DEPARTMENT OF BIOLOGICAL STANDARDISATION, OMCL
NETWORK & HEALTHCARE (DBO)

GR/nko

Working document, with no legally binding status, intended exclusively for the addressees and their associates, under the responsibility of the addressees (listed opposite). Level 2

English / Anglais

PA/PH/TS (19) 5

Strasbourg, May 2019

EUROPEAN COMMITTEE (PARTIAL AGREEMENT) ON BLOOD TRANSFUSION (CD-P-TS)

GOOD PRACTICE GUIDELINES
for standards and specifications for implementing the quality system in blood establishments

-Draft text for the 20th Ed. of the Blood Guide to be submitted to the stakeholder consultation-

EDQM Responsible Scientific Officer: Guy Rautmann

Distribution

For action :

DG SANTE Policy Officers

For information :

EDQM address : 7 allée Kastner, CS 30026, FR-67081 Strasbourg (France)

GOOD PRACTICE GUIDELINES for standards and specifications for implementing the quality system in blood establishments

Introductory note

Good Practice Guidelines have been prepared through an *ad hoc* co-operation between the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM/CoE) and the Commission of the European Union (EU).

These Good Practice Guidelines were first published in the 19th Edition of the Guide to the preparation, use and quality assurance of blood components, Appendix to Recommendation No. R (95) 15 of the Committee of Ministers on the preparation, use and quality assurance of blood components.

With the publication of the 20th Edition of the Guide to the preparation, use and quality assurance of blood components, the text of the GPG was slightly amended by considering comments, mainly of editorial nature, to the text of the 19th Edition. These amendments are highlighted in the text to facilitate their identifications.

EU Member States shall ensure, according to Directive 2005/62/EC, that the quality system in place in all blood establishments complies with the standards and specifications set out in the Annex to that Directive.

In order to implement the standards and specifications set out in the Annex to Directive 2005/62/EC, its Article 2, as amended by Directive (EU) 2016/1214, is replaced by the following:

> *Member States shall ensure that, in order to implement the standards and specifications set out in the Annex to this Directive, there are good practice guidelines available to and used by all blood establishments, in their quality system, good practice guidelines which take fully into account, where relevant for blood establishments, the detailed principles and guidelines of good manufacturing practice, as referred to in the first subparagraph of Article 47 of Directive 2001/83/EC. In doing so, Member States shall take into account the Good Practice Guidelines jointly developed by the Commission and the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe and published by the Council of Europe.*

Council of Europe Member States should take the necessary measures and steps to implement the Good Practice Guidelines published in this 19th Edition of the Guide to the preparation, use and quality assurance of blood components. These Good Practice Guidelines provide guidance on how to implement the standards and specifications of quality systems that Member States shall ensure are in place in blood establishments and hospital blood banks.

Good Practice Guidelines for blood establishments and hospital blood banks

1.^> General principles

1.1. General requirements

1.1.1. Each blood establishment must develop and maintain a Quality System that is based on EU Good Manufacturing Practices (GMP) Directive 2003/94/EC and meets the requirements identified in Directive 2005/62/EC and its Article 2, as amended by Directive (EU) 2016/1214.

1.1.2. For blood and blood components imported from third countries and intended for use or distribution in the EU, there must be a Quality System for blood establishments in the stages preceding importation equivalent to the Quality System provided for in Article 2 of Directive 2005/62/EC.

1.1.3. Quality must 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 (Directive 2005/62/EC/Annex 1.1.1).

1.1.4. Attainment of this quality objective is the responsibility of executive 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 ~~must~~ 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.

1.2. Quality system

1.2.1. Quality Management is a wide-ranging concept covering all matters, which 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 and internal auditing, contract management, non-conformance and self-inspection (Directive 2005/62/EC/Annex 1.1.2).

1.2.3. The Quality System must 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 as set out in the chapters on Standards in this *Guide* (which includes the Annex to Directive 2005/62/EC).

1.2.4. The Quality System ~~must~~ should be designed to assure the quality and safety of prepared blood and blood components, as well as ensure donor and staff safety and customer service. This strategy requires the development of clear policies, objectives and responsibilities. It also requires implementation by means of quality planning, quality control, quality assurance and quality improvement to ensure the quality and safety of blood and blood components, and to provide customer satisfaction.

