be introduced. Acceptance and rejection criteria should be specified. The following should be given special attention:

- Initial reactive results should be identified by means of a secure and validated system.
- An acceptable system should be in place to confirm repeat reactive results, including sampling, labelling, testing and entry of results.
- Computer algorithms should edit reactive status to repeat reactive, or the editing should be performed by two authorized staff members.
- An appropriate deferral system should exist for repeat reactive results.
- There should be appropriate documentation justifying the re-entry of deferred donors.
- Donors should be informed of the reason for deferral and should be counselled about social behaviours and their status as a future donor.

If the infectious disease marker is positive, there is a high probability that the previous donation was tested false-negative due to the window period. Therefore, a system should be established to allow for retrospective investigation such as look back system. The NRA and others should decide how far back to investigate. Reference is made to the WHO Recommendations on Screening donated blood for transfusion transmissible infections.

Regarding re-entry mechanisms, reference is made to the WHO Recommendations on Screening donated blood for transfusion transmissible infections.

6.4. Blood group serological testing of donors and donations

Each donation should be tested for ABO and RhD blood groups. When plasma is used for fractionation it should be tested in compliance with the specifications of the fractionator as agreed by the relevant NRAs. Testing should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Molecular methods may be used to determine blood groups, as necessary. Competent Authority may set different (stronger) requirements. The ABO/RhD labelling of the red-cell concentrates of all first-time donations should be based on two independent ABO/RhD tests.

6.5 Retention samples

As specified by the NRASs, an aliquot of the original testing sample should be retained from each donation and stored under conditions recommended by the test manufacturer that would permit retesting if indicated. The procedure for additional testing should be validated to ensure the integrity of the sample (including storage conditions) and the test results. The sample volume, the retention vial, the kind of specimen (serum or plasma), the storage conditions and length of storage should each be defined and should be included in the validation to ensure the integrity of test results.

6.6. Processing and validation

The quality of the components is assured by control of all stages of manufacture, including donor identification, collection, separation of components, labelling, storage, packaging and dispatch. 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. 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 should not be released for
distribution.

6.6.1 Starting material
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. 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 venepuncture. 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. 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. 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 defi-
ned and periodic audits should be conducted to ensure compliance.

6.6.2 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.

6.6.3 Centrifugation
The centrifugation parameters (revolutions per minute, temperature, time, acceleration, 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.

6.6.4 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.

6.6.5 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. 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.

6.6.6 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.

6.6.7 Irradiation
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.

6.7 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. There are detailed recommendations concerning the preparation and quality assurance of blood components. See for instance Guide to the preparation, use and quality assurance of blood components of the Council of Europe. In the following sections, examples of the most important blood components are described. Where national requirements exist, they should be followed. Specifications of a number of products are described below.

6.7.1 Whole blood
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 NRASs acceptance criteria. 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. The temperature of whole blood stored for transfusion should remain controlled between 1° and 6°C or in a more stringent range defined by the NRASs. 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.
The primary use of whole blood is as a source material for the preparation of blood components. Transportation and further manufacturing processes should be developed to maximize the number of components that may be produced from a whole blood donation. 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. 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. The period between collection and further processing depends on the product but should not exceed 24 hours. The whole blood may also be filtrated to reduce leukocyte content prior to further processing. Components should be manufactured by a method validated as meeting the predefined product specifications.

6.7.2 Red-cell concentrate

Red-cell concentrates are obtained from whole blood by centrifugation and removal of plasma with or without buffy coat, depending on the centrifugation parameters. After subsequent addition of an appropriate nutrient solution, the red cells should be stored at 1–6°C as soon as possible. Alternatively, red-cell concentrates may be obtained using an apheresis system and likewise stored at 1–6°C. 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. 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. A fully validated procedure should be established to determine optimum conditions for use of a leukocyte reduction method. 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. 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.

