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

21st Edition of the Guide to the preparation, use and quality assurance of blood components ("the Blood Guide")

-Draft for Stakeholder consultation-

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

Introductory note

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

GPG were first published in the 19th edition of the Guide to the preparation, use and quality assurance of blood components Appendix to Recommendation No. R (95) 15 of the Committee of Ministers on the preparation, use and quality assurance of blood components and are revised with each subsequent edition

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

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

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

Council of Europe Member States should take the necessary measures and steps to implement the GPG published in this 21st edition of the Guide to the preparation, use and quality assurance of blood components. The GPG are published within this edition of the Guide and have no separate glossary. Regarding terminology used in the GPG, reference is therefore made to the common abbreviation section of the Guide.

The GPG published in the Guide provide standards and specifications of quality systems that Member States shall ensure are in place in blood establishments and hospital blood banks. When GPG requirements are taken from the EU Directives the term ‘must’ is used as a replacement for ‘shall’. This reflects the legal status of the requirements within EU countries.

Consistent with the approach used in Codes of GMP, the requirements in the GPG section of the Guide are defined using the term ‘should’. The intention is that the requirements identify what needs to be achieved but are not specific on how this is done. GPG requirements are also replicated in other chapters of the Guide. When this occurs the term ‘should’ is retained for the purposes of consistency.

Good Practice Guidelines for blood establishments and hospital blood banks

1. General principles

1.1. General requirements

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

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

1.1.3. Quality must be recognised as being the responsibility of all persons involved in the processes of the blood establishment, with management ensuring a systematic approach towards quality and the implementation and maintenance of a quality system (Directive 2005/62/EC Annex 1.1.1).

1.1.4. Attainment of this quality objective is the responsibility of executive management. It requires the participation and commitment both of staff in many different departments and at all levels within the organisation and of the organisation's suppliers and distributors. To achieve this quality objective reliably there should be a comprehensively designed and correctly implemented quality system incorporating Good Practice and quality risk management.

1.1.5. Each actor in the supply chain should establish, document, and fully implement a comprehensively designed quality system to deliver quality assurance based on the principles of quality risk management by incorporating Good Practice and Quality Control.

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

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

1.2. Quality system

1.2.1. Quality management is a wide-ranging concept covering all matters, 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 Standards in this *Guide* (which includes the Annex to Directive 2005/62/EC).

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

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

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

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

1.2.8. All blood establishments and hospital blood banks must be supported by a quality assurance function (whether internal or related) for fulfilling quality assurance. That function must be involved in all quality-related matters, and must review and approve all appropriate quality-related documents (Directive 2005/62/EC Annex 1.2.1).

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

1.2.10. All procedures, premises and equipment that have an influence on the quality and safety of blood and blood components must be validated before introduction and must be re-validated at regular intervals, as determined as a result of these activities (Directive 2005/62/EC Annex 1.2.2).

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

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

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

1.2.14. Management must review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary (Directive 2005/62/EC Annex 1.1.3).

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

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

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

1.2.17.1. review of starting materials;

1.2.17.2. review of critical in-process controls;

1.2.17.3. review of results of quality control and quality monitoring;

1.2.17.4. review of all changes;

1.2.17.5. review of the qualification status of equipment;

1.2.17.6. review of technical agreements and contracts;

1.2.17.7. review of all significant deviations, non-conformances, and the effectiveness of the corrective actions implemented;

1.2.17.8. review of the findings of internal and external audits and inspections, and the effectiveness of the corrective actions implemented;

1.2.17.9. review of complaints and recalls;

1.2.17.10. review of donor acceptance criteria;

1.2.17.11. review of donor deferrals;

1.2.17.12. review of look-back cases.

1.3. Good practice

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

1.3.1.1. All processes are defined clearly and reviewed systematically in the light of experience and shown to be capable of consistently delivering blood and blood components of the required quality and complying with their specifications. This strategy includes ensuring that:

1.3.1.1.1. critical steps and significant changes to the process are validated;

1.3.1.1.2. all requirements are provided including:

1.3.1.1.2.1. appropriately qualified and trained personnel;

1.3.1.1.2.2. adequate premises and space;

1.3.1.1.2.3. suitable equipment and services;

1.3.1.1.2.4. correct materials, containers and labels;

1.3.1.1.2.5. approved procedures and instructions;

1.3.1.1.2.6. suitable storage and transport;

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

1.3.1.1.4. operators are trained to carry out procedures correctly;

1.3.1.1.5. records are made, manually and/or by recording instruments, during preparation which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the blood or blood component was as expected;

1.3.1.1.6. any significant deviations are fully recorded and investigated;

1.3.1.1.7. records of preparation (including distribution) that enable the complete history of the blood or blood component to be traced are retained in a comprehensible and accessible form;

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

1.3.1.1.9. a system is available to recall any blood or blood component (including those prepared using a batch of critical materials that have been distributed or issued);

1.3.1.1.10. complaints about blood and blood components are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective blood components to prevent reoccurrence.

1.3.1.2. Quality control is the part of Good Practice that is concerned with sampling, specifications and testing, as well as with the organisation, documentation and release procedures which ensure that materials are not released for use in preparation, and blood and blood components are not released for distribution, until their quality has been judged to be satisfactory and that the necessary and relevant tests have been carried out. The basic requirements are:

1.3.1.2.1. adequate facilities, trained personnel and approved procedures are available for sampling, inspecting/testing starting materials, packaging materials, intermediate components, and finished blood and blood components and, if appropriate, for monitoring environmental conditions;

1.3.1.2.2. samples of starting materials, packaging materials, intermediate, and finished blood components are taken by approved personnel and methods;

1.3.1.2.3. test methods are validated;

1.3.1.2.4. records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are recorded and investigated fully;

1.3.1.2.5. the finished blood and blood components comply with the specifications and are correctly labelled;

1.3.1.2.6. records are made of the results of inspection, and that testing of materials, intermediate and finished blood and blood components are formally assessed against specifications;

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

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

1.4. Quality risk management

1.4.1. Quality risk management is the part of the quality system that ensures that the process performance and quality monitoring and review systems are based on risk. Appropriate

statistical tools should be used (where appropriate) in the assessment of ongoing process capability.

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

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

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

2. **Personnel and organisation**

2.1. Personnel must be available in sufficient numbers to carry out the activities related to the collection, testing, processing, storage and distribution of blood and blood components and be trained and assessed to be competent to perform their tasks (Directive 2005/62/EC Annex 2.1).

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

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

2.3.1. a ‘Responsible Person’ following Article 9 of Directive 2002/98/EC;

2.3.2. a processing manager, responsible for all processing activities;

2.3.3. a quality control manager, responsible for all quality control activities;

2.3.4. a quality assurance manager, responsible for ensuring that there are appropriate quality systems and protocols in place for the safe and secure release of all materials, equipment, reagents and blood and blood components;

2.3.5. a physician with the responsibility for ensuring the safety of donors.

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

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

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

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

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

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

2.10. The contents of training programmes must be periodically assessed and the competence of personnel evaluated regularly (Directive 2005/62/EC Annex 2.4).

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

2.12. 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.

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

2.14. 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.

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

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

2.17. 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.

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

3. **Premises**

3.1. General

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

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

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

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

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

3.1.6. Requirements for temperature and humidity of the preparation areas should be defined according to the operations undertaken within them and taking into account the external environment.

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

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

3.2. Blood donor area

3.2.1. There 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 3.2).

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

3.3. Blood collection area

3.3.1. Blood collection must be carried out in an area intended for the safe withdrawal of blood from donors that is appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation. This area must be organised in such a way as to ensure the safety of both donors and personnel as well as to avoid errors in the collection procedure (Directive 2005/62/EC Annex 3.3.3).

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

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

3.3.2.2. safety for staff and donors;

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

3.3.2.4. reliable communication, interim blood storage and transport.

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

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

3.4. Blood testing and processing areas

3.4.1. There must be a dedicated laboratory area for testing that is separate from the blood-donor and blood-component processing area, with access restricted to authorised personnel, and must be used only for the intended purpose (Directive 2005/62/EC Annex 3.3.4).

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

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

3.5. Storage area

3.5.1. Storage areas must provide for appropriately secure and segregated storage of different categories of blood and blood components and materials, including quarantine and released materials as well as units of blood or blood components collected under special criteria (e.g. autologous donation). Access must be restricted to authorised persons (Directive 2005/62/EC Annex 3.3.5.1).

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

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

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

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

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

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

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

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

3.6. Ancillary areas

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

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

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

3.7. Waste disposal area

3.7.1. An area 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).

3.7.2 Special procedures should be defined for potentially contaminated waste disposal.

4. **Equipment and materials**

4.1. General requirements

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

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

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

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

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

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

4.1.9. Only reagents and materials from approved suppliers that meet the documented requirements and specifications should be used. Critical materials should be released by a person qualified to perform this task. If relevant, materials, reagents and equipment must meet the requirements of Regulation (EU) 2017/745 (repealing Directive 93/42/EEC) of the European Parliament and of the Council for medical devices and Regulation (EU) 2017/746 (repealing Directive 98/79/EC) of the European Parliament and of the Council for in vitro diagnostic medical devices, or comply with equivalent standards in the case of collection in third countries (Directive 2005/62/EC Annex 4.3).

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

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

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

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

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 should be kept as a means to build up a history for a processed component to facilitate recalls.

4.1.16. Repair and maintenance operations should not present any hazard to the donor, staff or quality of the blood and blood components.

4.1.17. Equipment should be designed or selected so that it can be thoroughly cleaned (and where necessary decontaminated). This should be performed according to detailed and written procedures. It should be stored only in a clean and dry condition.

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

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

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

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

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

4.2. Data processing systems

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

4.2.3. The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

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

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

4.2.6. For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.

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

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

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

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

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

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

4.2.13. Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

4.2.14. It should be possible to obtain clear printed copies of electronically stored data.

4.2.15 For records supporting blood and blood components release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.

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

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

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

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

4.2.20. There should be a hierarchy of permitted user access to enter, amend, read or print data.

4.2.21. Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.

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

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

4.2.23.1. have the same impact as hand-written signatures within the boundaries of the company,

4.2.23.2. be permanently linked to their respective record,

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

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

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

4.2.26. Computer systems designed to control decisions related to inventories and release of blood components should prevent the release of all blood or blood components considered not acceptable for release. Preventing release of any components from a future donation from a deferred donor should be possible.

4.3. Qualification and validation

4.3.1. General principles

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

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

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

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

4.3.2. Organising and planning for validation

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

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

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

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

4.3.2.4.1. qualification and validation policy;

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

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

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

4.3.2.4.5. guidance on developing acceptance criteria;

4.3.2.4.6. references to existing documents;

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

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

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

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

4.3.3. Documentation including VMP

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

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

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

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

4.3.3.5. The relationship and links between documents in complex validation projects should be established.

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

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

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

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

4.3.4. Qualification stages for equipment, facilities, and systems

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

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

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

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

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

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

4.3.4.5.2. verification of the correct installation against pre-defined criteria;

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

4.3.4.5.4. calibration requirements;

4.3.4.5.5. verification of construction materials.

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

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

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

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

4.3.4.7.1. tests, using production materials, qualified substitutes or simulated blood components proven to have equivalent behaviour, under normal and worst case operating conditions. The frequency of sampling used to confirm process control should be justified;

4.3.4.7.2. tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

4.3.5. Re-qualification

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

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

4.4. Process validation

4.4.1. General

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

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

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

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

4.4.1.5. Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable blood component quality, can be consistently met by the process. A critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired component quality. A critical process parameter (CPP) is a process parameter whose variability has an impact on a critical quality attribute and which therefore should be monitored or controlled to ensure the process produces the desired quality. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

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

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

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

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

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

4.4.2. Concurrent validation

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

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

4.4.3. Prospective validation

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

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

4.4.3.3 A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.

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

4.4.3.4.1. short description of the process;

4.4.3.4.2. functions and responsibilities;

4.4.3.4.3. summary of the CQAs to be investigated;

4.4.3.4.4. summary of CPPs and their associated limits;

4.4.3.4.5. summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;

4.4.3.4.6. list of the equipment/facilities/personnel to be used (including measuring/monitoring/recording equipment) together with the calibration status;

4.4.3.4.7. list of analytical methods and method validation, as appropriate;

4.4.3.4.8. proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;

4.4.3.4.9. additional testing to be carried out with acceptance criteria;

4.4.3.4.10. sampling plan and the rationale behind it;

4.4.3.4.11. methods for recording and evaluating results;

4.4.3.4.12. process for release and certification of units (if applicable);

4.4.3.4.13. conclusion.