1.2.5. Executive 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. ~~Executive~~ 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. ~~Executive~~ 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 ~~must~~ should be supported by a quality assurance function (whether internal or related) for fulfilling quality assurance. That function must be involved in all quality-related matters, and must review and approve all appropriate quality-related documents (Directive 2005/62/EC/Annex 1.2.1).

1.2.9. An independent function with responsibility for quality assurance ~~must~~ 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 must be validated before introduction and must be re-validated at regular intervals, as determined as a result of these activities (Directive 2005/62/EC/Annex 1.2.2).

1.2.11. A general policy regarding qualification of facilities and equipment as well as validation of processes, automated systems and laboratory tests ~~must~~ 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 ~~must~~ 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 must be evaluated, and the degree of revalidation or additional testing, qualification and validation needed must be determined.

1.2.13. A formal system for the handling of deviations and non-conformances ~~must~~ 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 must review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary (Directive 2005/62/EC/Annex 1.1.3).

1.2.15. There should be periodic management review and monitoring both of its effectiveness, with the involvement of ~~executive~~ senior management and of the operation of the Quality System to identify opportunities for continual improvement of blood and blood components processes and the system itself.

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 improvements in both component and process.

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 manufacturing 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, non-conformances, and the corrective actions implemented;

1.2.17.8. review of the findings of internal and external audits and inspections, and 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:

1.3.1.1.1. 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;

1.3.1.1.3. instructions and procedures are written in an instructional form in clear and unambiguous language, and are applicable specifically to the facilities provided;

1.3.1.1.4. operators are trained to carry out procedures correctly;

1.3.1.1.5. 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;

1.3.1.1.6. any significant deviations are fully recorded and investigated;

1.3.1.1.7. 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;

1.3.1.1.8. the distribution of the blood and blood components minimises any risk to their quality;

1.3.1.1.9. 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);

1.3.1.1.10. 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, 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. Rolling 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; 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.

2.^> Personnel and organisation

2.1. Personnel must 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 (Directive 2005/62/EC/Annex 2.1).

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’ following Article 9 of Directive 2002/98/EC;

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, equipment, reagents and blood and blood components;

2.3.5. a physician with the responsibility for ensuring the safety of donors and a physician or pharmacist with responsibility for the safety of the distributed blood components.

2.4. All personnel must have up-to-date job descriptions, which clearly set out their tasks and responsibilities. Responsibility for processing management and quality assurance must be assigned to different individuals, and who function independently (Directive 2005/62/EC/Annex 2.2).

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 must receive initial and continued training appropriate to their specific tasks. ~~Training records must be maintained.~~ Training programmes must be in place and must include Good Practice (Directive/2005/62/EC/Annex 2.3). Training records ~~must~~ should be maintained.

2.8. Training should be provided for all personnel whose duties take them into preparation areas or into laboratories (including the 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 programmes must be periodically assessed and the competence of personnel evaluated regularly (Directive/2005/62/EC/Annex 2.4).

2.11. Only persons who are authorised by defined procedures and documented as such may be involved in the collection, processing, testing and distribution processes, including quality control and quality assurance.

2.12. There must be written safety and hygiene instructions in place, adapted to the activities to be carried out, and in compliance with Council Directive 89/391/EEC and Directive 2000/54/EC of the European Parliament and of the Council (Directive/2005/62/EC/Annex 2.5).

2.13. 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.

2.14. It is the organisation's responsibility to provide instructions on hygiene and health conditions that can be of relevance to the quality 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 to use the hand-washing facilities.

2.15. 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 of blood and blood components are reported by the personnel.

2.16. 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.

2.17. Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the processing, testing 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

3.1.1. Premises including mobile sites must be located, constructed, adapted and maintained to suit the activities to be carried out. They must enable work to proceed in a logical sequence so as to minimise the risk of errors, and must allow for effective cleaning and maintenance in order to minimise the risk of contamination (Directive/2005/62/EC/Annex 3.3.1).

3.1.2. 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.

3.1.3. Premises should be designed and equipped so as to afford protection against the entry of insects or other animals.

