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

TS066 - Good Practice Guidelines for elements of the Quality System

Good Practice Guidelines adopted by the CD-P-TS
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“Good Practice Guidelines for Blood Establishments and Hospital Blood Banks Required to Comply with EU Directive 2005/62/EC”

Introductory remarks:

The Good Practice Guidelines have been elaborated as an ad hoc co-operation between the European Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM/CoE), and the Commission of the European Union under the Grant Agreement No 2010 53 05. They are published on the EDQM website to make them accessible to a large audience.

The Good Practice Guidelines were adopted by the European Committee on Blood Transfusion (CD-P-TS) of the Council of Europe during its plenary session in November 2013. The document will become an integral part of the 18th Edition of the Council of Europe *Guide to the Preparation, Use and Quality Assurance of Blood Components* and will replace “Appendix 1: Interim elements of good practice guidelines for blood establishments and hospital blood banks that are required to comply with EU Directive 2005/62/EC” published in the 17th Edition.

The Good Practice Guidelines are considered, as is the section “Standards”, to be “minimum standards”. These parts of the *Guide to the Preparation, Use and Quality Assurance of Blood Components* are intended to assist legislators to transpose these into national legislation.

The document identifies the quality system elements that must be met by blood establishments and hospital blood banks that are required to comply with EU Directive 2005/62/EC. It incorporates the “quality system standards and specifications” contained in the Annex of EU Directive 2005/62/EC, the quality system Standards and Principles derived from the *Guide to the Preparation, Use and Quality Assurance of Blood Components* (17th edition), as well as quality system elements derived from the detailed principles of GMP (as referred to in Article 47 of EU Directive 2001/83/EC).

Good Practice Guidelines for Blood Establishments and Hospital Blood Banks Required to Comply with EU Directive 2005/62/EC

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 the Directive 2005/62/EC.
- 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. The attainment of this quality objective is the responsibility of executive management and requires the participation and commitment by staff in many different departments and at all levels within the organisation, by the organisation's suppliers and by its distributors. To achieve this quality objective reliably there must 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, incorporating Good Practice and Quality Control.
- 1.1.6. The basic concepts of Quality Management, Good Practice and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their 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 of Directive 2005/62/EC).
- 1.2.4. The Quality System must be designed to assure the quality and safety of prepared blood and blood components and also ensure donor and staff safety and customer service. This requires the development of clear policies, objectives and responsibilities, and implementation by means of quality planning, quality control, quality assurance and quality improvement in order 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 an effective Quality System is in place, adequately resourced and that roles and responsibilities, are defined, communicated and implemented throughout the organisation. Executive 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 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 and should 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 should contain a description of the Quality System including management responsibilities.

- 1.2.8. All blood establishments and hospital blood banks must be supported by a quality assurance function, whether internal or related, in 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 be established. This quality assurance function will be responsible for 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 prior to introduction and be re-validated at regular intervals, 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 and validation of processes, automated systems and laboratory tests must 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 be in place to plan, evaluate and document all changes that may affect the quality, traceability, availability or effect of components or safety of components, donors or patients. The potential impact of the proposed change must be evaluated and the degree of re-validation 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 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 can be determined using Quality Risk Management principles. In cases where 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 those. 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 preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line 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 of its effectiveness, with the involvement of Executive management, of the operation of the Quality System to identify opportunities for continual improvement of blood and blood components, processes and the system itself.

1.3. Good Practice

1.3.1. Good Practice is that part of Quality Management which ensures that blood and blood components are consistently produced and controlled 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 clearly defined, systematically reviewed 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 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, specifically applicable 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 which 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 and to prevent reoccurrence.
- 1.3.1.2. Quality Control is that part of Good Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that materials are not released for use in preparation, and blood and blood components not released for distribution, until their quality has been judged to be satisfactory and that the necessary and relevant tests have actually been carried out. The basic requirements are:
- 1.3.1.2.1. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate components, and finished blood and blood components, and where 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 fully recorded and investigated;
 - 1.3.1.2.5. the finished blood and blood components comply with the specifications and are correctly labeled;
 - 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 are not in accordance 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, the appropriateness of current specifications for both starting materials and finished blood components to highlight any trends and to identify product and process improvements.

1.4. Quality Risk Management

1.4.1. Quality Risk Management is that part of the Quality System which 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 on-going process capability.

1.4.2. The Quality System should ensure that processes are in place to ensure the control of out-sourced 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 is ultimately connected to the 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 should 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 effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.3. 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).