4.4.4. Ongoing process, verification and maintenance of the validated state

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

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

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

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

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

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

4.4.4.6.1. calibration and monitoring;

4.4.4.6.2. preventive maintenance;

4.4.4.6.3. training and competency;

4.4.4.6.4. supplier requalification;

4.4.4.6.5. periodic review;

4.4.4.6.6. performance monitoring;

4.4.4.6.7. system retirement.

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

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

4.5. Validation of test methods

4.5.1. All analytical test methods used in qualification or validation exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in 11.2.

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

4.6. Change control

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

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

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

4.6.4. Quality risk management should be used to evaluate planned changes to determine the potential impact on blood component quality, the blood establishment's quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.

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

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

4.7. Control of equipment and materials

4.7.1. General principles

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

4.7.1.2. The contracting process should include:

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

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

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

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

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

4.7.1.2.6. performance of regular audits.

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

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

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

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

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

4.7.2. Calibration and monitoring of equipment

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

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

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

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

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

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

5. **Documentation**

5.1. General principles

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

5.1.2. Documentation may exist in various forms: paper-based, electronic or photographic. The main objective of the system of documentation used should be to establish, control, monitor and record all activities that directly or indirectly impact on all aspects of the quality and safety of blood and blood components as well as any derived medicinal products. The quality management system should include sufficient instructional detail to facilitate common understanding of the requirements, in addition to providing for adequate recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

5.1.3. There are two primary types of documentation used to manage and record Good Practice compliance: instructions (directions, requirements) and records/reports. Appropriate practices should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of

documents. Instruction documents should be free from errors and available in writing. The term ‘written’ means recorded or documented on media from which data may be rendered in a readable form for humans.

5.2. Required good practice documentation (by type)

5.2.1. Documents setting out specifications, procedures and records covering each activity undertaken by a blood establishment must be in place and kept up-to-date (Directive 2005/62/EC Annex 5.1).

5.2.2. Instructions (directions or requirements)

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

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

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

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

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

5.2.3. Records/reports

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

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

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

5.3. Generation and control of documentation

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

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

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

5.3.4. Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. This may also be undertaken electronically. Documents should have unambiguous content and be uniquely identifiable. The effective date should be defined.

5.3.5. Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard operating procedures, work instructions and methods should be written in an imperative mandatory style.

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

5.3.7. All significant changes to documents must be acted upon promptly, and must be reviewed, dated and signed by a person authorised to undertake this task (Directive 2005/62/EC Annex 5.3).

5.3.8. Instructional documents should not be handwritten; 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 should ensure continuous documentation of the procedures performed from the blood donor to the recipient. That is, each significant step should be recorded in a manner that permits a component or procedure to be traced, in either direction, from the first step to final use/disposal.

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

5.5. Retention of documents

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

5.5.2. Specific retention requirements for certain documentation apply.

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

5.5.2.2. Traceability data (that allow tracing from donor to recipient and vice versa) must 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 should be defined on the basis of the business activity that the documentation supports. These retention periods should be specified.

5.6. Specifications

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

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

5.6.2.1. a description of the materials, including:

5.6.2.1.1. the designated name and the internal code reference;

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

5.6.2.1.3 a sample of printed materials;

5.6.2.2. directions for sampling and testing;

5.6.2.3. qualitative and quantitative requirements with acceptance limits;

5.6.2.4 storage conditions and precautions;

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

5.6.3. Specifications for in-process and finished components should be available (specifications set out in the Standards section of Chapter 5, Blood component monographs contained in the Guide to the preparation, use and quality assurance of blood components published by the Council of Europe may be used). Components must be labelled in accordance with Directive 2002/98/EC.

5.7. Preparation instructions

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

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

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

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

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

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

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

5.7.1.7. any special precautions to be observed.

5.8. Labelling

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

The label on an intermediate component should always allow the stage of processing to be determined and should always include:

5.8.1.1. the name of the component;

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

5.8.1.3. the name of the producing blood establishment.

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

blood establishment. In general, the blood establishment should have access to the following processing records for each unit:

5.8.2.1. the name and unique identifier of the component;

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

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

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

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

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

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

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

5.9. Procedures and records

5.9.1. Receipt

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

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

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

5.9.1.1.3. date of receipt;

5.9.1.1.4 the names of the supplier and manufacturer;

5.9.1.1.5. the batch or reference number of the manufacturer;

5.9.1.1.6 the total quantity and number of items received;

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

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

5.9.1.1.9. any relevant comments.

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

5.10. Sampling

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

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

5.11. Other

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

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

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

5.11.3.1. validation and qualification of processes, equipment and systems;

5.11.3.2. equipment assembly and calibration;

5.11.3.3. maintenance, cleaning and sanitation;

5.11.3.4. personnel matters, including signature lists, training in Good Practice and technical matters, clothing and hygiene, and verification of the effectiveness of training;

5.11.3.5. environmental monitoring;

5.11.3.6. pest control;

5.11.3.7. complaints;

5.11.3.8. recalls;

5.11.3.9. returns;

5.11.3.10. change control;

5.11.3.11. investigations of deviations and non-conformances;

5.11.3.12. audits of compliance with internal quality/Good Practice;

5.11.3.13. summaries of records, where appropriate (e.g. review of the quality of blood components);

5.11.3.14. supplier qualification and audits.

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

6. **Blood collection, testing and processing**

6.1. Donor eligibility

6.1.1. Procedures for safe identification of donors, suitability interview, and eligibility assessment must be implemented and maintained. They must take place immediately before each donation and comply with the requirements set out in Annex II and Annex III to Directive 2004/33/EC (Directive 2005/62/EC Annex 6.1.1).

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

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

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

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

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

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

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

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

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

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

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

6.2. Collection of blood and blood components

6.2.1. The procedure for blood collection must be designed to ensure that the identity of the donor is verified and recorded securely, and that the link between the donor and blood, blood components and blood samples is established clearly (Directive 2005/62/EC Annex 6.2.1).

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

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

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

6.2.5. Systems of sterile blood bags used for the collection of blood and blood components and their processing must be CE-marked or comply with equivalent standards if the blood and blood components are collected in third countries. The batch number of the bag must be traceable for each blood component (Directive 2005/62/EC Annex 6.2.2).

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

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

6.2.8. Blood collection procedures must minimise the risk of microbial contamination (Directive 2005/62/EC Annex 6.2.3).

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

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

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

6.2.8.4. The skin at the venepuncture site should be free from lesions, including eczema.

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

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

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

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

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

6.2.9. Laboratory samples must be taken at the time of donation and be appropriately stored prior to testing (Directive 2005/62/EC Annex 6.2.4).

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

6.2.11. After blood collection, blood bags must be handled in a way that maintains the quality of the blood and at a storage temperature and transport temperature appropriate to the requirements for further processing (Directive 2005/62/EC Annex 6.2.6).

6.2.12. Blood and blood components should be placed in controlled and validated conditions as soon as possible after venepuncture. Donations and samples should be transported to the processing site in accordance with procedures that ensure a constant approved temperature and secure confinement. There should be validation data to demonstrate that the method of transport maintains the blood within the specified temperature range throughout the period of transportation. Alternatively, portable temperature loggers may be used to record the temperature during transportation of blood to the processing site.

6.2.13. If a deviation occurs, it should be approved in writing by a competent person.

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

6.2.15. There must be a system in place to ensure that each donation can be linked to the collection and processing system into which it was collected and/or processed (Directive 2005/62/EC Annex 6.2.7).

6.3. Laboratory testing

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

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

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

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

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

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

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

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

6.3.7. There must be data confirming the suitability of any laboratory reagents used in testing of donor samples and blood-component samples (Directive 2005/62/EC Annex 6.3.4).

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

6.3.9. Pre-acceptance testing should be performed on samples before purchasing batches of commercial reagents. Prospective purchasers should require potential suppliers to provide them with full validation data for all lots of reagents. Each lot of reagent should be qualified by the purchaser to demonstrate suitability for its intended purpose within the system used for testing.

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

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

6.4. Testing for infectious markers

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

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

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

6.4.4. Serological testing should be performed on samples transferred directly into the analyser from the original sample tube or aliquoted in a fully automated environment. Secondary aliquot samples may be used for nucleic acid amplification technique (NAT) testing of mini-pools of individual samples.

6.4.5. If NAT testing is performed by assembling various samples in mini-pools, a thoroughly validated system of labelling/identification of samples, a validated strategy and pooling process, and a validated algorithm to reassign pool results to individual donations should be in place.

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

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

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

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

6.5. Blood group serological testing of donors and donations

6.5.1. Blood group serology testing must include procedures for testing specific groups of donors (e.g. first-time donors, donors with a history of transfusion) (Directive 2005/62/EC Annex 6.3.6).

6.5.2. Each donation should be tested for ABO and RhD blood groups and at least all first-time donors should be tested for clinically significant irregular red-cell antibodies. This should not normally apply to plasma for fractionation.

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

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

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

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

6.5.7. Regulation (EU) 2017/746 classifies ABO, Rh (D, C, E, c, e), K, Jka, Jkb, Fya, Fyb reagents as class D in Annex VIII. 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.

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

6.6. Processing and validation

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

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

6.6.3. The use of closed systems is strongly recommended for all steps in component processing. Open systems may exceptionally be necessary due to local constraints and should be undertaken in an environment specifically designed to minimise the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures and the premises used should preferably be a grade A environment with a grade B background. A less stringent background may be acceptable if in combination with additional safety measures such as preparing the blood component just in time for transfusion as predefined in the specifications, or immediately after preparation applying storage conditions which are unfavourable to microbial growth.

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

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

6.7. Labelling

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

6.7.2 Type of label to be used, as well as the labelling methodology, should be defined and established in written standard operating procedures.

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

6.7.4. Labelling system for collected blood, intermediate and finished blood components, and samples must unmistakably identify the type of content, and comply with the labelling and traceability requirements referred to in Article 14 of Directive 2002/98/EC and Directive 2005/61/EC.

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

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

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

6.8. Release of blood and blood components

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

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

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

6.8.4. Before release, blood and blood components must be kept administratively and physically segregated from released blood and blood components. In the absence of a validated computerised system for status control, the label of a unit of blood or blood component must identify the release status in accordance with point 6.5.1 stated above (Directive 2005/62/EC Annex 6.5.1 and 6.6.2).

6.8.5. There should be a system of administrative and physical quarantine for blood and blood components to ensure that components cannot be released until all mandatory requirements have been met.

6.8.6. In the event that the final component fails to be released due to a confirmed positive test result for infection with an agent mentioned in Annex IV of Directive 2002/98/EC, a check must be made to ensure that other components from the same donation and components prepared from previous donations given by the donor have been identified. An immediate update must be made to the donor record (Directive 2005/62/EC Annex 6.3.2, 6.3.3 and 6.6.3).

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

7. **Storage and distribution**

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

7.2. Procedures for storage and distribution must be validated to ensure the quality of blood and blood components during the entire storage period, and to exclude mix-ups of blood components. All transportation and storage actions, including receipt and distribution, must be defined by written procedures and specifications (Directive 2005/62/EC Annex 7.2).