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

3.1.5. Facilities should permit ease of maintenance and cleaning. Open drains should be avoided.

3.1.6. Preparation areas should be ventilated effectively, with air-control facilities (including temperature and, if necessary, humidity and filtration) appropriate to the operations undertaken within them and to the external environment.

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

3.1.~~6~~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 must be an area for confidential personal interviews with, and assessment of, individuals to assess their eligibility to donate. This area must be separated from all processing areas (Directive/2005/62/EC/Annex 3.3.2).

3.2.2. Premises ~~must~~ should satisfy ~~common-sense~~ 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 must 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 must 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 (Directive/2005/62/EC/Annex 3.3.3).

3.3.2. Before premises are accepted for mobile donor sessions, their suitability ~~must~~ 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 supply, lighting, toilet and hand-washing facilities;

3.3.2.4. reliable communication, blood storage and transport;

3.3.2.5. guarantee of adequate interim storage.

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 must 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 must be used only for the intended purpose (Directive/2005/62/EC/Annex 3.3.4).

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 must 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 must be restricted to authorised persons (Directive/2005/62/EC/Annex 3.3.5.1).

3.5.2. Provisions must be in place in the event of equipment failure or power failure in the main storage facility (Directive/2005/62/EC/Annex 3.3.5.2).

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 ~~must~~ 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. ~~Special attention should be paid to the safe and secure storage of printed packaging materials (including sets of donation identifier labels).~~ Printed packaging materials (including sets of donation identifier labels) should be stored safely and in a secured 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 processing, laboratory or storage 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 must be designated for the safe disposal of waste, disposable items used during collection, testing and processing and for rejected blood or blood components (Directive/2005/62/EC/Annex 3.6).

4.^> Equipment and materials

4.1. General requirements

4.1.1. All equipment must be qualified, calibrated and maintained to suit its intended purpose. Operating instructions must be available and appropriate records kept (Directive/2005/62/EC/Annex 4.1).

4.1.2. Equipment must be selected to minimise any hazard to donors, personnel or blood components (Directive/2005/62/EC/Annex 4.2).

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

4.1.4. All critical equipment ~~must~~ should have regular, planned maintenance to detect or prevent avoidable errors and keep the equipment in its optimum functional state. The maintenance intervals and actions ~~must~~ should be determined for each item of equipment.

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

4.1.6. All modifications, enhancements or additions to validated systems and equipment ~~must~~ 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, ~~must~~ should be determined to identify the extent of revalidation required.

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

4.1.8. Procedures ~~must~~ 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 ~~must~~ should be used. Critical materials ~~must~~ should be released by a person qualified to perform this task. If relevant, materials, reagents and equipment must meet the requirements of Council Directive 93/42/EEC for medical devices and Directive 98/79/EC of the European Parliament and of the Council for in vitro diagnostic medical devices, or comply with equivalent standards in the case of collection in third countries (Directive/2005/62/EC/Annex 4.3).

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-~~in~~expiring first-out' principle (i.e. the material that ~~entered storage~~ expires first should be used first) ~~taking into account the expiry date of materials~~.

4.1.14. Inventory records must be retained for a period acceptable to and agreed with the competent authority (Directive/2005/62/EC/Annex 4.4).

4.1.15. Equipment and material inventory records ~~must~~ 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 ~~must~~ 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 standard. The report and/or calibration certificate ~~must~~ 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 must be checked regularly to ensure reliability, be validated before use, and be maintained in a validated state. Hardware and software must be protected against unauthorised use or unauthorised changes. The back-up procedure must prevent loss of or damage to data at expected and unexpected down-times or function failures (Directive/2005/62/EC/Annex 4.5).

4.2.2. Systems ~~must~~ should be properly maintained at all times. Documented maintenance plans ~~must~~ should be developed and implemented. This strategy ~~must~~ should include audits of quality assurance systems.

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

4.2.4. There ~~must~~ should be a hierarchy of permitted user access to enter, amend, read or print data. Methods of preventing unauthorised entry ~~must~~ should be in place, such as personal identity codes or passwords that are changed regularly.

4.2.5. All necessary measures ~~must~~ should be taken to ensure protection of data. These measures ~~must~~ 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.

4.2.6. 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. Preventing release of any components from a future donation from a deferred donor should be possible.