6.7.3 Platelet concentrate

Platelet concentrates are derived from whole blood or are obtained by apheresis. 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 NRASs recommendations. The whole blood unit is centrifuged so that an optimal number of platelets remain in plasma (platelet-rich plasma, or PRP). Platelet concentrates are then obtained by hard-spin centrifugation of PRP and are then resuspended. 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. The platelet content per unit depends on the method of preparation. Similarly, the residual leukocyte content will vary according to the centrifugation parameters. 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. 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). A storage time should be defined in accordance with national regulations set by the NRASs; 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. 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.

### 6.7.4 Plasma for transfusion

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. 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. 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. 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 NRASs 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. The freezing process should be validated and should take place in a system that will allow complete freezing to a predetermined core temperature in a predefined time. 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. 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;
- leakage;
- visual changes;
- total protein (for plasma for fractionation).

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 plasma derived medicinal products, and in other publications. Plasma for transfusion is suitable as source material for the production of plasma derived medicinal 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 NRASs. Further complementary guidance with respect to the production of plasma for fractionation is available in WHO Recommendation on the production, control and regulation of human plasma for fractionation.

### 6.7.5 Plasma for fractionation

Plasma for fractionation 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. Regarding the quality indicators and the preparation process, as well as the infectious disease marker tests, the plasma has to fulfil the relevant pharmacopoeia monographs as well as the plasma specifications as defined by the manufacturer of the plasma-derived medicinal products. 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. 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. Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent. At a minimum, the defined critical parameters should be checked during the quality control assays, including total protein. Plasma should meet the specifications of the plasma fractionators and the requirements of the pharmacopoeia and NRAs. Further complementary guidance with respect to the production of plasma for fractionation is available in WHO Recommendation on the production, control and regulation of human plasma for fractionation.(5)

6.7.6 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;
- clottable fibrinogen;
- von Willebrand factor activity (if applicable).

Virus inactivation and/or quarantine are applied in some countries and should be implemented to ensure the safety of these products.

Under certain circumstances the use of small pool preparations of cryoprecipitate (by pooling single-donor cryoprecipitate units) may be desired.

6.8. Labelling

6.8.1 Label information

The collected blood, as well as intermediate and finished blood components, should be labelled with relevant information regarding their identity and release status. The type of label to be used, as well as the labelling methodology, should be established in written standard operating procedures. Whenever possible, machine-readable labels (barcodes) should be used. Information regarding the use of the blood product may also be applicable. In some countries the signature of the donor is also required.

6.8.2 Product name

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.

6.8.3 Expiry date

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 relabelling
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.

6.9. Release of blood and blood components

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. The release criteria and specifications of blood components should be defined, validated, documented and approved by quality assurance. Electronic release of products should be fully validated. The documented manufacturing processes should be followed at all times using validated methods and procedures. 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 should not be released for distribution. 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. The decision to release the component should not be made on the basis of a review of the collection processes alone; 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. Products that cannot be released should be destroyed and the record of destruction should be retained.

6.10. Quality monitoring

Quality control is one aspect of the quality assurance program. Its purpose is to determine, through testing or observation, if a process or particular task within a process is working as expected. If QC results are not within specifications, it may indicate a problem, either with the process itself or with how the process is being executed. Trends in QC results may indicate the potential for a problem in the future. Quality control data should demonstrate that critical manufacturing processes are under control. Blood and blood components should comply with specifications and their testing should be performed using test methods approved by the NRAS. Quality control of blood and blood components should be carried out according to a defined sampling plan based on statistical methods. The sampling plan should take into account different collection and production sites, transport, methods of preparation, and equipment used. Acceptance criteria should be based on a defined specification for each type of blood component. Whole blood or blood components should not be released for use if the quality control test indicates that the integrity of the product has been compromised. The work record should identify the test(s) employed so as to ensure that entries, such as the calculation of results, are available for review. Test results that do not meet the acceptance criteria should be clearly identified to ensure that blood components of that donation remain in quarantine and that relevant samples are selected for further testing. An investigation should be conducted into the cause of failure prior to additional or repeat testing. The results of quality monitoring testing should be subject to periodic review and trend analysis. If the results of quality monitoring suggest that the process is not meeting validated parameters and specifications, then corrective and preventive actions should be taken to correct identified problems before product manufacturing and distribution is continued. The compliance of the final blood components with their specifications should be periodically assessed to make sure they meet the defined standards of blood components.