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

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

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

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

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

7.8. Records should be kept of the distribution of blood components between blood establishments, blood establishments and hospital blood banks and between hospital blood banks. These records should show the date of supply, unique component identifier and name of the blood component, the quantity received or supplied, name and address of the supplier or consignee.

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

7.10 Verification of transportation

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

7.10.2 It is recognised that verification of transportation may be challenging due to the variable factors involved; however, the different modes of transportation should be clearly defined. Seasonal and other variations should also be considered during verification of transport.

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

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

7.11. Return of blood and blood components into inventories for subsequent re-issue must be allowed only if all requirements and procedures relating to quality as laid down by the blood establishment to ensure the integrity of blood components are fulfilled (Directive 2005/62/EC Annex 7.6).

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

8. **Outsourced activities management**

8.1. General principles

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

8.1.2. Outsourced activities that may impact on the quality, safety or efficacy of the blood components should be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a blood component or work of unsatisfactory quality. There should be a written contract covering these activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

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

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

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

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

8.2. The contract giver

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

8.2.2. The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly and in accordance with the specification and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the materials, samples or the contracted operations that might pose a hazard to the premises, equipment, personnel, other materials or other blood components of the contract acceptor.

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

8.3. The contract acceptor

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

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

8.3.3. The contract acceptor should not pass to a third party any of the work entrusted under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the relevant blood collection, processing and testing information is made available in the same way as between the original contract giver and contract acceptor.

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

8.4. The contract

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

8.4.2. The contract should specify the procedure, including the necessary requirements to be provided by the contract acceptor, by which the Responsible Person or other authorised person releasing the blood and blood components for sale or supply can ensure that each component has been prepared and/or distributed in compliance with the requirements of Good Practice and regulatory requirements.

8.4.3. The contract should clearly describe who is responsible for purchasing materials, testing and releasing materials, undertaking blood collection, and for processing and testing (including in-process controls). In the case of subcontracted analyses, the contract should state the arrangements for the collection of samples and the contract acceptor should understand that they may be subject to inspections by the competent authorities.

8.4.4. Preparation and distribution records, including reference samples if relevant, should be kept by, or be available to, the contract giver. Any records relevant to assessment of the quality of the blood or a blood component in the event of complaints or a suspected defect should be accessible and specified in the defect/recall procedures of the contract giver.

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

8.4.6. Where contracts are defined at a higher level than the blood establishment (e.g. Regional, National) a system should be in place that permit an appropriate evaluation of the suitability (in terms of quality and safety) and the availability of the concerned materials and equipment.

9. Non-conformance and recall

9.1. Deviations

9.1.1. Blood components deviating from required standards set out in Annex V to Directive 2004/33/EC 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. The same principle applies to components not listed in Annex V to Directive 2004/33/EC when considering release of components deviating from defined quality and safety specifications.

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

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

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

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

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

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

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

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

9.2. Complaints

9.2.1. All complaints and other information, including serious adverse reactions and serious adverse events that may suggest that defective blood components have been issued, must be documented, carefully investigated for causative factors of the defect and, where necessary, followed up by recall and the implementation of corrective actions to prevent recurrence. Procedures must be in place to ensure that the competent authorities are notified, as appropriate, of serious adverse reactions or serious adverse events in accordance with regulatory requirements (Directive 2005/62/EC Annex 9.2).

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

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

9.2.4. All the decisions and measures taken as a result of a complaint should be recorded. Complaint records should be reviewed regularly for any indication of specific or recurring problems requiring attention and the possible recall of distributed blood and blood components.

9.2.5. The Competent Authorities should be informed in cases of complaints resulting from possible faulty processing, component deterioration or any other serious quality problems, including the detection of counterfeiting.

9.3. Recall

9.3.1. There must be personnel authorised within the blood establishment to assess the need for blood and blood component recalls and to initiate and co-ordinate the necessary actions (Directive 2005/62/EC Annex 9.3.1).

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

9.3.3. Actions must 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. Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public health prior to establishing the root cause(s) and full extent of the quality defect.

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

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

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

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

9.4. Deviation management and corrective and preventive actions

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

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

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

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

9.4.5. Investigations should include a review of previous reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action. Processes and relevant data should be monitored with

a view to taking preventive action to avoid potential deviations occurring in the future. Where appropriate, statistical or other tools should be used to assess and monitor process capabilities. As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations.

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

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

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

10. **Self-inspection, audits and improvements**

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

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

11. **Quality monitoring and control**

11.1. Quality monitoring

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

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

11.2. Quality control

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

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

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

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

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

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

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

Chapter 1

General notices

1.0. Overview

The *Guide to the preparation, use and quality assurance of blood components*, hereafter the *Guide*, is the appendix to Council of Europe (CoE) Recommendation No. R (95) 15. It provides a compendium of widely accepted European harmonised standards for the preparation, use and quality control of blood components to provide safety, efficacy and quality requirements for blood components in member states of the CoE. A limited amount of information is given on the clinical use of blood components. The *Guide* does not cover issues of cost- effectiveness of preparation of blood components.

The *Guide* is regularly updated. The task was assigned to the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS), an intergovernmental committee, which has according to Resolution CM/Res (2021) 3, entrusted a subordinate body, the 'GTS *ad hoc* Working Group TS Guide' (GTS), with the revision of the *Guide*.

1.1. Tasks and responsibilities of the GTS

To undertake the periodic revision of the *Guide*:

- Based on monitoring and expert evaluation of scientific pro- gress and regulatory changes in the field, and
- Supported by assessment of current evidence on the aspects of preparation, use and quality control of blood components as published in the scientific literature and guidelines.

The GTS may also liaise with other subordinate bodies nominated by the CD-P-TS to benefit from their specific field of expertise and where necessary contribute to the revision of the text of the *Guide* accordingly.

Revisions to the *Guide* are subject to a stakeholder consultation process. Feedback from this is reviewed by the GTS. A final version is then developed and submitted for adoption by the CD-P-TS prior to publication.

The stakeholder consultation and its process provides valuable input to both the edition under publication and subsequent editions.

1.2. Structure and content of the *Guide*

121 Good Practice Guidelines

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

EU/EEA Member States shall ensure, according to Directive 2005/62/ EC and its Article 2, as amended by Directive (EU) 2016/1214 that the quality system in place in all blood establishments complies with good practice guidelines which take fully into account, where relevant for blood establishments, the detailed principles and guidelines of good manufacturing practice, as referred to in the first subparagraph of Article 47 of Directive 2001/83/EC. In doing so, Member States shall take into account the Good Practice Guidelines published in the Guide.

Council of Europe member states should take the necessary measures and steps to implement the Good Practice Guidelines published in the *Guide*.

Although in other jurisdictions or in other international guidelines (e.g. WHO), principles of Good Manufacturing Practice (GMP) are applied to blood components, the GPG presented in this document are equivalent to GMP and the two terms can be used interchangeably, depending on national legislation.

The GPG published in the *Guide* provide standards and specifications of quality systems that Member States shall ensure are in place in blood establishments and hospital blood banks. When GPG requirements are taken from the EU Directives the term 'must' is used as a re- placement for 'shall'. This reflects the legal status

of the requirements within EU countries.

Consistent with the approach used in Codes of GMP, the require- ments in the GPG section of the *Guide* are defined using the term 'should'. The intention is that the requirements identify what needs to be achieved but are not specific on how this is done. GPG requirements are also replicated in other chapters of the *Guide*. When this occurs the term 'should' is retained for the purposes of consistency.

122. Standards

The standards are developed to support high-quality transfusion practice in CoE member states. They may also be of benefit to other jurisdictions or organisations involved in blood transfusion activities outside Europe.

The *Guide* includes recommendations for minimum standards for blood establishments and hospital blood banks that are required to comply with EU Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC as amended by Directive (EU) 2016/1214.

Those standards that are transcribed from EU Directives and the GPG are legally binding on blood establishments and, where applicable, hospital blood banks within the EU. When standards are taken from the EU directives, the term "must" is used as a replacement for "shall". This reflects the legal status of the standard and is consistent with the GPG.

All other standards included in the *Guide* reflect the current state of the art and should be followed.

Consistent with the approach used in the GPG, these standards are defined using the term "should" and identify what needs to be achieved but are not specific on how this is done.

Standard(s) are identified by the title Standard(s) and by a 4-digit numbering in level 4:

Level 1 Chapter;

Level 2 Section;

Level 3 Subsection;

Level 4 Standard(s).

The standards are also supported by non-standard text which can be seen as guidance or background information. The term "should" is also used in the non-standard text. For clarity, standards are clearly distinguished from non-standard text in the *Guide*.

To ensure the *Guide* is contemporary, new or modified standards may be proposed by the GTS for consideration where provided with the supporting rationale.

This rationale is broadly classified as either information on regulatory status, scientific evidence, international recommendations/practices, or expert opinion as described below:

a) EU directives;

b) Good Practice Guidelines;

c) Scientific documentation;

d) International recommendations (organization and reference)

e) Expert opinion (consensus within the GTS)

This process involves consideration of supporting evidence followed by discussion leading to consensus.

Where new or modified standards are included in the *Guide* based on regulatory status (i.e. a) EU Directives or b) Good Practice Guidelines) there will be a direct reference in the text to the relevant legislation or Good Practice Guideline standard.

Where new or modified standards are included in the *Guide* based on scientific evidence, international recommendations/practices, or expert opinion, there will be reference to the evidence level (c, d and/or e) to indicate the basis for their inclusion.

The supporting evidence for the inclusion of all new or modified standards is made available as part of the consultation process for the *Guide*.

123. Monographs

Blood components are described in monographs, mirroring the structure used in the European Pharmacopoeia. These monographs prescribe requirements that are to be regarded as harmonised standards

for the quality and safety of blood components across Europe. However, some components are in use only in a few countries. An overview of the monograph structure is provided in Chapter 5 of this *Guide*.

124. Appendices

Several appendices are provided at the end of the *Guide*. These appendices provide detailed information on specific areas of relevance to blood establishments and hospital blood banks which are not addressed in detail elsewhere in the *Guide*.

125. Abbreviations

Commonly used terms and abbreviations are defined, following the Directive definitions if applicable.

126. References

Recommendations and Resolutions of the Council of Europe in the field of blood transfusion are listed at the end of this *Guide*.

Chapter 2

Donor selection

2.0. Overview

Donor selection is a critical process in the chain from a safe blood donation to a safe blood product with high quality. This chapter considers the principles for the selection of donors of whole blood and also donors of components obtained by different apheresis procedures.

2.1. Responsibilities of blood establishments in the selection process

2.1.1. Principle of voluntary non-remunerated donation

Standard

2.1.1.1. Measures must be taken to promote the collection of blood and blood components from voluntary non-remunerated donations according to the principles set out in the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine, ETS No. 164).

Council of Europe Recommendation No. R (95) 14 Art. 2 identifies that 'Donation is considered voluntary and non-remunerated if the person gives blood, plasma or cellular components of his/her own free will and receives no payment for it, either in the form of cash, or in kind which could be considered a substitute for money. This would include time off work other than that reasonably needed for the donation and travel. Small tokens, refreshments and reimbursements of direct travel costs are compatible with voluntary, non-remunerated donation.'

2.1.2. Sex and gender

The term sex is generally used to refer to physical or genetic attributes that comprise biological sex, including male, female or intersex and is generally assigned at birth. Gender, on the other hand refers to how a person identifies to the various socially constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender-diverse people including those outside of gender spectrums.

In blood donation and transfusion practice the sex / gender of donors' and recipients has traditionally been defined as a binary variable and based on the biological and physiological differences between male and female individuals.

Accurate awareness of donor gender by Blood Establishments in both written records and verbal communications is necessary to allow donors to be appropriately addressed. Accurate awareness of donor sex is necessary to determine appropriate sex-related biological parameters to ensure donor and recipient safety and to assess donor eligibility in relation to the risk of sexually transmitted infections.