- 2.4. 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.
- 2.5. Individual responsibilities should be clearly understood by the individuals and recorded. Personnel signature lists should be available.
- 2.6. 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).
- 2.7. Training should be provided for all personnel whose duties take them into preparation areas or into laboratories (including the technical, maintenance and cleaning personnel).
- 2.8. There should be written policies and procedures to describe the approach to training, including a record of training that has taken place, including its contents, and its effectiveness.
- 2.9. 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.
- 2.10. 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. There must be written safety and hygiene instructions in place, adapted to the activities to be carried out, and are 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).
- 2.12. 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.
- 2.13. 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. Personnel should be instructed to use the hand-washing facilities.

- 2.14. 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.
- 2.15. 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.
- 2.16. 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 the 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, either the 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 in order to prevent the entry of unauthorised people. Processing, laboratory storage and quality control areas 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.

- 3.1.5.1. Preparation areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate to the operations undertaken within them and to the external environment.
- 3.1.5.2. Preparation areas should be suitably lit, particularly where visual checks are carried out.
- 3.1.6. 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. The premises must satisfy common-sense requirements for the health and safety of both the staff (including those of the 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, appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation, and 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 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, toilet, lighting, 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 and 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, extremes of temperature, etc.

3.5. Storage Area

- 3.5.1. Storage areas must provide for properly secure and segregated storage of different categories of blood and blood components and materials, including quarantine and released materials and 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 or power failure in the main storage facility (Directive/2005/62/EC/Annex 3.3.5.2).
- 3.5.3. The storage facilities should be clean and free from litter, dust and pests (e.g. insects, rodents, etc.).
- 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 of 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. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked 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 properly identified for the 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 donation identifier label sets.

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 easily 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. Whenever parts and tools are stored in the 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 use qualified equipment. Qualification results must be documented. Regular maintenance and calibration must be carried out and documented according to established procedures. The maintenance status of each item of equipment must be available.
- 4.1.4. All critical equipment must 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 be determined for each item of equipment.
- 4.1.5. New and repaired equipment must meet qualification requirements when installed and must be authorised before use.
- 4.1.6. All modifications, enhancements or additions to validated systems and equipment must be managed through the blood establishment's change control procedure. The effect of each change to the system or equipment, and its impact on quality and safety, must be determined in order to identify the extent of re-validation that is required.
- 4.1.7. Instructions for use, maintenance, servicing, cleaning and sanitation must be available.
- 4.1.8. Procedures must be available for each type of equipment, detailing the action to be taken when malfunctions or failures occur.
- 4.1.9. Only reagents and materials from approved suppliers that meet the documented requirements and specifications must be used. Critical materials must be released by a person qualified to perform this task. Where 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. The 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, the manufacturer, compliance with the relevant requirements (e.g. pharmacopoeia or medical device regulations) and confirmation that the materials are sterile and pyrogen-free.
- 4.1.11. The status of material (quarantined, released, rejected, etc.) should be clearly indicated.

- 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 and stock rotation.
- 4.1.13. Storage and use of materials should follow the “first-in first-out” principle (i.e. the material that entered storage 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 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 and cleaning solutions and equipment should be chosen and used in order not to be a source 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. The parts of the equipment and materials that come into contact with the blood and blood component must not be reactive, additive or absorptive to such an extent that it will 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. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by 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 be reviewed and signed to show acceptance of the document. Any failed calibrations will require the raising of a non-conformance to investigate the potential impact.
- 4.1.22. Defective equipment should be clearly labelled as such and, if possible, be removed from preparation areas.

4.2. Data processing systems

- 4.2.1. When 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 be properly maintained at all times. Documented maintenance plans must be developed and implemented. This must include quality assurance system audits.
- 4.2.3. Changes in computerised systems must be validated; the applicable documentation must be revised and the relevant personnel properly trained before any change is introduced into routine use. Computerised systems must be maintained in a validated state. This must 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 be a hierarchy of permitted user access to enter, amend, read or print data. Methods of preventing unauthorised entry must be in place, such as personal identity codes or passwords which are changed on a regular basis.
- 4.2.5. All necessary measures must be taken to ensure protection of data. These measures must ensure that safeguards against unauthorised data additions, deletions or modifications 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 inventory and blood component release decisions should prevent the release of all blood or blood components considered not acceptable for release. It should be possible to prevent the release of any components from a future donation from a deferred donor.