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 collection, preparation, testing, 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 through 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 lifecycle 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/hospital blood banks 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, process and product 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;

534	4.3.2.4.6.	references to existing documents;
535	4.3.2.4.7.	the qualification and validation strategy, including requalification, where applicable.
536 537	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.
538 539 540 541 542	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.
543 544	4.3.2.7	Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.
545	4.3.3.	Documentation including VMP
546 547 548 549	4.3.3.1	Good documentation practices are important to support knowledge management throughout the product lifecycle. 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.
550 551	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.
552 553	4.3.3.3.	Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).
554 555	4.3.3.4.	Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.
556 557	4.3.3.5.	The ~~inter~~relationship and links between documents in complex validation projects should be ~~clearly defined~~ established.
558 559 560 561	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.
562 563 564	4.3.3.7.	Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.
565 566 567 568	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.
569 570 571 572 573 574	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.
575	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 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 user requirements specification should be verified during the design qualification.

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, at 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). It 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. installations 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 pre-defined 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 Installation/Operation Qualification (IOQ). OQ should include, but is not limited to, the following:

4.3.4.6.1. tests that have been developed from knowledge of processes, systems and equipment to ensure the system is operating as designed;

4.3.4.6.2. tests to confirm upper and lower operating limits, and/or ‘worst case’ conditions.

4.3.4.7. 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:

4.3.4.7.1. 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;

4.3.4.7.2. 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. Re-qualification

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, subsequent validation of modified processes or site transfers for maintaining of 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 manufacture. 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. A critical quality attributes (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 quality. A critical process parameter (CPP) is a process parameter whose variability has an impact on a critical quality attribute and which therefore should be monitored or controlled to ensure the process produces the desired quality. 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 ~~utilities~~ 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 process validation a variety of personnel may be involved in the preparation of blood components. Blood components should only be prepared by trained personnel in accordance with good practice using approved documentation. It is expected that processing personnel are involved in the preparation of blood components during validation to facilitate understanding of the process.

4.4.1.9. The suppliers of critical materials should be qualified prior to 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 pre-defined. 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 and 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 ~~assurance~~ 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 critical process parameters (CPP), critical quality attributes (CQA) 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) why each in-process control is selected;

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 manufacture.

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 lifecycle 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, as defined in 11.2.

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

4.6. Change control

4.6.1. 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.

4.6.2. 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, equipment, environment (or site), product range, method of production or testing or any other change that may affect donor safety , blood component quality or reproducibility of the process.

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

4.6.4. 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.

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

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

4.7. Control of equipment and materials

4.7.1. General principles

4.7.1.1. 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.

4.7.1.2. The contracting process should include:

4.7.1.2.1. checks prior to awarding the contract to help ensure suppliers meet the organisation's needs;

4.7.1.2.2. appropriate checks on received goods to confirm they meet specifications;

4.7.1.2.3. the requirement for manufacturers to provide a certificate of analysis for critical material;

4.7.1.2.4. checks to ensure that goods in use continue to meet specifications;

4.7.1.2.5. regular contact with suppliers to help understand and resolve problems;

4.7.1.2.6. performance of regular audits.

4.7.1.3. Assessment of the performance of equipment should occur in the following situations:

4.7.1.3.1. upon commissioning of new equipment, which ~~must~~ should include design, installation, operational and performance qualifications, and full validation data from the manufacturer;

4.7.1.3.2. after any relocation, repairs or adjustments that might potentially alter equipment functioning;

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

4.7.1.4. Consideration should be given to the quality, safety and efficacy of any blood components prepared before discovery of the fault adjustment.

4.7.2. Calibration and monitoring of equipment

4.7.2.1. 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.

4.7.2.2. 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 international standard. The calibration status of all equipment that requires calibration should be readily available.

4.7.2.3. 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.

4.7.2.4. 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.

4.7.2.5. The training programme should be reassessed for any critical change in environment, equipment or processes. Training records (including plans and protocols of training status) ~~must~~ should ensure that training needs are identified, planned, delivered and documented appropriately for maintenance of validated systems and equipment.

4.7.2.6. The ability of a supplier to maintain its activities relating to a system or equipment ~~must~~ should be re-qualified 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 re--qualification process depends on the level of risk of using the system or equipment, and should be planned for each supplier.