Standard

2.1.2.1. Blood Establishments should have systems in place that accommodate both the gender and sex of the donor to allow donors to be appropriately addressed, to enable determination of appropriate sex-related biological parameters to ensure donor and recipient safety and to assess donor eligibility in relation to the risk of sexually transmitted infections. Safety considerations include, for example, donor haemoglobin values, total blood volume estimation, pregnancy related risks including risks for HLA/HNA-antibodies and risks associated with sexual behaviour. (Evidence level C,E)

2.1.3. General requirements

Standards

2.1.3.1. Procedures for safe identification of donors, 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).

2.1.3.2. Blood establishments are ultimately responsible for the quality and safety of the blood and blood components collected, and must be entitled to decide on the final acceptance or deferral of a donor or a prospective donor, taking into account Resolution CM/Res (2008) 5 on donor responsibility and on the limitations to donation of blood and blood components.

2.1.4. Information to be provided to donors of blood or blood components

Standards

2.1.4.1. Information must be provided to prospective donors of blood or blood components. This information provides the basis for informed consent that must be obtained from the donor before proceeding to donation (Directive 2004/33/EC Annex II).

2.1.4.2. Accurate educational materials, which are understandable for members of the general public, about the essential nature of the blood donation procedure, components derived from whole blood and apheresis donations and the important benefits to patients must be provided (Directive 2004/33 EC Annex II).

2.1.4.3. The following information must be provided:

For both allogeneic and autologous donations: the reasons for requiring a medical assessment, health and medical history, the testing of donations and the significance of 'informed consent.

For allogeneic donations: self-deferral, temporary and permanent deferral and the reasons why individuals must not donate blood or blood components if there could be a risk for the recipient or the donor.

For autologous donations: the possibility of deferral and the reasons why the donation procedure cannot take place in the presence of a health risk to the individual, whether as a donor or recipient of the autologous blood or blood components

(Directive 2004/33 EC Annex II).

2.1.4.4. Information on the protection of personal data: no unauthorised disclosure of the identity of the donor, of information concerning the donor's health or of the results of the tests performed must be provided (Directive 2004/33 EC Annex II).

2.1.4.5. The reasons why individuals must not make donations that may be detrimental to their health must be provided (Directive 2004/33/EC Annex II).

2.1.4.6. Specific information on the nature of the procedures involved in the allogeneic or autologous donation process and their respective associated risks must be provided. For autologous donations, information on the possibility that the autologous blood and blood components may not suffice for the intended transfusion requirements must be provided (Directive 2004/33/EC Annex II).

2.1.4.7. Information on the option for donors to change their mind about donating before proceeding further, or the option to withdraw or self-defer at any time during the donation process without undue embarrassment or discomfort must be provided (Directive 2004/33/ EC Annex II).

2.1.4.8. The reasons why it is important that donors inform the blood establishment of any subsequent event that may render any prior donation unsuitable for transfusion must be provided (Directive 2004/33/ EC Annex II).

2.1.4.9. Information on the responsibility of the blood establishment to inform the donor, through an appropriate mechanism, if test results show any abnormality of significance to the donor's health must be provided (Directive 2004/33/EC Annex II).

2.1.4.10. Information why unused autologous blood and blood components are discarded and not transfused to other patients must be provided (Directive 2004/33/EC Annex II).

2.1.4.11. Information that test results detecting markers for viruses, such as HIV, HBV, HCV or other relevant blood-transmissible microbiologic agents, will result in donor deferral and destruction of the collected unit (Directive 2004/33/EC Annex II) and when required by law, that the results should be reported to the

relevant health authorities

2.1.4.12. Information on the opportunity for donors to ask questions at any time must be provided (Directive 2004/33/EC Annex II).

2.1.4.13. All blood donors should be provided with information about behaviours associated with an increased risk of blood-borne infectious agents, such as HIV/AIDS and hepatitis transmission and be given the opportunity for self-exclusion so that those persons refrain from donating.

2.2. Medical assessment of donors

221. Donor eligibility

Standards

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

2.2.1.2. There must be an area for confidential personal interviews and assessment of individuals to determine their eligibility to donate. This area must be separated from all processing areas (Directive 2005/62/EC Annex 3.2).

2.2.1.3. There should be secure and unique identification, as well as recording of the contact details, of donors (GPG 6.1.2).

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

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

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

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

In practice, a complete medical and physical examination of the donors is not possible. It is necessary to rely on the donors' appearance, their answers to questions concerning their medical history, general health, and relevant risk factors (e.g. risk behaviour, travel history) and on laboratory tests.

Based on this information, a decision on the eligibility of the donor will be made using accepted guidelines. Conditions that are not covered by guidelines should be referred to the physician in charge with responsibility for making the final decision.

222. Donor age

Standards

2.2.2.1. The age limits for donation are a minimum of 18 years and maximum of 65 years. (Directive 2004/33/EC Annex III).

2.2.2.2. Donation by first-time donors above the age of 60 years is at the discretion of the responsible physician (Directive 2004/33/EC Annex III).

2.2.2.3. Donation by donors over 65 years is with permission of the physician in the blood establishment, given annually. (Directive 2004/33/EC Annex III).

2.2.2.4. Permission to continue donating after the age of 65 years should be given annually by the responsible physician either individually to each donor or based on a medical risk assessment for a given donor population.

223. Donor haemoglobin

Standards

2.2.3.1. Haemoglobin concentration must be determined each time the donor donates whole blood or cellular

components (Directive 2004/33/EC Annex III).

2.2.3.2. Haemoglobin values at donation must not be lower than the values shown in the table below (Directive 2004/33/EC Annex III):

Table 2-1. **Haemoglobin values**

	Female	Male
Whole blood and cellular components	125 g/L or 7.8 mmol/L	135 g/L or 8.4 mmol/L

Individual donations may be accepted below these levels after consultation with the responsible physician or as established by a competent authority based on norms for their specific populations.

Haemoglobin should be measured preferably before the donation, but always before donation when donors were deferred from donation at the last visit because of its low level.

Abnormal high and low haemoglobin values should be confirmed by full blood count and subsequently investigated, as should a fall in haemoglobin concentration of more than 20 g per L between 2 successive donations.

2.2.4. Iron stores

There is increasing awareness of the risk of iron deficiency following regular whole blood donation. This is particularly apparent in women in childbearing years, frequent whole blood donors and in donors with inadequate dietary iron intake who may present as a first-time donor with low or borderline iron stores. Each whole blood donation results in the loss of 200 to 250 mg of iron. Replenishment of this may take up to 6 months based on a normal healthy diet.

Iron deficiency may occur despite a normal pre-donation haemoglobin measurement.

Standard

2.2.4.1. Blood establishments should have measures in place to minimise iron depletion in frequent blood donors

Measures to prevent iron depletion and to protect donor health may include:

- Provision of materials for donor education particularly in regard to the impact of blood donation on iron stores;
- Individual tailoring of donation frequency or the interval between donations and/or of the type of blood component donation based on sex, age, Hb-values andiron status; (Evidence level C,E)
- Use of tests to assess iron status, such as ferritin, soluble transferrin receptor, and RBC indices;
- Iron supplementation taking into account the risk of delaying the diagnosis of unapparent underlying diseases and adverse effects of the iron preparations;
- In plasmapheresis donations destined for plasma for fractionation: the use of samples taken from the plasma collection container (instead of whole blood samples from the donor) for mandatory laboratory screening tests in order to avoid a loss of iron from testing samples (see also Chapter 3, Standard 3.6.2.2). (Evidence level C)
- Saline wash-back of residual red cells in the apheresis harness

2.2.5. Questionnaire and interview

Standards

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

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

2.2.5.3. The confidential interview should be conducted by specifically trained staff who may also ask further direct

questions to supplement the information in the questionnaire. The person who carries out the assessment should certify that the relevant questions have been asked (GPG 6.1.9).

2.2.5.4. During the interview the donor should be evaluated for physical attributes that may suggest an underlying condition where donation is not safe (for example cyanosis, dyspnoea, undernutrition, intoxication from alcohol or drugs).

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

The key topics for donor eligibility to be covered by the questionnaire or by direct questions, the intentions of the interview questions, and examples of sample questions are included in Appendix 1.

2.3. Donor deferral

2.3.1. General remarks

Donors with hazardous occupations or hobbies should be advised to wait for an interval of not less than 12 hours between donation and returning to the occupation or hobby. Examples of such hazardous occupations or hobbies include piloting, bus or train driving, crane operation, climbing of ladders or scaffolding, gliding, climbing and diving.

Donors presenting with any kind of medical condition or under medical treatment should be assessed to determine their eligibility and, where appropriate, either temporarily or permanently deferred from donation, in order to protect their health and/or the health of the recipients. Reasons for donor deferral include non-infectious medical conditions, infectious diseases and medical or surgical treatments.

Standard

2.3.1.1. Deferred individuals should be given a clear explanation of the reasons for deferral.

2.3.2. Non-infectious medical conditions

Standard

2.3.2.1. Prospective donors with serious active, chronic or relapsing disease must be permanently deferred (Directive 2004/33/EC Annex III)

Allergy and anaphylaxis

Standard

2.3.2.2. Donors with local / non-generalized allergic symptoms, which are controlled with medication (except for oral corticosteroids, or other immunosuppressive medical treatment) or without medication are accepted as donors (Evidence level C,E)

2.3.2.3. Donors who have had a recent episode of anaphylaxis or severe allergic reaction should be deferred for two weeks after recovery. (Evidence level C,E).

Donors with severe, widespread atopic eczema should be temporarily deferred until cessation of the symptoms (Evidence level C,E).

Donors requiring oral corticosteroids, or other immunosuppressive medical treatment should be deferred temporarily until such treatment has stopped. (Evidence level C,E)

Donors with any known allergy to agents used in blood collection (skin disinfection agent, other material used in collection process) should be deferred unless there is alternative material available (Evidence Level E).

Based on current evidence, the major risk for a recipient's anaphylactic reaction, is their own atopic condition. Selecting donors based on their allergic/anaphylactic anamnestic reactions is therefore not an effective risk reduction strategy and may cause an unacceptable loss of donors. Theoretically and based on case studies, the risk of an allergic /anaphylactic reaction in a recipient is higher, when there is a larger amount of plasma in the blood component (Evidence level C).

Therefore, consideration may be given to permanently deferring donors with recurrent severe allergic/anaphylactic reactions to food or antibiotics from donating blood components with a high

plasma volume, such as FFP for clinical use and platelets in plasma (Evidence level E).

Autoimmune disease

A person requiring systemic immune-modulatory therapy should be deferred until such treatment has stopped. Asymptomatic donors without severe complications can be accepted.

Blood pressure

A person with a systolic blood pressure of 180 mm Hg or higher, or a diastolic blood pressure of 100 mm Hg or higher should not be accepted as a blood donor.

Cancer/malignant diseases

Standard

2.3.2.4. Individuals with a malignant disease are permanently deferred, except donors with carcinoma in situ with complete recovery (Directive 2004/33/EC Annex III).

There is evidence to support the acceptance of donors with a history of cancer. Large observational studies have provided convincing evidence that the risk of transmitting cancer via blood transfusions is undetectable or not significant. (Evidence level C)

Therefore, the responsible physician may make exceptions other than carcinoma in situ if the donor has fully recovered with no expectation of recurrence (i.e. cured).

The following conditions apply:

- for cancers with negligible metastatic potential (for example basal cell carcinoma), the donor may be accepted immediately following successful removal and cure;
- for other cancers, at least 5 years should have elapsed since completion of treatment (Evidence Level C,D,E).
- No deferral is required for pre-malignant conditions.

Cardiovascular disease

Standard

2.3.2.5. Donors with active or past serious cardiovascular disease, except congenital abnormalities with complete cure, must be permanently deferred (Directive 2004/33/EC Annex III).

2.3.2.6. Persons with a history of coronary disease, angina pectoris, severe cardiac arrhythmia, a history of cerebrovascular diseases, arterial thrombosis or recurrent venous thrombosis should be classified as having "serious cardiovascular disease" and therefore be permanently deferred (Evidence level E).