4.3. Qualification and Validation

4.3.1. General Principles

- 4.3.1.1. Facilities and equipment need to be qualified prior to implementation. Systems, processes and tests must 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. These principles of qualification and validation are applicable to the preparation, distribution and issuance of blood components. It is a requirement of Good Practice that blood establishments and hospital blood banks identify what validation work is needed to prove quality control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the blood components, should be qualified and/or validated. A risk assessment approach should be used to determine the scope and extent of this.
- 4.3.1.3. New processes, facilities, systems, equipment or tests should be submitted to qualification and/or validation prior to implementation. Change to an existing process should also initiate a risk-based approach to prospective validation as part of the change control procedure.
- 4.3.1.4. The first steps in this process involve the identification of the requirements for the procedure or process and documenting these specifications.
- 4.3.1.5. Performing risk assessments at various stages facilitates the definition of requirements and alternatives, aids in the supplier selection process, and helps determine the scope and extent of qualification and/or validation and to determine any mitigation steps.
- 4.3.1.6. A strategy for undertaking validation should be implemented. The scope of validation should be proportionate to the degree of risk involved in the implementation. The validation should be mainly based on the different elements identified in the risk assessment, the user specification and the documents provided by the supplier.

4.3.2. Planning for Validation

- 4.3.2.1. All validation activities need to be planned. The key elements of the programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents. The VMP should be a summary document that is brief, concise and clear. It should contain data on at least the following:
 - 4.3.2.1.1. validation policy;
 - 4.3.2.1.2. organisational structure of validation activities;
 - 4.3.2.1.3. summary of facilities, systems, equipment and processes to be validated;
 - 4.3.2.1.4. documentation format, i.e. the format to be used for protocols and reports;
 - 4.3.2.1.5. planning and scheduling;
 - 4.3.2.1.6. change control;

4.3.2.1.7. reference to existing documents.

4.3.2.2. In the case of large projects, it may be necessary to create separate validation master plans, which should be linked and traceable.

4.3.3. Documentation

4.3.3.1. A written protocol should be established that specifies how qualification and validation should be conducted. The protocol should be reviewed and approved. The protocol should specify the critical steps and acceptance criteria. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommendations for any changes necessary to correct deficiencies. Any changes to the plan, as defined in the protocol, should be documented with appropriate justifications. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

4.3.4. Qualification. The tasks that have to be performed when validating new facilities, systems or equipment can be classified as follows.

4.3.4.1. Design Qualification (DQ). The first element of the validation of new facilities, systems or equipment can be considered as design qualification. This involves demonstration and documentation of the compliance of the design with Good Practice (i.e. the design is suitable for the intended purpose).

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

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

4.3.4.2.2. collection and collation of supplier operating and working instructions and maintenance requirements;

4.3.4.2.3. calibration requirements;

4.3.4.2.4. verification of construction materials.

4.3.4.3. Operational Qualification (OQ). The completion of a successful OQ should allow finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the

facilities, systems and/or equipment. Operational qualification (OQ) should follow IQ. OQ should include, but is not limited to, the following:

- 4.3.4.3.1. tests that have been developed from knowledge of processes, systems and equipment;
- 4.3.4.3.2. tests to include a condition or a set of conditions encompassing upper and lower operating limits (sometimes referred to as “worst case” conditions).
- 4.3.4.4. 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. PQ should follow successful completion of IQ and OQ. PQ should include, but is not limited to, the following:
 - 4.3.4.4.1. tests, using production materials, qualified substitutes or simulated product, which have been developed from knowledge of the process and the facilities, systems or equipment;
 - 4.3.4.4.2. tests to include a condition or set of conditions encompassing upper and lower operating limits.
- 4.3.4.5. Qualification of Established (in-use) Facilities, Systems and Equipment. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

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 and re-validation.
- 4.4.1.2. Process validation should normally be completed prior to the distribution and routine clinical use of the new component (prospective validation). In circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes that have been in use for some time should also be validated (retrospective validation).

4.4.1.3. The facilities, systems and equipment to be used should be qualified before use and analytical testing methods should be validated. The staff taking part in the validation work should be appropriately trained.

4.4.1.4. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating appropriately.