Unless determined otherwise by statistical process control, at least 1% but not less than four units of each product type is to be tested per month. If the work load is < 500 donors per month then a minimum of 4 per month should be checked for components quality. Fresh Frozen Plasma (FFP) and platelets should be prepared only from those whole blood bags which are filled within 15 minutes of aseptic phlebotomy. Components should be prepared and stored within 8 hours from the blood...
The haematocrit (HCT) of packed cells should be 55-79% to ensure sufficient nourishment and anticoagulant is available to keep the red cells viable during its shelf life. Sometimes platelet bag contains red cells; if 2 ml or more red cells are present in the platelet bag than unit should be cross matched before issuance. The formula to calculate red cells volume in the bag:

\[ \text{Volume of red cells} = \text{Platelet bag HCT} \times \text{Plasma in bag} \]

For example, plasma volume is 55 ml and HCT is 1%. To calculate amount of red cell in the bag we divide 1 by 100 which is equal to 0.01. So 55 x 0.01 = 0.55 ml red cells are present in platelet bag.

The count of platelets should be > 5.5 x 10^10 per unit and pH measured at the end of the recommended shelf-life should be > 6.4, to ensure proper platelet function in the recipient. The pH of > 6.2 indicates proper storage conditions as platelets secrete lactic acid under stress, therefore lowering the pH in the fibrinogen level >140 mg/unit. Cryoprecipitate is tested for factor VIII and fibrinogen level which should have minimum of 80 IU of Factor VIII and >150 mg of fibrinogen in 100% of the tested units. Low level of factor VIII is seen in FFP and cryoprecipitate bags if the total FFP volume is less than 200 ml.

In the following tables, the main aspects of quality monitoring for some components are summarized.

### A. For Packed Red Cell:

* A segment is required after thorough mixing from each blood unit with the appropriate segment number (segments should be made after the preparation of the packed cells, before making the segment, strip the tubing by mixing blood and the remaining plasma very well).

* For packed red cell haematocrit testing, detach one segment (newly made, from packed red cell not the original segment made from whole blood) from three or four donor units of different types, made on different shifts if possible.

* Take the contents of each segment and place into a 12" x 75" test tube which is properly labelled with each unit number and mix well.

* Run these samples on the haematology analyser and record the results on the QC form.

Acceptable results for packed RBCs QC: at least 100% of units tested should have HCT percentage less than 80% when collected in CPDA-1.

* For leucodepleted packed red cells, all specifications are the same except residual WBC count which should be <5x10^6/unit.

* Store at 2-6°C for up to 35 days (with CPDA-1) or 42 days (with SAGM)

* Visually inspect packed cells for
  * Physical haemolysis
  * Clots
  * Grossly lipemic (milky white colour)
  * Signs of bacterial contamination of units by observing colour (brownish/purplish/murky or greyish) and consistency.

* Further, bag segment should also be looked for signs of haemolysis (pinkish or reddish colour plasma).

* Record results on QC form.

### B. For platelets

* Segment is required from each platelet unit with an appropriate segment number.

* At least 1% or 4 bags per month should be checked for quality control.

* After their expiry date, i.e. on the morning of 6th day, the random platelet concentrate unit should have at least > 0.55 x 10^11 platelet yield and pH should be 6.2 in at 90% of the tested donor units.

* Document the unit numbers of platelet concentrate to be tested for QC.
Then after thorough gentle mixing, aspirate 10 ml of platelet concentrate in a syringe from platelets bags, incubated at 20-24 °C for 12 - 24 hours at continuous agitation.

Fill two plain tubes labelled with the donor number (approximately 3 ml each). Send one tube to the haematology laboratory to have a platelet count and the other to chemistry laboratory to have a pH measurement (if the departments are separate).

For platelet count, run the sample on the haematology analyser and the platelet count for each donor on QC form.