Diabetes

Standard

2.3.2.7. Donors with diabetes must be deferred if insulin therapy is required (Directive 2004/33/EC Annex III).

Epilepsy

Standard

2.3.2.8. Donors with repeated episodes of syncope or a history of convulsions must be deferred until 3 years off treatment and free of attacks (Directive 2004/33/EC Annex III).

Kidney disease

Standard

2.3.2.9. Following acute glomerulonephritis donors should be deferred for 12 months after full recovery (feeling well, no treatment and discharged from specialist care).

Pregnancy

Standard

2.3.2.10. Pregnant women must be deferred 6 months after delivery or termination. The responsible physician may make exceptions under exceptional circumstances (Directive 2004/33/EC Annex III).

Pulse

A person with a pulse under 50 beats per minute (bpm), or above 100 bpm or presenting with an irregular pulse should be deferred. Exceptions may be made to accept donors with a lower pulse rate following individual medical review, e.g. athletes.

Respiratory disease

Standard

2.3.2.11. Prospective donors with serious active, chronic, or relapsing respiratory system diseases must be permanently deferred (Directive 2004/33/EC Annex III).

Rheumatic fever

Standard

2.3.2.12. Donors suffering from rheumatic fever must be deferred for 2 years following the last attack or permanently if any evidence of chronic heart disease (Directive 2004/33/EC Annex III).

Thalassaemia

Donors with thalassaemia should be deferred permanently if they are not in good health or if the haemoglobin levels are below acceptable values. Individuals with thalassaemia trait may give blood provided they are in good health and have a haemoglobin level within acceptable values.

2.3.3. Infectious diseases

Transmission of infectious agents by transfusion can be minimised by careful and appropriate use of donor questionnaires and/or laboratory testing.

Other measures are needed for infections where there is a possibility of asymptomatic infection or existence of a carrier state. Questioning donors about symptoms in these circumstances does not always prevent transmission.

Donors should be questioned on their risk of exposure to infectious agents, which includes taking a travel history:

- For infections in which the agent has been fully cleared from the donor's blood on recovery, the donor should be deferred from donation until they are no longer infectious (usually 2 weeks from cessation of symptoms);
- In cases of known contact with an infectious agent, the donor should be deferred for approximately twice the length of the incubation period In case of a geographical risk of exposure to multiple infectious agents, the longest deferral period applies;
- Many infections that can be transmitted by transfusion have defined geographical limits, and the risk of transfusion transmission can be minimised by temporary deferral or testing donors travelling from affected areas. Testing becomes especially relevant when deferral policies may potentially affect supply.

Blood services should maintain a watching brief on changes to risks of infectious diseases worldwide. Risk-benefit analyses should be carried out to determine appropriate measures to decrease the risks of transfusion transmission. The risk of importation of an infectious agent through donors visiting an affected area should be balanced by considering the likelihood of this occurring, and the impact of introducing a new donor deferral ruling on blood supply. This risk will vary between countries.

New and emerging infectious agents or those that have moved to infect a new geographical area can also pose a significant challenge. In this situation, donor deferral may not be an option in the newly affected area. Donation testing is then the main tool to reduce the risk of transmission. For plasma and platelets, pathogen inactivation technology may also be considered.

Information about new and emerging infections should be communicated between countries without delay to allow blood establishments to consider their own risks and appropriate actions.

Babesiosis

Standard

2.3.3.1. Donors with babesiosis must be deferred permanently (Directive 2004/33/EC Annex III).

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Brucellosis

Standard

2.3.3.2. Donors with brucellosis must be deferred for at least two years following full recovery (Directive 2004/33/EC Annex III)

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Chikungunya virus

Standards

2.3.3.3. Donors visiting endemic regions for chikungunya virus infections should be deferred for 28 days after leaving the risk area.

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

2.3.3.4. Donors suffering from chikungunya virus infections should be deferred for 120 days after resolution of the symptoms.

Common cold

Donors presenting with the common cold should be deferred until cessation of symptoms.

Creutzfeldt–Jakob disease

Standards

2.3.3.5. Individuals who have been treated with extracts derived from human pituitary glands and recipients of *dura mater* or corneal grafts must be deferred permanently (Directive 2004/33/EC Annex III).

2.3.3.6. Individuals with a family risk of Creutzfeldt–Jakob disease (CJD) or any other transmissible spongiform encephalopathy must be deferred permanently (Directive 2004/33/EC Annex III).

A family history of CJD carries a presumption of family risk unless it is determined that:

- The affected family member had vCJD, not CJD; or
- The affected family member did not have a genetic relationship to the donor; or
- The cause of CJD in the affected family member was iatrogenic; or
- The donor was tested and is known to have a normal genetic polymorphism for PrPc.

Standard

2.3.3.7. Deferral of donors as a preventative measure for vCJD should be based on appropriate risk assessment.

Variant Creutzfeldt–Jakob disease (vCJD) was first described in the UK in 1996. Estimating the potential size of the vCJD epidemic has been very difficult. Transfusion transmission of vCJD has been documented in animal studies and in humans. Endogenous risk of vCJD differs between countries. Therefore, the need for different measures to reduce risk will depend on each country's own risk assessment, balancing risk with sufficiency of supply.

Many countries outside the UK defer donors who have lived in the UK for a minimum defined period between 1980 and 1996; the European Medicines Agency (EMA) mandates 1 year of UK residence for donors of plasma for fractionation. In some instances, the deferrals have been extended to include donors from other countries with a significant number of cases.

Dengue fever

Standards

2.3.3.8. Donors visiting endemic regions for dengue fever should be deferred for 28 days after leaving the risk area.

2.3.3.9. Donors suffering from dengue fever should be deferred for 120 days after resolution of the symptoms.

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Fever above + 38 °C, flu-like illness

Standard

2.3.3.10. Donors presenting with fever above + 38 °C or flu-like illness must be deferred for 2 weeks following cessation of symptoms (Directive 2004/33/EC Annex III).

Hepatitis B (HBV)

Standards

2.3.3.11. Individuals infected with HBV must be deferred permanently unless HBsAg negative and demonstrated to be immune (Directive 2004/33/EC Annex III).

2.3.3.12. Persons who have been in close household contact with an individual infected by the hepatitis-B virus (acute or chronic) must be deferred for 6 months (4 months if appropriate testing has been performed) from the time of contact unless demonstrated to be immune (Directive 2004/33/EC Annex III).

2.3.3.13. Current sexual partners of people with HBV should be deferred, unless demonstrated to be immune.

2.3.3.14. Previous sexual partners of people with HBV are acceptable after 6 months since the last sexual contact. This can be reduced to 4 months if HBV NAT and anti-HBc are performed and both test results are negative.

Hepatitis C (HCV)

Standard

2.3.3.15. Individuals infected with HCV or history thereof must be deferred permanently (Directive 2004/33/EC Annex III).

HIV 1/2

Standard

2.3.3.16. Individuals infected with HIV 1/2 must be deferred permanently (Directive 2004/33/EC Annex III).

HTLV 1/2

Standard

2.3.3.17. Individuals infected with HTLV 1/2 must be deferred permanently (Directive 2004/33/EC Annex III)

Jaundice and hepatitis

Standard

2.3.3.18. Individuals with a history of jaundice or hepatitis may be accepted as blood donors at the discretion of the appropriate competent authority, provided a CE-marked test for HBsAg and anti-HCV is negative.

Hospital staff coming into direct contact with patients with hepatitis may be accepted at the discretion of the physician in charge of the blood-collecting unit providing they have not suffered an inoculation injury or mucous membrane exposure, in which case they must be deferred.

Leishmaniasis (kala-azar), visceral leishmaniasis

Standard

2.3.3.19. Individuals with a history of visceral leishmaniasis (kala-azar) must be deferred permanently (Directive 2004/33/EC Annex III).

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Malaria

Standard

2.3.3.20. A donor should be questioned to identify the country(s) they were born in, have lived in or have visited.

This is essential for effective detection of donors at increased risk of malaria who may need to be deferred. These deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Standards

2.3.3.21. Blood establishments should have access to a current map or list of endemic areas and seasonal risk

periods at the site of blood collection.

2.3.3.22. The following rules should apply for individuals who give a history of malaria:

- They should be deferred for a period of at least 4 months following departure from a malarial area and 4 months following cessation of treatment/last symptoms. They may then be accepted if the result of a validated immunological test for antibodies to the malaria parasite is negative;
- If the test is repeatedly reactive, the donor should be deferred and may be re-evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested);
- If the test is not performed, the donor should be deferred until the test is performed and negative.

2.3.3.23. The following rules should apply for individuals who report an undiagnosed febrile illness consistent with malaria during a visit to or within 6 months following departure from a malarial area:

- They should be deferred for a period of at least 4 months following departure from a malarial area and 4 months following cessation of treatment/last symptoms. They may then be accepted if the result of a validated immunological test for antibodies to the malaria parasite is negative;
- If the test is repeatedly reactive, the donor should be deferred and may be re-evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested);
- If the test is not performed, the donor should be deferred until the test is performed and negative.

2.3.3.24. The following rules should apply for individuals who have lived in a malaria-endemic area for a continuous period of 6 months or more at any time in their life at the time of their first donation and after each return from a malarial area:

- They may be accepted as blood donors if the result of a validated immunological test for antibodies to the malaria parasite, per- formed at least 4 months after leaving the malarial area, is negative;
- If the test is repeatedly reactive, the donor should be deferred and may be re-evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested);
- If the test is not performed, the donor should be deferred until the test is performed and negative.

2.3.3.25. The following rules should apply for all other individuals who have visited a malarial area without reporting any clinical symptoms consistent with malaria:

- They should be deferred for a period of 4 months following departure from the malarial area and may then be accepted as blood donors if the result of a validated immunological test for antibodies to the malaria parasite is negative;
- If the test is not performed, the donor may be accepted once a period of 12 months has elapsed following departure from the malarial area;
- If the test is repeatedly reactive, the donor should be deferred and may be re-evaluated after a suitable period when the antibody test may have reverted to negative (a period of 3 years is suggested).

Osteomyelitis

Standard

2.3.3.26. Donors suffering from osteomyelitis must be deferred until two years after having been declared cured (Directive 2004/33/EC Annex III).

Q fever

Standard

2.3.3.27. Donors suffering from Q fever must be deferred until two years after having been declared cured (Directive 2004/33/EC Annex III).

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Syphilis

Standard

2.3.3.28. Donors suffering from syphilis must be deferred until one year after having been declared cured (Directive 2004/33/EC Annex III).

Tests and deferral periods may be waived if the donation is used exclusively for plasma for fractionation.

Toxoplasmosis

Standard

2.3.3.29. Donors suffering from toxoplasmosis must be deferred until 6 months following clinical recovery (Directive 2004/33/EC Annex III).

Deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

***Trypanosomiasis cruzi* (Chagas disease)**

Standard

2.3.3.30. Individuals with Chagas disease or who have had Chagas disease must be deferred permanently (Directive 2004/33/EC Annex III).

In some countries, individuals who were born or have been transfused in areas where the disease is endemic are also deferred unless a validated test for infection with *T. cruzi* is negative.

Test and deferral requirements may be waived if the donation is used exclusively for plasma for fractionation.

Sexual risk behaviour

Standards

2.3.3.31. Individuals whose sexual behaviour puts them at a high risk of acquiring severe infectious diseases that can be transmitted by blood must be deferred permanently (Directive 2004/33/EC Annex III).

2.3.3.32. Sexual partners of people in 2.3.3.31 above should be deferred for a period determined by national risk assessment for the infectious disease in question, and by the availability of appropriate tests.

Tuberculosis

Standard

2.3.3.33. Donors suffering from tuberculosis must be deferred until two years after having been confirmed cured (Directive 2004/33/EC Annex III).