4.7.2.7. 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 ~~must~~ 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 must be in place and kept up-to-date (Directive/2005/62/EC/Annex 5.1).

5.2.2. Instructions (directions or requirements)

5.2.2.1. Specifications describe in detail the requirements to which the blood and blood components or materials used or obtained during preparation and distribution ~~must~~ should conform. They serve as a basis for quality evaluation (specifications set out in the Standards section of *Chapter 5 – Component monographs* contained in the *Guide to the preparation, use and quality assurance of blood components* published by the Council of Europe 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 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'.

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~~ homogenous systems.

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

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

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. Standard Operating Procedures, 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 must be acted upon promptly, and must be reviewed, dated and signed by a person authorised to undertake this task (Directive/2005/62/EC/Annex 5.3).

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

5.4. Good documentation practices

5.4.1. Records must be legible and may be handwritten, transferred to another medium such as microfilm, or documented in a computerised system (Directive/2005/62/EC/Annex 5.2).

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, processing, testing and distribution of blood and blood components are traceable.

5.4.3. The record system ~~must~~ should ensure continuous documentation of the procedures performed from the blood donor to the recipient. That is, each significant step ~~must~~ 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 ~~must~~ should be in place to ensure the integrity of the record throughout the retention period. These controls ~~must~~ should be validated if appropriate.

5.5.2. Specific retention requirements for certain documentation apply.

5.5.2.1. Records ~~must~~ should be retained for a period according to local, national or EU requirements, as appropriate.

5.5.2.2. Traceability data (that allow tracing from donor to recipient and vice versa) should be retained for a minimum of 30 years (Directive 2002/98 Article 14.3).

5.5.2.3. Documentation regarding investigations into Serious Adverse Events and Serious Adverse Reactions should be retained for a minimum of 15 years.

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 ~~must~~ 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 (specifications set out in the Standards section of Chapter 5 - Component monographs contained in the Guide to the preparation, use and quality assurance of blood components published by the Council of Europe may be used). Components must be labelled in accordance with Directive 2002/98/EC.

5.7. Preparation instructions

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

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

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

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

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

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

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

5.7.1.7. any special precautions to be observed.

5.8. Labelling

5.8.1. At all stages of the preparation, labelling should identify the individual components and their nature clearly.

~~Requirements for in-process labelling.~~ The label on an intermediate component should always allow the stage of processing to be determined and should always include:

5.8.1.1. the name of the component;

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

5.8.1.3. the name of the producing blood establishment.

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

5.8.2.1. the name and unique identifier of the component;

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

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

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

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

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

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

5.8.2.8. information on the processing of non-standard components with signed authorisation.

5.9. Procedures and records

5.9.1. Receipt

5.9.1.1. 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:

5.9.1.1.1. the name of the material on the delivery note and the containers;

5.9.1.1.2. the 'in-house' code (if any) of the material;

5.9.1.1.3. date of receipt;

5.9.1.1.4 the names of the supplier and manufacturer;

5.9.1.1.5. the batch or reference number of the manufacturer;

5.9.1.1.6 the total quantity and number of items received;

5.9.1.1.7. the batch number assigned after receipt (as applicable);

5.9.1.1.8. the name/ID of the person who received the shipment;

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

5.10.3. There should be written procedures for 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 release and rejection procedures should be available.

5.11.2. Records should be maintained of the distribution of blood components to facilitate recall of any unit, 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 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 ~~must~~ should be implemented and maintained. They ~~must~~ should take place immediately before each donation and comply with the requirements set out in Annex II and Annex III to Directive 2004/33/EC (Directive/2005/62/EC/Annex 6.1.1).

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

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

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

6.1.5. The selection process ~~must~~ 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 ~~direction~~ responsibility of a physician. This assessment involves an interview, a questionnaire and further direct questions, if necessary.

6.1.6. The questionnaire ~~must~~ should be designed to elicit information relevant to the health and lifestyle of the donor. It ~~must~~ should be designed to be understandable by the donor and given to all donors each time they attend. On completion, it ~~must~~ should be signed by the donor.

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

6.1.8. The donor interview must be conducted in such a way as to ensure confidentiality (Directive/2005/62/EC/Annex 6.1.2).