4.4.2. Prospective Validation

4.4.2.1. Prospective validation should include, but is not limited to, the following:

- 4.4.2.1.1. a short description of the process;
- 4.4.2.1.2. a summary of the critical processing steps to be investigated;
- 4.4.2.1.3. a list of the equipment/facilities to be used (including measuring/monitoring/recording equipment), together with their calibration statuses;
- 4.4.2.1.4. finished blood component specifications for release;
- 4.4.2.1.5. a list of analytical methods, as appropriate;
- 4.4.2.1.6. proposed in-process controls with acceptance criteria;
- 4.4.2.1.7. additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
- 4.4.2.1.8. a sampling plan;
- 4.4.2.1.9. methods for recording and evaluating results;
- 4.4.2.1.10. functions and responsibilities;
- 4.4.2.1.11. a proposed timetable.

4.4.2.2. Using this approach, a number of blood components may be prepared under the proposed new conditions. In theory, the number of process runs carried out and the number of observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

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

- 4.4.2.4. If it is intended that validation batches will be issued for clinical use, the conditions under which they have been prepared should comply fully with the requirements of Good Practice, including compliance with the approved specification.
- 4.4.3. Concurrent Validation. In exceptional circumstances, based on a risk assessment and in order to ensure continuity of supply, it may be necessary to commence routine production and supply without a phase of prospective validation. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel. Documentation requirements for concurrent validation are the same as for prospective validation.
- 4.4.4. Retrospective Validation
 - 4.4.4.1. Retrospective validation is only acceptable for well-established processes and is inappropriate where there have been recent changes in the composition of the blood component, operating procedures or equipment.
 - 4.4.4.2. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
 - 4.4.4.3. The source of data for this validation should include, but not be limited to production and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies and finished blood component data (including trend cards and storage stability results).
 - 4.4.4.4. Components selected for retrospective validation should be representative of all components made during the review period, including any that failed to meet specifications, and should be sufficient in number to demonstrate process consistency.
 - 4.4.4.5. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
 - 4.4.4.6. For retrospective validation, a statistically-appropriate sample should be examined to assess process consistency.
- 4.4.5. Documentation and Review of Results
 - 4.4.5.1. All generated results and documentation must be reviewed upon completion of the qualification process. The review should confirm that:
 - 4.4.5.1.1. documentation is complete and that the qualifications prove, with a high degree of confidence, that the system consistently meets its acceptance criteria

(including percentage conformance to pre-defined specifications within pre-established confidence limits);

- 4.4.5.1.2. any non-conformance has been addressed through problem resolution;
- 4.4.5.1.3. training requirements have been met;
- 4.4.5.1.4. written procedures for operation, calibration, maintenance, etc. are in place;
- 4.4.5.1.5. business continuity plans are in place;
- 4.4.5.1.6. validation activities are approved by the person responsible for Quality Management.

4.5. Change Control

- 4.5.1. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process results in a blood component of the desired quality, consistent with the approved specifications.
- 4.5.2. Written procedures should be in place to describe the actions to be taken if a change is proposed for a starting material, blood component specification, equipment, environment (or site), method of production or testing or any other change that may affect donor safety, blood component quality or reproducibility of the process.
- 4.5.3. All changes that may affect blood component quality or the reproducibility of the process should be formally requested, documented and accepted.
- 4.5.4. The likely impact of the change of facilities, systems and equipment on the blood component should be evaluated, including a risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined.
- 4.5.5. Some changes may require notification to, or license amendment, from a national regulatory authority.

4.6. Re-validation and Maintenance of the Validated State

- 4.6.1. 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 re-validation.
- 4.6.2. The following items are essential to maintain a validated state:

4.6.2.1. Calibration and monitoring.

4.6.2.2. Preventive maintenance.

4.6.2.3. Training and competency.

4.6.2.4. Supplier re-qualification.

4.6.2.5. Periodic review.

4.6.2.6. Performance monitoring.

4.6.2.7. System retirement.

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

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. on commissioning of new equipment, which must 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 the functioning of the equipment;

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

4.7.1.4. Consideration should be given to the quality, safety and efficacy of any blood components prepared prior to the 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. Calibration and monitoring intervals 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 proper 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 re-assessed for any critical change in environment, equipment or processes. Training records, including plans and protocols of the training status, must ensure that training needs are properly identified, planned, delivered and documented 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 has to 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 the detail of the re-qualification process depend on the level of risk of using the system or equipment and should be planned for every supplier concerned.
- 4.7.2.7. A periodic review process should be established to ensure that the system or equipment documentation 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. The various types of documents and media used should be fully defined in the organisation's Quality Management System.
- 5.1.2. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilised must 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 and any derived medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for adequate recording of the various processes and evaluation of any observations, so that on-going 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 documentation 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 human readable form.
- 5.2. Required Good Practice documentation (by type): Documents setting out specifications, procedures and records covering each activity performed by a blood establishment must be in place and kept up-to-date (Directive/2005/62/EC/Annex 5.1).