Calculate the platelet yield of each unit by the following formula:

1) Yield of the unit = platelets count x weight of unit in gm (or volume ml) x 1,000 x 1,000

2) Platelet Yield = Platelet count x Plasma volume in platelet bag = _____ 

For example, platelet count is 1,200 ul and plasma volume is 55 ml then;

\[ \frac{1200 \times 55}{100,000} = 0.66 \times 10^{11} \text{ Yield which is more than the required yield, i.e. } >0.55 \times 10^{11} \]

Note down the yield on the QC form. Yield should be > 0.55 x 10^{11} in 90 % of the donor units tested (single donor unit).

For apheresis platelets units, the yield should be > 3.0 x10^{11} in 90 % of the apheresis donor units tested.

Check the pH of each platelet unit which should be > 6.2 in 90% of donor units tested.

Perform swirling test which should be positive.

Positive Swirling Test is because of discoid shape of the platelets. They move in circular direction when the bag is tilted upward and downward in light.

Negative Swirling Test is when the platelets are not moving in circular direction rather moving straight upward and downward indicating they are functionless and should not be transfused to the patients.

Also check for physical haemolysis or any bacterial contamination, by observing colour and consistency.

Record results on QC form.

---

C. For FFP

A segment is required from each FFP unit with an appropriate segment number (at least one segment will be sufficient).

At least 1% or 4 bags per month should be checked for quality control.

Allow FFP segments to thaw at 37 °C.

Transfer 3 ml plasma from the segment to a properly labelled 3 ml plastic serum tube.

Immediately send the tube to test for Factor VIII level and Fibrinogen.

Factor VIII level should be > 0.7 IU/ml or > 700 IU/L (if chromogenic Factor VIII kit is used for testing) and Fibrinogen level should be >140 mg/unit.

FFP volume should be 150 – 250 ml

FFP should be stored for 36 months at -25 °C or bellow; for 3 months between minus 18 °C and minus 25 °C. (EDQM)

Record results on QC form.

---

D. For Cryoprecipitate

At least 1% or 4 bags per month should be checked for quality control
Examine physical appearance of cryoprecipitate for abnormal colour, clots, precipitate, etc.

Volume should be 10-15 ml.

Factor VIII level should be > 80 IU per ml (with chromogenic Factor VIII kit).

Fibrinogen should be >150 mg/unit.

Cryoprecipitate should be stored at less than minus 18°C for one year.

Record results on QC form.

---

E. For Plasma for fractionation

Examples of reporting sheets are presented hereafter.

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Parameter</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cell Concentrates (RCC)</td>
<td>Volume</td>
<td>250 - 250 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% Hot</td>
<td>55 - 70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemolysis</td>
<td>&lt; 0.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sterility</td>
<td>Sterile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clot</td>
<td>Absent</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Parameter</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Concentrates</td>
<td>Volume</td>
<td>45 - 65 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swirling</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelet yield</td>
<td>≥ 6.5 x 10^9 / unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td>≥ 6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sterility</td>
<td>Sterile</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Parameter</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Concentrates (Apheresis)</td>
<td>Volume</td>
<td>150 - 300 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swirling</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelet yield</td>
<td>≥ 3.0 x 10^9 / unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH</td>
<td>≥ 6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sterility</td>
<td>Sterile</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Parameter</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>Volume</td>
<td>150 - 250 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F VIII</td>
<td>≥ 0.7 IU/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen</td>
<td>≥ 140 mg/unit</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>Parameter</th>
<th>Specification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoprecipitate (Single Donor Pack)</td>
<td>Volume</td>
<td>10-15 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F VIII</td>
<td>≥ 80 IU/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen</td>
<td>≥ 150 mg/unit</td>
<td></td>
</tr>
</tbody>
</table>
The quality monitoring data should be documented and assessed. An example of a form for this purpose is included.