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

6.1.10. Records of suitability and final assessment of donors must be signed by a qualified healthcare professional (Directive/2005/62/EC/Annex 6.1.3).

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 ~~must~~ should be in place to ensure that the donor is prevented from making future donations during a permanent or temporary deferral period (including for the duration of a temporary deferral).

6.1.12. Donors ~~must~~ should be instructed to inform the blood establishment 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 donation unsuitable for transfusion.

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

6.2. Collection of blood and blood components

6.2.1. The procedure for blood collection must 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 (Directive/2005/62/EC/Annex 6.2.1).

6.2.2. Donor identity ~~must~~ 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 must be CE-marked or comply with equivalent standards if the blood and blood components are collected in third countries. The batch number of the bag must be traceable for each blood component (Directive/2005/62/EC/Annex 6.2.2).

6.2.6. All handling of materials and reagents, such as receipt and quarantine, sampling, storage, labelling, processing, packaging and distribution, 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. Blood collection procedures must minimise the risk of microbial contamination (Directive/2005/62/EC/Annex 6.2.3).

6.2.8.1. Sterile collection and processing systems for blood should be used for blood and blood components. Collection systems should be used in accordance with manufacturer 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 discolouration 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 ~~must~~ should be free from lesions, including eczema.

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

6.2.8.6. The effectiveness of the disinfection procedure ~~must~~ 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 ~~must~~ 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. Standard Operating Procedures 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 must be taken at the time of donation and be appropriately stored prior to testing (Directive/2005/62/EC/Annex 6.2.4).

6.2.10. The procedure used for the labelling of records, blood bags, and laboratory samples with donation numbers must be designed to avoid any risk of identification error and mix-up (Directive/2005/62/EC/Annex 6.2.5).

6.2.11. After blood collection, blood bags must 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 (Directive/2005/62/EC/Annex 6.2.6).

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, it 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 must 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 (Directive 2005/62/EC/Annex 6.2.7).

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 to the recipient.

6.3.2. All laboratory testing procedures must be validated before use (Directive 2005/62/EC/Annex 6.3.1).

6.3.3. In addition to the validation of the test system by the manufacturer, an on-site validation 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 must be data confirming the suitability of any laboratory reagents used in testing of donor samples and blood-component samples (Directive 2005/62/EC/Annex 6.3.4).

6.3.8. Testing of blood components should be carried out in accordance with the recommendations of the manufacturer 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 ~~must~~ should be performed on samples before purchasing batches of commercial reagents. Prospective purchasers ~~must~~ should require potential suppliers to provide them with full validation data for all lots of reagents. Each lot of reagent ~~must~~ should

be qualified by the purchaser to demonstrate suitability for its intended purpose within the system used for testing.

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

6.3.11. The quality of the laboratory testing must be assessed regularly by participation in a formal system of proficiency testing, such as an external quality-assurance programme (Directive/2005/62/EC/Annex 6.3.5).

6.4. Testing for infectious markers

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

6.4.2. Each donation must be tested in conformity with the requirements laid down in Annex IV to Directive 2002/98/EC (Directive 2005/62/EC/Annex 6.3.2).

6.4.3. Additional testing for other agents or markers may be required, taking into account the epidemiological situation in any given region or country.

6.4.4. Serological testing should be performed on samples transferred directly into the analyser from the original sample tube. 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 ~~must~~ should be clearly defined procedures to resolve discrepant results.

6.4.7 Blood and blood components that have a repeatedly reactive result in a serological screening test for infection with the viruses mentioned in Annex IV to Directive 2002/98/EC must be excluded from therapeutic use and must be stored separately in a dedicated environment.

6.4.8 Appropriate confirmatory testing must take place. In the case of confirmed positive results, appropriate donor management must take place, including the provision of information to the donor and follow-up procedures (Directive 2005/62/EC/Annex 6.3.3).

6.4.~~7~~9. Screening algorithms should be defined precisely in writing (i.e. Standard Operating Procedures) 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 must include procedures for testing specific groups of donors (e.g. first-time donors, donors with a history of transfusion) (Directive/2005/62/EC/Annex 6.3.6).

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.