5.2.1. Instructions (directions or requirements):

- 5.2.1.1. Specifications describe in detail the requirements with which the blood and blood components or materials used or obtained during preparation and distribution have to conform (see Council of Europe *Guide to the Preparation, Use and Quality Assurance of Blood Components*, Standards - Chapter 5: Component Monographs). They serve as a basis for quality evaluation.
- 5.2.1.2. 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.
- 5.2.1.3. Procedures (otherwise known as Standard Operating Procedures or SOPs) give directions for performing certain operations.
- 5.2.1.4. Protocols give instructions for performing certain discreet operations and may record the outcome (e.g. qualification and validation protocols).
- 5.2.1.5. Technical Agreements are agreed between contract givers and acceptors for out-sourced activities.

5.2.2. Records/Reports:

- 5.2.2.1. 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.
- 5.2.2.2. 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.
- 5.2.2.3. 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. The 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 as electronic and others as paper-based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems.

- 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. The reproduction of working documents from master documents should not allow any error 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.
- 5.3.4. 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 perform 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 ensure continuous documentation of the procedures performed, from the blood donor to the recipient, i.e. each significant step must be recorded in a manner that permits a component or procedure to be traced, in either direction, from the first step to final use/disposal.
- 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 be in place to ensure the integrity of the record throughout the retention period. These controls must be validated where appropriate.
- 5.5.2. Specific retention requirements for certain documentation applies.
 - 5.5.2.1. Records must be retained for a period according to local, national or EU requirements, as appropriate.
 - 5.5.2.2. Traceability data (that allows 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 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, and 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 (see Council of Europe *Guide to the Preparation, Use and Quality Assurance of Blood Components*, Standards - Chapter 5: Component Monographs). 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. The methods, or reference to the methods, to be used for starting up and for maintaining the 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 step-wise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters such as time and temperature, etc.).

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

5.7.1.6. The 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.

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

5.8.1. In-process labelling requirements. 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. While each unit is considered to be a unique batch, 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. Dates and times of commencement of significant intermediate stages and of completion of processing.

5.8.2.3. 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. 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 the identity of the person(s) carrying them out, and 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 the 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. supplier's name and manufacturer's name;

5.9.1.1.5. manufacturer's batch or reference number;

5.9.1.1.6. 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 those specified in the relevant blood component monographs of the Council of Europe *Guide to the Preparation, Use and Quality Assurance of Blood Components*.

5.10.3. There should be written procedures for testing 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 in order 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, where 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. Internal quality/Good Practice compliance audits.
 - 5.11.3.13. Summaries of records, where appropriate (e.g. blood component quality review).
 - 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 donor identification, suitability interview and eligibility assessment must be implemented and maintained. They must take place 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 be secure and unique donor identification, contact details and robust mechanisms linking the donor to each of their donations.
- 6.1.3. Upon arrival at the blood establishment, donors must provide evidence of their identity. All donors must 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 include an assessment of each donor, carried out by a suitably qualified individual that has been trained to use accepted guidelines and who works under the direction of a physician. This assessment involves an interview, a questionnaire and further direct questions, if necessary.
- 6.1.6. The questionnaire must be designed to elicit information relevant to the health and lifestyle of the donor. It must be designed to be understandable by the donor and given to all donors each time they attend. On completion, it must be signed by the donor.
- 6.1.7. Relevant acceptance/deferral criteria must be in place at the blood establishment to control donor acceptance and deferral.
- 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 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 certify that the relevant questions have been asked.
- 6.1.10. The donor suitability records and final assessment must be signed by a qualified health professional (Directive/2005/62EC/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, taking into consideration the medical history, donor deferral history, the donor interview and the results of the physical examination. The rejection of a donor and the reason for the deferral should