**Form 4:2: Single Donor Platelets Quality Control Form**

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Unit #</th>
<th>Donors</th>
<th>Platelet Count</th>
<th>pH (expected pH 6.3)</th>
<th>Product Volume (ml)</th>
<th>Product Count</th>
<th>Product Yield* (Expected 3.0 ± 10^11 in 300 ml)</th>
<th>Procedure Done By</th>
<th>Culture &amp; Sensitivity (Negative)</th>
<th>QC by Tech</th>
<th>Remarks</th>
</tr>
</thead>
</table>

---

Examples of controls to be included in quality monitoring of blood components in a broader sense, are given here.

- Whole blood quality monitoring
  - Visual Inspection: Regularly inspecting blood bags for leaks, discoloration, or other abnormalities.
  - Temperature Monitoring: Monitoring temperature during storage and transportation to ensure it stays within the recommended range for whole blood.
  - Label Verification: Confirming accurate information on blood bags like blood type, collection date, and expiration.

- PRBCs quality monitoring
  - Visual Inspection: Regularly checking PRBC units for leaks, discoloration, haemolysis (red blood cell breakdown), or other abnormalities.
  - Haemoglobin Content: Testing PRBC units to ensure haemoglobin content meets established standards, indicating sufficient oxygen-carrying capacity.
  - Haematocrit: Measuring the volume of red blood cells in the PRBC unit to confirm it falls within the acceptable range.
  - Storage Temperature: Monitoring storage temperatures to ensure they stay within the recommended range for optimal PRBC quality.
  - Expiry Date: Verifying the expiry date on PRBC units to prevent issuing outdate blood components.

**7. Storage and distribution**

Storage

Standard operating procedures should describe the receipt, handling and storage of material, blood and blood components. There should be a system in place to maintain and control storage conditions, including any transportation that may be required. Storage areas for blood components to be dispatched should be located near an entrance or exit to facilitate dispatch and to limit the number of
persons entering the main working areas. Only authorized persons should have access to storage areas. 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. A temperature monitoring and recording system that is independent from the temperature regulation system should be in place. 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. If the temperature sensor is placed in a reference solution, no delay of the alarm should be accepted, and a person should be authorized to decide on the use or rejection of affected products. Temperature excursions may occur and each event should be evaluated using the deviation management system. An alternative storage area of appropriate temperature is recommended for recovery in case of temperature control failure of the primary system. 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. There should be a separate area for rejected components and material. 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 plasma or blood component quality. For the main blood components, the common storage temperatures are as follows:

- red-cell concentrate: 1–6°C;
- plasma for transfusion: minus 25°C or colder;
- platelets: 20–24°C;

or in a more stringent range defined by the NRAS. Higher storage temperatures (e.g., minus 20°C) might be acceptable for plasma for transfusion but may result in a significantly shorter shelf-life. Storage of platelets should also be controlled. Besides the temperature, the continuous agitation is very important. 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. During the whole collection and manufacturing process it should be ensured that blood or blood components are never placed in direct sunlight or near a heating source. All storage equipment should be subject to qualification, cleaning and preventive maintenance. Thermometers or temperature sensors should be calibrated annually. The temperature deviation to the standard measuring device should not exceed 1°C.

Distribution

There should be a record that identifies the person distributing and the hospitals or patients receiving the components. Dispatch of blood components should be made by authorized personnel. 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. Distribution should take place in a safe and controlled way in order to assure product quality during transport. All transportation and intermediate storage actions, including receipt and distribution, should be defined by written standard operating procedures and specifications. The shipping 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). The transportation and storage conditions for blood components, the packaging format and the responsibilities of the persons involved should be in accordance with standard operating procedures agreed between the sites in question.

8. Outsourced activity management

Although in Part A § 8.4.2 it is mentioned that blood components should not be released for sale or supply, it is not the intention to allow commercial selling of blood components.
The scope of this chapter is mainly focusing on outsourced activities that are relevant for the preparation, testing, storage or distribution of blood components by the blood establishments. It does not focus on contract aspects linked with external plasma contract manufacturing for production of plasma-derived medicinal products where other WHO guidelines are more relevant. (9)

**Authors and acknowledgments**

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