West Nile virus (WNV)

Standards

2.3.3.34. Individuals visiting regions with ongoing transmission of WNV to humans must be deferred for 28 days after leaving the risk area unless an individual NAT is performed (Directive 2014/110/EU).

2.3.3.35. Individuals with a diagnosis of WNV should be deferred until 120 days after recovery.

Tests and deferral periods may be waived if the donation is used exclusively for plasma for fractionation.

Zika virus

Standards

2.3.3.36. Individuals visiting regions with ongoing transmission of Zika virus infections to humans should be deferred for 28 days after leaving the risk area unless a validated NAT is performed.

2.3.3.37. Individuals with a diagnosis of Zika virus infection should be deferred until 120 days after recovery.

Tests and deferral periods may be waived if the donation is used exclusively for plasma for fractionation.

2.3.4. Interventions and treatments

Acupuncture, tattooing, body piercing and aesthetic medical procedures

Standard

2.3.4.1. Individuals having acupuncture (unless performed by a qualified practitioner and with sterile single use needles), tattooing or body piercing must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

There is evidence, that by using a risk-based approach based on national TTI disease prevalence and incidence, modifications to standard 2.3.4.1 can be accepted for acupuncture, tattooing, body piercing, or skin/mucosal penetrating aesthetic medical procedures. These may be implemented nationally or by the decision of the

responsible physician (Evidence level C,E)

Where modified standards are implemented, the following should be considered when assessing eligibility of such donors:

- The reason for acupuncture and complications of acupuncture, tattooing, body piercing and other aesthetic procedures;
- Secondary infection; inspect or ask about local complications, such as redness, swelling or skin lesions.

Cell transplant of human origin

Standard

2.3.4.2. Individuals having a tissue or cell transplant of human origin must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

Exceptions may be made according to national risk assessments.

Drugs

Standard

2.3.4.3. Individuals with any history of intravenous or intramuscular non-pre- scribed drug use, including bodybuilding steroids or hormones, must be deferred permanently (Directive 2004/33/EC Annex III).

Endoscopy with biopsy using flexible instruments

Standard

2.3.4.4. Donors having an endoscopy with biopsy using flexible instruments must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

Exceptions may be made according to national risk assessments.

Inoculation injury or mucosal splashes with blood

Standard

2.3.4.5. Individuals having an inoculation injury or mucosal splashes with blood must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

Exceptions may be made according to national risk assessments.

Medication

Standard

2.3.4.6. Donors treated with drugs with proven teratogenic effect must be deferred for a period at least consistent with the pharmacokinetic properties of the drug.

The taking of a medication may indicate an underlying disease which may disqualify the donor. It is recommended that a list of commonly used drugs, with rules for acceptability of donors, approved by the medical staff of the blood establishment, be made available.

Surgery

Standard

2.3.4.7. After major surgery, donors must be deferred for 6 months, or for 4 months provided a NAT test for hepatitis C is negative. (Directive 2004/33/EC Annex III).

2.3.4.8. After minor surgery, donors must be deferred for 1 week. (Directive 2004/33/EC Annex III).

There is no clear evidence that exactly supports the deferral periods of 4 to 6 months after major surgery and 1 week after minor surgery (Evidence level C,E). By using a risk based approach, modifications to standards 2.3.4.7 and 2.3.4.8 can be accepted and implemented nationally or by the decision of the responsible physician.

Where modified standards are implemented, the following should be considered when assessing eligibility of such donors:

- For major surgery: persons should not donate until they have fully recovered (typically about 6 months). A shorter deferral period is possible after medical evaluation, if the donor has totally recovered from the surgery (i.e. wound healed, no signs of post-operative infection and in a healthy condition) (Evidence level C, E)

- For planned major surgery: homologous whole blood donation should be avoided for an appropriate time interval before major surgery. (Evidence level, E)

- For minor surgery: deferral until wound healed (stitches removed, no signs of infection). (Evidence level C, E)

When considering revised donor eligibility following surgery, the responsible physician should take into consideration the following:

- The indication for the surgery;
- Whether the donor received a transfusion of labile blood products; if so, refer to specific rules;
- The need to measure the haemoglobin pre-donation after major surgery.

Dental care / Oral health care

Standard

2.3.4.9. Individuals after tooth extraction, root filling and similar treatments must be deferred for 1 week (Directive 2004/33/EC Annex III).

2.3.4.10. Donors undergoing minor treatment by a dentist or dental hygienist must be deferred until the next day (Directive 2004/33/EC Annex III).

The available evidence indicates that bacteraemia immediately following minor dental treatments is transient, lasting only up to 30 minutes. Poor oral health, such as acute or chronic gingivitis, is a risk factor for bacteraemia (Evidence level C). By using a risk based approach, modifications to standard 2.3.4.10 can be accepted and implemented nationally or by the decision of the responsible physician.
Modifications to the standard can be made by the responsible physician as follows;

- Minor dental treatment by the dentist or dental hygienist: 60 minutes deferral (Evidence level C, E);

- Acute oral infection (for example gingivitis needed treatment): defer until cessation and/or two weeks after oral course of antibiotics (Evidence level C, E).

Transfusion of blood components

Standard

2.3.4.11. Individuals having a transfusion of blood components must be deferred for 6 months (or 4 months, provided a NAT test for hepatitis C is negative) (Directive 2004/33/EC Annex III).

Injection of red cells as part of an approved immunisation programme will need clinical assessment.

Blood or blood components used for treatment other than transfusion

Donors who have received treatment with allogeneic blood or blood components for topical use or injections should be treated as though they had received blood components for transfusion (Evidence level C,E).

Vaccines

Standards

2.3.4.12. Individuals after vaccination with attenuated bacteria and viruses
e.g. BCG, yellow fever, rubella, measles, poliomyelitis (oral), mumps, live attenuated typhoid fever, vaccinia, live attenuated cholera vaccine must be deferred for 4 weeks (Directive 2004/33/EC Annex III);

2.3.4.13. Individuals after vaccination for smallpox must be deferred for 8 weeks.

2.3.4.14. Individuals may, if well, be accepted as donors after vaccination (Directive 2004/33/EC Annex III):

- With inactivated viruses: e.g. poliomyelitis (injection), influenza;
- With killed bacteria: e.g. cholera, typhoid, capsular polysaccharide typhoid fever vaccine;
- With toxoids: e.g. diphtheria, tetanus;

- With hepatitis A or tick-borne encephalitis vaccines, if no exposure is reported.

2.3.4.15. Individuals receiving rabies vaccines are (Directive 2004/33/EC Annex III):

- Accepted without deferral if well and no exposure;
- Deferred for 12 months following exposure to rabies.

2.3.4.16. Individuals should be deferred for 2 weeks following administration of hepatitis B or a combined hepatitis A and hepatitis B vaccine in order to prevent vaccine-related positivity in the HBsAg test.

Xenotransplantation

Standard

2.3.4.17. Individuals after xenotransplantation must be deferred permanently (Directive 2004/33/EC Annex III).

2.4. Specific standards for donors of different types of components

Below are specific standards for donors of blood and blood components for both whole blood and apheresis collection. The interval between donations is provided in Table 2-3 at the end of the chapter.

2.4.1. Whole blood donation

Volume of whole blood donation

Standards

2.4.1.1. A standard donation of whole blood must not be collected from persons weighing less than 50 kg (Directive 2004/33/EC Annex III).

2.4.1.2. The volume of a standard donation of whole blood (excluding anticoagulants) should not exceed 500 mL and usually consists of a donation of 450 mL ± 10 per cent. This does not include any allowance for samples taken for laboratory tests and for retention of a donor sample.

2.4.1.3. The volume of a standard donation of whole blood (including samples) should not exceed 15 per cent of the calculated blood volume of the donor.

The total blood volume (TBV) of the donor can be estimated from their weight, height and gender using a validated formula. The estimates developed by the International Council for Standardization in Haematology (ICSH) are recommended and are available in Appendix 2.

It is generally accepted that all men weighing ≥ 50 kg have a sufficiently large blood volume to donate a total 535 mL of blood (500 mL plus 35 mL for testing and retention of a donation sample), whilst all women weighing ≥ 50 kg have a sufficiently large blood volume to donate a total 485 mL of blood (450 mL plus 35 mL for testing and retention of a donation sample).

In the case of women weighing < 65 kg and donating a total of > 485 mL, the blood volume should be estimated. This volume should exceed the minimum acceptable blood volume for the volume of blood to be collected (see Table 2-2).

Table 2-2. **Predicted minimum blood volume of a female donor donating 485 mL, 510 mL or 535 mL**

Volume of blood to be collected	Maximum percentage of blood volume collected	Minimum acceptable blood volume
450 mL + 35 mL	15 %	3 233 mL
475 mL + 35 mL	15 %	3 400 mL
500 mL + 35 mL	15 %	3 567 mL

Frequency of whole blood donation

Standards

2.4.1.4. A maximum of 6 standard donations of whole blood per year can be taken from men and up to 4 per year from women, with a minimum interval between standard donations of 8 weeks.

2.4.1.5. These maximum limits of donation frequency should never be exceeded and should only be adopted after careful consideration of the dietary habits of the population concerned and in the knowledge that extra care may be necessary, beyond routine haemoglobin or haematocrit estimation, in the monitoring of donors for iron deficiency.

It is therefore recommended that an active donor panel of sufficient size be maintained to allow donors to be bled less often than the maximum annual rates.

2.4.2. Apheresis donation

Written informed consent should be obtained before the first apheresis procedure and again subsequently if the risk profile of the procedure increases.

Standards

2.4.2.1. The medical supervision and care of apheresis donors should be the responsibility of a physician specially trained in these techniques.

2.4.2.2. Other than in exceptional circumstances (to be decided by the responsible physician), donors for apheresis procedures should meet the criteria for whole blood donations unless otherwise identified in this *Guide*.

The impact of prematurely terminated apheresis procedures, including consideration of a failed return of red cells resulting in a red cell loss and the amount of primary component already collected, needs to be taken into account when determining compliance with these requirements.

There are concerns about long-term effects in donors in intensive apheresis programmes. These include risks associated with citrate exposure in regular platelet apheresis donors, which might lead to problems with bone mineral density and reduced IgG levels. Regular monitoring of IgG in plasmapheresis donors for adjusting of donation frequency has been shown to improve donor safety.

Special attention should be given to the following conditions:

- Abnormal bleeding episodes;
- Adverse reactions to previous donations;
- Frequency of donation and maximal amounts of plasma and red cells to be collected.

Standards

2.4.2.3. The interval between one plasmapheresis or plateletpheresis procedure and a donation of whole blood or apheresis procedure incorporating collection of a single or double unit of red cells (whereby one unit is equivalent to a red cell component obtained from one whole blood donation) should be at least48 hours.

2.4.2.4. The interval between a whole blood donation, an apheresis red cell collection or a failed return of red cells during apheresis, and the next apheresis procedure without red cell collection, should be at least 4 weeks.

2.4.2.5. The interval between two single-unit red cell collections should be the same as for collections of whole blood.

Additional requirements for donors undergoing plasmapheresis

Sampling and residual blood remaining in the plasmapheresis devices can result in a non-negligible loss of red cells, with a consequent reduction in serum iron and ferritin. This is especially important for female donors.

Where frequent plasmapheresis is undertaken, consideration should be given to the implementation of measures to reduce residual blood loss in the equipment e.g. end procedure saline infusion. Loss of iron in donors can also be mitigated by using samples from plasma collection container (instead of whole blood samples) for mandatory laboratory screening tests (See also Chapter 3, Standard 3.6.2.2. Evidence level C).

The following standards identify requirements for donors undergoing plasmapheresis.

Standards

2.4.2.6. The maximum number of plasma donations allowed is 33 per year (Evidence level C).

2.4.2.7. The collection volume for each plasmapheresis should be based on estimation of an allowed/permitted volume for an individual donor. The limits for allowed volumes should be based on estimated total blood volume (TBV) and/or body mass index (BMI) and can be set either by national/regional regulations or based on TBV estimation in Appendix 2a or BMI in Appendix 2b.