be recorded. A system must 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 be instructed to inform the blood establishment when signs or symptoms occur after a donation, indicating that the donation may have been infectious or of any other information not disclosed during the health screening that may render any prior donation unsuitable for transfusion.
- 6.1.13. Procedures must 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 blood collection procedure must be designed to ensure that the identity of the donor is verified and securely recorded and that the link between the donor and the blood, blood components and blood samples is clearly established (Directive/2005/62/EC/Annex 6.2.1).
- 6.2.2. Donor identity must be confirmed prior to each critical step in the process but, at the very least, before donor selection and venipuncture.
- 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, and 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. The sterile blood bag systems 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, where 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 blood collection and processing systems should be used for blood and blood component collection. The collection systems should be used in accordance with the instructions of the manufacturer.
- 6.2.8.2. Prior to venipuncture, 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. Any abnormal moisture or discolouration could suggest a defect.
- 6.2.8.3. Appropriate hand disinfection and personal hygiene procedures should be in place and should be performed by the personnel before each donation.
- 6.2.8.4. The skin at the venipuncture site must be free from lesions, including eczema.
- 6.2.8.5. The venipuncture site must be prepared using a defined and validated disinfection procedure. The antiseptic solution must be allowed to dry completely before venipuncture. The prepared area must not be touched with fingers before the needle has been inserted.
- 6.2.8.6. The effectiveness of the disinfection procedure must 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 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 and then removed.
- 6.2.8.9. A standard operating procedure should be in place describing the actions to be taken following an unsuccessful donation. It should specify how to handle already labelled material and the circumstances under which a repeat venipuncture 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, the blood bags must be handled in a way that maintains the quality of the blood and at a storage 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 venipuncture. Donations and samples should be transported to the processing site in accordance with procedures that ensure both 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 the 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 2005/762/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 patient diagnostic testing.

- 6.3.5. Each step of sample handling and processing 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. On receipt of samples at the laboratory, a positive identification of the samples received against those expected should be performed.
- 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 prior to using it) before release of the blood component.
- 6.3.9. Pre-acceptance testing must be performed on samples before purchasing batches of commercial reagents. Prospective purchasers must require potential suppliers to provide them with full validation data for all lots of reagents. Each lot of reagent must be qualified by the purchaser to demonstrate suitability for its intended purpose within the system used for testing.
- 6.3.10. There must be a reliable process in place for transcribing, collating and interpreting results.
- 6.3.11. The quality of the laboratory testing must be regularly assessed 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. The testing of donations for infectious agents is a key factor in ensuring that the risk of disease transmission is minimised and that the 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 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 sample labelling/identification, a validated strategy and pooling process and a validated algorithm to re-assign pool results to individual donations should be in place.
- 6.4.6. There must be clearly defined procedures to resolve discrepant results. 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. 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. Screening algorithms should be precisely defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens and to resolve discrepancies in results after re-testing.
- 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. The ABO and RhD blood group should be verified on each subsequent donation.
 - 6.5.5. A 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 been unequivocally resolved.
 - 6.5.6. 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 where applicable, the blood or blood component should be labelled accordingly.
 - 6.5.7. Only test reagents that have been licensed or evaluated and considered suitable by a responsible National Health Authority/Competent Authority must be used. In the EU, these reagents are considered as in vitro diagnostic devices and must be CE-marked.

- 6.5.8. 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 have a full Quality System certified by an authorised body and must submit an application containing all the control results for each lot.
- 6.5.9. Quality control procedures must be implemented for equipment, reagents and techniques used for ABO and RhD blood grouping, phenotyping and allo-antibody detection and identification. 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 minimize the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures.
 - 6.6.4. The validation of freezing processes should consider worst-case scenarios that take into account both minimum and maximum loads and positions in the freezer.
 - 6.6.5. Sterile connecting devices must be used in accordance with a validated procedure. When validated, connections made using sterile connecting devices are regarded as closed system processing. The resulting weld must be checked for satisfactory alignment and its integrity must be confirmed.
- 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 The 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 blood establishment's agreed format.
- 6.7.4. The labelling system for the 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. 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).
- 6.7.5. 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.
- 6.7.6. 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 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 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 a standard operating procedure that details 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 the exceptional release of non-standard blood and blood components under a planned non-conformance system. The decision to allow such release should be clearly documented 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. 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 release due to a confirmed positive infection test result 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 are 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 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 storage and distribution requirements 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 blood and blood component quality 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 be controlled, monitored and checked. Appropriate alarms must be present and regularly checked and the checks must be recorded. Appropriate actions on alarms must be defined.
- 7.4. There should be a system to ensure stock rotation with 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. Prior to distribution, blood components must 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, between blood establishments and hospital blood banks, and between hospital blood banks, showing the date of supply, unique component identifier and name of the blood component, the quantity received or supplied, and the name and address of the supplier or consignee.
- 7.9. Packaging 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. Return of blood and blood components into inventory for subsequent re-issue must only be allowed when all quality requirements and procedures laid down by the blood establishment to ensure blood component integrity are fulfilled (Directive 2005/62/EC/Annex 7.6).
- 7.11. Blood components must not be returned to the blood establishment for subsequent distribution unless there is a procedure for return of blood components that is regulated by a contract and where there is documented evidence for each returned blood component that the agreed storage conditions have been met. Before subsequent distribution, the records must identify that the blood component has been inspected before re-issue.