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 and, 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 ~~Health~~ Authority/Competent Authority ~~must~~ should be used. In the EU, these reagents are considered as in vitro diagnostic devices and ~~must~~ should be CE-marked.

6.5.7. EU Directive 98/79/EC classifies ABO, Rh (C, c, D, E, e) anti-Kell reagents in list A of Annex II. The manufacturer of such reagents ~~must~~ should have a full Quality System certified by an authorised body, and ~~must~~ should submit an application containing all the control results for each lot.

6.5.8. Quality-control procedures ~~must~~ should be implemented for the equipment, reagents and techniques used for ABO and RhD blood grouping and phenotyping as well as detection and identification of allo-antibodies. The frequency of the control is dependent on the method used.

6.6. Processing and validation

6.6.1. All equipment and technical devices must be used in accordance with validated procedures (Directive/2005/62/EC/Annex 6.4.1).

6.6.2. The processing of blood components must be carried out using appropriate and validated procedures, including measures to avoid the risk of contamination and microbial growth in the prepared blood components (Directive/2005/62/EC/Annex 6.4.2).

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 undertaken 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.

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 ~~must~~ 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 ~~must~~ should be checked for satisfactory alignment and its integrity ~~must~~ should be confirmed.

6.7. Labelling

6.7.1. At all stages, all containers must be labelled with relevant information on their identity. In the absence of a validated computerised system for status control, the labelling must clearly distinguish released from non-released units of blood and blood components (Directive 2005/62/EC/Annex 6.5.1).

6.7.2 Type of label to be used, as well as the labelling methodology, should be defined and established in written Standard Operating Procedures.

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 must unmistakably identify the type of content, and comply with the labelling and traceability requirements referred to in Article 14 of Directive 2002/98/EC and Directive 2005/61/EC.

6.7.5 The label for a final blood component must comply with the requirements of Annex III to Directive 2002/98/EC (Directive 2005/62/EC/Annex 6.5.2).

6.7.6. Blood establishments responsible for the preparation of blood components must provide clinical users of blood components with information on their use, composition, and any special conditions that do not appear on the component label.

6.7.7. For autologous blood and blood components, the label must also comply with Article 7 of Directive 2004/33/EC and the additional requirements for autologous donations specified in Annex IV to that Directive (Directive 2005/62/EC/Annex 6.5.3).

6.8. Release of blood and blood components

6.8.1. There must be a safe and secure system to prevent any single blood sample and blood component from being released before all mandatory requirements set out in Directive 2005/62/EC have been fulfilled. Each blood establishment must be able to demonstrate that each blood or blood component has been formally ~~released~~ approved for release by an authorised person. Records must demonstrate that before a blood component has been released, all current declaration forms, relevant medical records, and test results have met all acceptance criteria (Directive 2005/62/EC/Annex 6.6.1).

6.8.2. There should be Standard Operating Procedures 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 must 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 must identify the release status in accordance with point 6.5.1 stated above (Directive 2005/62/EC/Annex 6.5.1 and 6.6.2).

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 component fails to be released due to a confirmed positive test result for infection for an agent mentioned in Annex IV of Directive 2002/98/EC, a check must 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 must be made to the donor record (Directive 2005/62/EC Annex 6.3.2, 6.3.3 and 6.6.3).

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

7.^> Storage and distribution

7.1. The Quality System of the blood establishment must ensure that, for blood and blood components intended for the manufacture of medicinal products, the requirements for storage and distribution must comply with Directive 2003/94/EC (Directive 2005/62/EC/Annex 7.1).

7.2. Procedures for storage and distribution must 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, must be defined by written procedures and specifications (Directive 2005/62/EC/Annex 7.2).

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

7.6. Autologous blood and blood components, as well as blood components collected and prepared for specific purposes, must be stored separately (Directive 2005/62/EC/Annex 7.3).

7.7. Appropriate records of inventory and distribution must be kept (Directive 2005/62/EC/Annex 7.4).

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

7.9. Packaging must maintain the integrity and storage temperature of blood and blood components during distribution and transportation (Directive 2005/62/EC/Annex 7.5).

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 re-issue must 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 (Directive 2005/62/EC/Annex 7.6).

7.12. Blood components ~~must~~ 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 ~~must~~ should identify that the blood component has been inspected before reissue.