2.4.2.8. The collection volume for each plasmapheresis (including anticoagulant) should never exceed 880 mL.

2.4.2.9. When the collection volume (including anticoagulant) is deter- mined by the estimation of TBV (Appendix 2a) the donated volume (excluding anticoagulant) should not exceed 16 per cent of the estimated TBV and in any type of apheresis procedure the total volume of all components donated (plasma, platelets and red cells) should not exceed 16 per cent of the estimated TBV.

2.4.2.10. The donation interval should be at least one week (see the IgG algorithm provided below).

2.4.2.11. Haemoglobin values at plasmapheresis donation should not be less than 120 g/L or 7.5 mmol/L for female and not less than 130 g/L or 8.1 mmol/L for male donors.

Individual donations may be accepted below these levels after consultation with the responsible physician or as established by a competent authority based on norms for their specific populations.

2.4.2.12. Total proteins must be measured at least annually and must not be less than 60 g/L. (Directive 2004/33/EC Annex III)

2.4.2.13. Serum-IgG levels should be within reference values of the normal population and should not fall below 6.0 g/L.

2.4.2.14. Serum-IgG should be measured at least annually and at every 26th donation, whichever comes first. (Evidence level C,E)

The maximum donation frequency for an individual donor should be guided by the results of the testing. An approach for the calculation of the maximum donation frequency for an individual donor based on its IgG levels could be as follows:

- IgG< 6.0 g/L results in a deferral from plasmapheresis of at least 3 weeks. Repeated measurements of <6.0 g/L should lead to either a significant increase in the inter-donation interval or permanent deferral from plasmapheresis;
- IgG 6.0–8.0 g/L supports donations with a minimum interval of two weeks;
- IgG> 8.0g/L supports donations with a minimum interval of one week

Additional requirements for donors undergoing platelet apheresis

Standards

2.4.2.15. Platelet apheresis must not be carried out on individuals whose platelet count is less than 150 × 10^9/L. (Directive 2004/33/EC Annex III)

2.4.2.16. Haemoglobin values at platelet apheresis donation must not be less than 125 g/L or 7.8 mmol/L for female and not less than 135 g/L or 8.4 mmol/L for male donors. (Directive 2004/33/EC Annex III)

Individual donations may be accepted below these levels after consultation with the responsible physician or as established by a competent authority based on norms for their specific populations.

2.4.2.17. Donors should not be subjected to a platelet apheresis procedure more often than once every 2 weeks.

An exception to the donation interval and platelet count may be made in the case of HLA-/HPA-matched donations and for IgA-negative donors at the discretion of the physician responsible for the procedure.

Additional requirements for donors undergoing double unit red cell apheresis

Standards

2.4.2.18. Minimum limits for haemoglobin values at double unit red cell apheresis donation should not be less than 140 g/L or 8.4 mmol/L for both female and male donors.

2.4.2.19. The total amount of red cells collected should not exceed the theoretical amount of red cells that would reduce the donor haemoglobin level, in an isovolemic situation, to below 110 g/L.

2.4.2.20. The donor should have an estimated blood volume of > 4.5 L which must be calculated on the basis of gender, height and weight (see Appendix 2a, Tables 1 and 2).

2.4.2.21. The interval following a whole blood donation and the subsequent donation of a double unit of red cells should be at least 12 weeks. The interval following a double-unit red cell apheresis and a subsequent whole blood donation or double-unit red cell apheresis should be at least 24 weeks for women and 16 weeks for men.

2.4.2.22. The maximum volume of red cells collected should not exceed 400 mL (without re-suspension solution) per collection procedure.

2.4.2.23. Total red cell volume collected per year should not exceed that acceptable for whole blood donors.

Additional recommendations for granulocytapheresis

Clinical efficacy, indications and dosage of granulocyte transfusion have not been established. In view of this, provision of informed consent prior to collection of granulocytes is particularly important. Effective granulocyte collection involves administration of medication (corticosteroids and/or granulocyte colony-stimulating factor) to increase circulating granulocyte levels and the use of sedimenting agents (hydroxyethyl starch) during the procedure itself. Both of these have potentially severe side-effects, identified below, that need to be communicated to the donor.

Hydroxyethyl starch (HES): acts as a volume expander. Donors who have received HES may experience headaches or peripheral oedema because of expanded circulatory volume. HES may accumulate, which can result in pruritus, and allergic reactions are possible.

Corticosteroids: may cause, for example, hypertension, diabetes mellitus, cataracts, peptic ulcer and psychiatric problems.

Granulocyte colony-stimulating factor (G-CSF): the most common short-term complication following G-CSF administration in peripheral blood stem cell (PBSC) donors is bone pain; although, on very rare occasions, splenic rupture or lung injury may occur. Concerns have also been raised relating to the development of acute myeloid leukaemia (AML)/myelodysplasia (MDS) after G-CSF administration. To date, however, registry data from Europe and the United States of America have not identified any increased risk of AML/MDS in healthy individuals who donated PBSCs and received G-CSF as a pre-treatment. The median follow-up of these studies is, however, less than 5 years. Therefore, if G-CSF is given to a donor, a protocol for long-term follow-up should be in place

Additional recommendations for donors of red cells for anti-RhD immunisation

Specific protocols for donors of red cells for anti-RhD immunisation should be in place and should at least include the following:

- Additional testing for markers of infectious disease, such as anti-HTLV-1/2, anti-HBc and NAT tests for pro-viral HIV-DNA and HIV-RNA, antibodies against HCV-RNA, HBV-DNA, parvovirus B19/DNA or parvovirus B19-antibodies, HAV-RNA;
- Extensive red cell phenotyping should be performed at least twice, and may be supplemented by genotyping;
- The red cells for immunisation should be stored for at least 6 months. After 6 months, all the infectious markers stated above should have been found to be negative (or indicate absence of infection) on a new donor sample before release of the stored red cells for immunisation.

In order to manage the impact of changes in donor selection criteria and infectious marker testing that may occur over time, protocols should require:

- Maintenance of retention samples from each donation suitable for future testing;
- Re-qualification of past donations by assessing conformance with additional donor acceptance requirements including, where appropriate, testing of the donor and/or the retention sample

Exemption of past donations from current standards is not recommended and should only be considered in exceptional circumstances after careful consideration of the risks to the immunised donors and ultimate plasma product recipients.

2.4.3. Designated donations

Although blood donation is voluntary, non-remunerated and anonymous, in some special circumstances it may be necessary to make use of designated donations. This should happen only for clear medical indications. Designated donors should be screened and tested like volunteer allogeneic donors.

Designated donations are those intended for named patients based on medical indications. Circumstances where designated donations may be indicated include:

- Patients with rare blood types, where no compatible anonymous donations are available;
- Where donor-specific transfusions are indicated for immune modulation or immunotherapy; for instance, in the preparation procedure for kidney transplants or for lymphocyte trans- fusions aimed at a graft-versus-leukaemia effect;
- In certain cases of allo-immune neonatal thrombocytopaenia; for instance, if HPA-typed platelets are not available and intra- venous immunoglobulin therapy is not sufficient.

These donations may involve family members, in which case the responsible physician should weigh up the risks and benefits for the patient.

The practice of transfusing parental blood to infants is not without risk. Mothers may have antibodies to antigens that are present on the infant's red blood cells, platelets or white blood cells. Therefore, maternal plasma should not be transfused. Fathers should not serve as cell donors to neonates because maternal antibodies to antigens inherited from the father may have been transmitted through the placenta to the foetus. In addition, due to partial histocompatibility, transfusions of cells from parental or family donors carry an increased risk of transfusion-associated graft versus host disease, even in the immuno- competent recipient, and so such components should be irradiated. In the case of platelets, pathogen inactivation technologies for components may be used as an alternative to irradiation.

2.4.4. Directed donations

Directed donations are those intended for named patients, where the request for the donation has been made by patients, relatives or friends. The public often believes that directed donations are safer than anonymous, voluntary, non-remunerated donations. However, this is not the case, even if directed donations are screened and tested in the same manner as voluntary non-remunerated donations.

Directed donations are not considered good practice and should be discouraged.

2.5. Post-donation information

2.5.0. Overview

Blood establishments often receive information from blood donors after donation that should have resulted in their deferral and may attempt to retrieve distributed blood components that did not meet all quality standards and regulations.

Post-donation information (PDI) is largely a reflection of the inherent limitations of the current donor screening process, which uses broad, precautionary questions to guard against theoretical or extremely remote risks. Consequently, PDI is an important measure of the accuracy of donor suitability assessment and compliance with Good Practices.

2.5.1. Donor instruction

Standard

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

PDI includes information provided by the donor or other source and received by telephone or other means of communication following a donation. Blood establishments should evaluate PDI that is revealed by a third party without the donor's knowledge, weighing the reliability of the source of the information against the direct responses from the donor.

2.5.2. Control procedures

Systems should be in place to define the actions to be taken if a donor informs the blood establishment that he/she previously donated blood but should not have done so in the light of donor selection criteria.

Blood establishments should have control procedures that provide for the receipt and documentation of PDI reports that identify the source of the information (e.g., from a donor, competent healthcare professional).

Blood establishments should have control procedures that provide for the prompt medical evaluation by a qualified physician, following established criteria, to ensure that potential risks are consistently assessed and investigated for all donations potentially affected.

Blood establishments should have control procedures that provide for appropriate consignee notification and determination regarding the disposition of all affected products (in-date and expired) including those intended for transfusion and those intended for further manufacturing use where the quality of the final manufactured product may be compromised.

Blood establishments should have control procedures that provide for assessment of the donor's suitability to serve as a donor in the future.

Table 2-3. **Intervals between donations**

Previous donation / Current donation	whole blood or 1 unit of RBC apheresis or 1 unit RBC and plasma apheresis or 1 unit RBC and 1 unit platelets apheresis or 1 unit RBC and platelets and plasma apheresis or failed return of red cells during apheresis	plasmapheresis	plateletpheresis	plateletpheresis combined with plasmapheresis	2 units of RBC apheresis	granulocytapheresis
whole blood	8 weeks	48 hours	48 hours	48 hours	24 weeks woman, 16 weeks man	8 weeks
plasmapheresis	4 weeks	2 weeks (IgG 6.0-8.0 g/L) 1 week (IgG >8.0 g/L)	48 hours	2 weeks (IgG 6.0-8.0 g/L) 1 week (IgG >8.0 g/L)	4 weeks	4 weeks
plateletpheresis	4 weeks	48 hours	2 weeks	2 weeks	4 weeks	4 weeks
plateletpheresis combined with plasmapheresis	4 weeks	2 weeks (IgG 6.0-8.0 g/L) 1 week (IgG >8.0 g/L)	2 weeks	2 weeks	4 weeks	4 weeks
1 unit of RBC apheresis or failed return of red cells during apheresis	8 weeks	48 hours	48 hours	48 hours	24 weeks woman, 16 weeks man	8 weeks
1 unit RBC and 1 unit platelets apheresis or 1 unit RBC and platelets and plasma apheresis	8 weeks	48 hours	2 weeks	2 weeks	24 weeks woman, 16 weeks man	8 weeks
1 unit RBC and plasma apheresis	8 weeks	1 week	48 hours	1 week	24 weeks woman, 16 weeks man	8 weeks
2 units of RBC apheresis	12 weeks	48 hours	48 hours	48 hours	24 weeks woman, 16 weeks man	12 weeks
granulocytapheresis	4 weeks	48 hours	2 weeks	2 weeks	24 weeks woman, 16 weeks man	8 weeks*

*The interval should be individually set by a responsible physician, depend on the health status of the donor and the details of the previous leukapheresis (particularly the stimulation of the donor).