8. CONTRACT 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. Tasks that are performed externally and that may impact on the quality, safety or efficacy of the blood components must be defined in a specific written contract or agreement, including any technical arrangements made in connection with it.
 - 8.1.3. All out-sourced arrangements for blood collection, processing and testing, including any proposed changes, must be done 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 in the distribution chain must be documented to ensure that Good Practice principles are maintained.
- 8.1.5. The Contract Giver is the establishment or institution that sub-contracts 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 out-sourced 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.
- 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 sub-contracted 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 must 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

9.1. Deviations

- 9.1.1. Blood components deviating from the quality and safety standards set out in the Standards section of Chapter 5 - Component Monographs contained in the Council of Europe *Guide to the Preparation, Use and Quality Assurance of Blood Components* (and, where appropriate, Annex V to Directive 2004/33/EC) must 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. There must 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 must be clearly documented and authorised by a designated person and traceability must be ensured.
- 9.1.3. There must 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.
- 9.1.4. The Corrective and Preventive Actions (CAPAs) system must ensure that existing component non-conformity or quality problems are corrected and that recurrence of the problem is prevented.
- 9.1.5. Deviations from established procedures should be avoided as much as possible and must be documented and explained. Any errors, accidents or significant deviations that may affect the quality or safety of blood and blood components must be fully recorded and investigated in order to identify systematic problems that require corrective action. Appropriate Corrective and Preventative Actions (CAPAs) must be defined and implemented.
- 9.1.6. Investigations relating to serious deficiencies, significant deviations and serious component defects must include an assessment of component impact, including a review and evaluation of relevant operational documentation and an assessment of deviations from specified procedures.
- 9.1.7. There must be procedures for notifying responsible management in a timely manner of deficiencies, deviations or non-compliances 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.).
- 9.1.8. Executive 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 must be made available for their timely resolution.

9.1.9. 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 preventative 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 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 the case 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 be taken within pre-defined periods of time and must include tracing all relevant blood components and, where applicable, must 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. The personnel authorised to initiate and co-ordinate the recall actions should normally be independent of the commercial management within the organisation. If these personnel are not the Executive Management and the Responsible Person (Blood), the latter should be made aware of any recall operation.
- 9.3.5. Recalled blood components or products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 9.3.6. 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.
- 9.3.7. The effectiveness of the arrangements for recalls should be regularly evaluated.
- 9.4. Corrective and Preventive Actions (CAPAs)
 - 9.4.1. A system to ensure corrective and preventive actions for blood component non-conformity 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 unfavorable 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 must be documented. 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 to avoid recurrences.

- 9.4.5. 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.
- 9.4.6. As part of periodic Quality System reviews, an assessment should be made of whether CAPAs or any re-validation 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 on-going 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 regularly carried out 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 be based on a defined specification (see Chapter 5 – Component Monographs of the Standards section of the *Guide to the Preparation, Use and Quality Assurance of Blood Components*) for each blood donation and blood component.

11.2. Quality Control

- 11.2.1. All quality control procedures must be validated before use.
- 11.2.2. The results of quality control testing must be continuously evaluated and steps must be taken to correct defective procedures or equipment.
- 11.2.3. Standard procedures for the quality control of blood components must be in place. The suitability of each analytical method to provide the intended information must be validated.
- 11.2.4. Quality control of blood and blood components must be carried out according to a sampling plan designed to provide the intended information.

- 11.2.5. The testing must be performed 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 be regularly assessed by participation in a formal system of proficiency testing.
- 11.2.7. Records of quality control procedures must include identification of the person(s) performing the tests or procedures. Any corrective action taken must also be recorded. If corrections in records are necessary, the original recording must not be obliterated, but must remain legible.