8.^> Outsourced activities management

8.1. General principles

8.1.1. Tasks that are performed externally must be defined in a specific written contract (Directive 2005/62/EC/Annex 8).

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. All outsourced arrangements for blood collection, processing and testing, 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.

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

8.2.3. 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.

8.3. The contract acceptor

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

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

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

8.3.4. 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.

8.4. The contract

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

8.4.2. 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.

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

8.4.4. 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.

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

9.^> Non-conformance and recall

9.1. Deviations

9.1.1. Blood components deviating from required standards set out in Annex V to Directive 2004/33/EC shall be released for transfusion only in exceptional circumstances and with the recorded agreement of the prescribing physician and the blood establishment physician (Directive 2005/62/EC/Annex 9.1).

9.1.2. The same principle applies to ~~For~~ components not listed in Annex V to Directive 2004/33/EC when considering release of components deviating from defined quality and safety specifications ~~standards set out in the Standards section of *Chapter 5 – Component monographs* contained in the Guide to the preparation, use and quality assurance of blood components published by the Council of Europe may be used to meet the intent of 9.1.1 above~~.

9.1.3. 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.

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

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

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

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

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

9.1.9. ~~Executive~~ 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 resource should be made available for their timely resolution.

9.1.10. A regular review of all significant deviations or non-conformances should be conducted, including their related investigations, to verify the effectiveness of the corrective and preventive actions taken.

9.2. Complaints

9.2.1. All complaints and other information, including serious adverse reactions and serious adverse events that may suggest that defective blood components have been issued, ~~must~~ 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 must 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 (Directive 2005/62/EC/Annex 9.2).

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

9.2.3. 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.

9.2.4. 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.

9.2.5. 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 counterfeiting.

9.3. Recall

9.3.1. There must 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 (Directive 2005/62/EC/Annex 9.3.1).

9.3.2. An effective recall procedure must be in place, including a description of the responsibilities and actions to be taken. This must include notification of the Competent Authority (Directive 2005/62/EC/Annex 9.3.2).

9.3.3. Actions ~~must~~ should be taken within pre-defined periods of time and ~~must~~ should include tracing all relevant blood components and, where applicable, ~~must~~ 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 (Directive 2005/62/EC/Annex 9.3.3).

9.3.4. 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.

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

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

9.3.7. 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.

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

9.4. Deviation management and corrective and preventive actions

9.4.1. A system to ensure corrective and preventive actions for blood component nonconformity and quality problems must be in place (Directive 2005/62/EC/Annex 9.4.1).

9.4.2. Data must be routinely analysed to identify quality problems that may require corrective action or to identify unfavourable trends that may require preventive action (Directive 2005/62/EC/Annex 9.4.2).

9.4.3. All errors and accidents must be documented and investigated in order to identify problems for correction (Directive 2005/62/EC/Annex 9.4.3).

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

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

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

9.4.7. The decisions that are made during and following investigations should reflect the level of risk that is presented by the deviation as well as the seriousness of any non-compliance with respect to the requirements of the blood component specifications or ~~GP~~ 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.

9.4.8. As part of periodic Quality System reviews, an assessment should be made of whether corrective and preventive actions 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.

10.^> Self-inspection, audits and improvements

10.1. Self-inspection or audit systems must be in place for all elements of operations to verify compliance with the standards set out in the Annex to Directive 2005/62/EC. They must be carried out regularly by trained and competent persons, in an independent way, and according to approved procedures (Directive 2005/62/EC/Annex 10.1).

10.2. All results must be documented and appropriate corrective and preventive actions must be taken in a timely and effective manner (Directive 2005/62/EC/Annex 10.2).

11.^> Quality monitoring and control

11.1. Quality monitoring

11.1.1. Acceptance criteria ~~must~~ should be based on a defined specification for each blood donation and blood component (specifications set out in the Standards section of *Chapter 5 – Component monographs* contained in the Guide to the preparation, use and quality assurance of blood components published by the Council of Europe may be used).

11.2. Quality control

11.2.1. All quality control procedures ~~must~~ should be validated before use.

11.2.2. Results of quality-control testing ~~must~~ should be evaluated continuously and steps taken to correct defective procedures or equipment.

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

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

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

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

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