Chapter 3

Collection of blood and blood components

3.0. Overview

The quality system used by blood establishments for the collection of blood and blood components should be designed to assure their quality and safety, as well as to ensure donor and staff safety. All processes should be defined and systematically reviewed for their effectiveness. All critical steps and critical changes to the collection process should be validated to ensure that the process is fit for purpose and outcomes are reproducible.

Records should be kept for each activity associated with the donation. The premises for collection should be adequate, with suitable equipment and services.

There should be processes in place to ensure that the sample tubes and blood bag are from the same donor, uniquely labelled and linked to the donor's record to allow for full blood product traceability. Donor identification and assessment of eligibility to donate should take place before each donation. The donor should be re-identified immediately prior to venepuncture.

The skin surface is not sterile; therefore, appropriate preparation of the venepuncture site is important to reduce the risk of bacterial contamination. Collection systems should be sterile and used in accordance with the manufacturer's instructions. A check should be made before use to ensure that the collection system is not damaged or contaminated and that it is appropriate for the intended collection.

A system for donor vigilance and the management of adverse reactions related to blood donation should be in place.

3.1. Documentation

Documentation is an essential part of the quality system and is key to operating in compliance with good practice requirements. As far as possible, the records of blood donation sessions should allow blood establishment staff to identify each important phase associated with the donation.

The main objective of the system of documentation utilised is to establish, control, monitor and record all activities that directly or indirectly impact on all aspects of the quality and safety of blood and blood components as well as any derived medicinal products. Donor collection documentation may exist in various forms: paper-based, electronic or photographic.

3.1.1. General requirements

Standards

3.1.1.1. Documents setting out specifications, procedures and records covering each activity undertaken by a blood establishment must be in place and kept up to date (Directive 2005/62/EC Annex 5.1).

3.1.1.2. Records should be kept for each activity associated with the selection of the donor, including the decision to accept the donor by taking into consideration the medical history, history of deferral, donor interview and results of the physical examination, deferral of a donor and the reason for deferral.

3.1.1.3. A system should be in place to ensure that the donor is prevented from making future donations during a permanent or temporary deferral period.

3.1.1.4. Records should be maintained of the collection of the donation, including the blood component(s) collected, the date, donation number, identity and medical history of the donor. In the case of unsuccessful donations, the reasons for the failure of the donation; details of any adverse events and reactions involving a donor at any stage of the procedure should also be maintained. In the case of apheresis, the volumes of blood collected, blood processed, and replacement solution and anticoagulant used should be recorded.

3.2. Premises for blood and blood component collection

Collection of blood and blood components should take place in premises that assure the health and

safety of donors and staff, support privacy during the donor assessment process, provide for appropriate clinical oversight of donors, prevent errors during the collection procedure and maintain quality and safety of the blood and blood components.

3.2.1. General requirements

Standards

3.2.1.1. Premises including mobile sites must be located, constructed, adapted and maintained to suit the activities to be carried out. They must enable work to proceed in a logical sequence so as to minimise the risk of errors and must allow for effective cleaning and maintenance in order to minimise the risk of contamination (Directive 2005/62/EC Annex 3.1).

3.2.1.2. Blood collection should be carried out in an area intended for the safe withdrawal of blood from donors and which is equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation.

3.2.1.3. This area must be organised in such a way as to ensure the safety of both donors and personnel as well as to avoid errors in the collection procedure (Directive 2005/62/EC Annex 3.3).

3.2.1.4. Premises, including those of mobile sessions, should satisfy general requirements for the health and safety of the staff and donors concerned with due regard to relevant legislation or regulations.

3.2.1.5. Suitable facilities should be provided to allow a private interview with each donor, assuring privacy and confidentiality.

3.2.1.6. Before premises are accepted for mobile donor sessions, their suit- ability should be assessed against the following criteria: sufficient size to allow proper operation and ensure donor privacy; safety for staff and donors; presence of ventilation, electrical supply, lighting, ancillary facilities, reliable communication, blood storage and access to transport of blood.

3.3. Procedures and equipment used during the collection of blood and blood components

All equipment should be fit for purpose and designed to maintain the quality and safety of the blood and blood components.

3.3.1. General requirements

Standards

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

3.3.1.2. 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).

3.3.1.3. 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 blood bag must be traceable for each blood component (Directive 2005/62/EC Annex 6.2.2).

3.3.1.4. Sterile collection systems should be used in accordance with the manufacturer's instructions.

3.3.1.5. Blood collection procedures must minimise the risk of microbial contamination (Directive 2005/62/EC Annex 6.2.3).

3.3.1.6. Procedures should be designed to minimise the risk of deterioration of the samples and to prevent potential misidentification of donations and samples.

3.3.1.7. Defects in blood bags should be monitored and reported to the sup- plier, and to national authorities where required.

3.4. Pre-donation checks

Pre-donation checks are performed to ensure that the collection consumables and equipment are fit for purpose. There is a risk that blood containers may become contaminated with micro-organisms prior to use, particularly if there is a defect such as a pinhole. Abnormal moisture or discolouration on the surface of the bag or label after unpacking suggests leakage through a defect. Defects may be hidden behind the label pasted on the container.

Verification of donor identity is essential in all phases of the collection process to avoid collection errors.

3.4.1. General requirements

Standards

3.4.1.1. A visual check should be made before use to ensure that the collection system employed has not been damaged or contaminated, and that it is appropriate for the intended collection procedure.

3.4.1.2. The blood container should be inspected before use for defects and must be inspected for the prescribed content and appearance of the anticoagulant solution. If any package is found to be abnormally damp, then the contents should be rejected.

3.4.1.3. The donor should be re-identified immediately prior to venepuncture.

3.5. Labelling

There must be processes in place to ensure that blood in the sample tubes and blood bag is from the same donor, uniquely labelled and linked to the donor's record to allow for full blood product traceability, whilst ensuring that the donor's identity is kept confidential. The unique identity number provides the link between the donor, the donation and the sample tubes.

3.5.1. General requirements

Standards

3.5.1.1. 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).

3.5.1.2. Each donor bed should have individual facilities for the handling of samples during donation and labelling and the process should minimise the possibility of labelling errors.

3.5.1.3. At the time of blood donation, the blood container and those of the samples collected for testing should be labelled to uniquely identify the blood donation. The labelling system should comply with relevant national legislation and international agreements.

3.5.1.4. The blood donation should be identified by a unique identity number which is both eye- and machine-readable. The labelling system should allow full traceability to all relevant data registered by the blood establishment about the donor and the blood donation.

3.5.1.5. A careful check should be made of the identity indicator of the donor against the labels issued for that donation.

3.5.1.6. The manufacturer's label on the blood containers (plastic blood bags and bag systems) should contain the following eye-readable information: the manufacturer's name and address; the name of the blood bag and/or the name of the blood bag plastic material; the name, composition and volume of anticoagulant or additive solution (if any); the product catalogue number and the lot number.

3.6. Venepuncture, bleeding and mixing

Preparation of the venepuncture site

The skin surface is not sterile, therefore appropriate preparation of the venepuncture site is important to reduce the risk of microbial contamination. The presence of skin lesions may reduce the effectiveness of skin disinfection. An antiseptic solution needs to be completely dry to optimise its effectiveness. The time taken for this will vary with the product used. The manufacturer's instructions should be followed.

The cleaning of the skin prior to venepuncture with the appropriate disinfectant is important to prevent skin

commensals from entering into the collection bag and bag systems. The effectiveness of the disinfection procedure should be monitored, and corrective action taken where indicated.

3.6.1. General requirements

Standards

3.6.1.1. The skin at the venepuncture site should be free from lesions, including eczema.

3.6.1.2. The venepuncture site should be prepared using a defined and validated disinfection procedure. The antiseptic solution should be allowed to dry completely before venepuncture. The prepared area should not be touched with fingers after disinfection and before the needle has been inserted.

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

3.6.2. Venepuncture and mixing of donation during collection

The collected blood should be regularly mixed with the anticoagulant during the donation to prevent clot formation. Interruption of blood flow during donation is to be avoided as this may lead to clotting of blood in the cannula and/or plastic tubing. The volume of blood collected should be in accordance with the specification set by the bag manufacturer to avoid dilution and ensure adequate anticoagulation. Maximum collection times should not be exceeded as this might result in clot formation, platelet activation and loss of coagulation factors.

Standards

3.6.2.1. Where the needle is not inserted into the vein at the first attempt, a second venepuncture with a new needle in the other arm is acceptable with the consent of the donor, provided that microbial sterility of the system is not compromised.

3.6.2.2. Laboratory samples must be taken, from the bleed line or the sample pouch, at the time of each donation, and be appropriately stored prior to testing (Directive 2005/62/EC Annex 6.2.4). Laboratory samples from plasmapheresis donations destined for plasma for fractionation can be taken from the plasma collection container, provided this is in accordance with the manufacturer's instructions for the testing kit assay in use.

3.6.2.3. Where an anticoagulant solution is used in the collection of whole blood, the collection bag should be mixed gently immediately after starting collection and at regular intervals during the entire collection period. The flow of blood should be sufficient and uninterrupted.

3.6.2.4. The maximum collection time for acceptance of the donation for component processing should be specified and controlled. Donations that exceed the maximum time period should be recorded and discarded.

3.6.2.5. If the duration of the bleeding for a whole blood collection is longer than 15 minutes, the blood should not be used for the preparation of platelets (Evidence Level C)

3.6.2.6. If the duration of the bleeding for a whole blood collection is longer than 15 minutes, the plasma should not be used for direct transfusion or the preparation of coagulation factors (Evidence Level C)

3.6.2.7. If manual mixing is used, the blood bag should be inverted every 30-45 seconds. When an automated mixing system is used, an appropriately qualified system is required.

3.6.2.8. At completion of the donation, the donation number should be checked on all records, blood bags and laboratory samples. Donation number labels of a given donation that have not been used should be destroyed via a controlled procedure. Procedures to prevent mislabelling should be in place.

3.6.2.9. Each activity associated with the donation should be recorded. This also applies to any unsuccessful donations, the rejection of a donor, adverse reactions and adverse events.

3.7. Handling of filled blood bags and samples

The quality of the blood post-donation is maintained by appropriate sealing of the tubing, checking for defects and transporting at the required temperature.

Procedures should be designed to minimise the risk of bacterial contamination of the collected blood or

deterioration of the sample.

Samples should be stored appropriately to avoid contamination and deterioration prior to testing to prevent erroneous results.

3.7.1. General requirements

Standards

3.7.1.1. 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 further processing requirements (Directive 2005/62/EC Annex 6.2.6).

3.7.1.2. 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).

3.7.1.3. The blood container should be checked after donation for any defect. During separation from the donor, a fail-safe method of sealing the bleed line should be in place.

3.7.1.4. The blood bag and corresponding samples should not be removed from the donor's bedside until labelling has been checked and is verified as correct.

3.7.1.5. After collection, blood bags should be placed promptly into controlled temperature storage and transported to the processing site under temperature conditions appropriate for the component that is to be prepared. Validation data should be available to demonstrate that the storage parameters after collection and the method of transport used maintains the blood within the specified temperature range throughout the period of transportation.

Immediately after sealing the distal end of the collection tubing, the contents of the bag line should be completely discharged into the bag.

If integral blood bag collection tubing is used to prepare segments for testing, it should be sealed off at the distal end, filled with anti- coagulated blood as soon as possible after blood collection and sealed at the proximal end.

3.8. Special requirements for apheresis

Processes should be in place to ensure correct connection of all components of the apheresis harness and especially fluids (anticoagulant and saline) as deaths have been reported from accidental administration of large volumes of anticoagulant. Automated apheresis is now widely available and provides superior safety features compared with manual apheresis which should no longer be performed. No pre-medication is required for apheresis with the exception of granulocyte donors. Caution is recommended regarding pre-treatment of donors with corticosteroids and granulocyte-colony stimulating factor.

3.8.1. General requirements

Standards

3.8.1.1. Separation and collection of blood components by cell separators requires premises of suitable size, regular servicing and maintenance of machines and adequately trained personnel for operating such machines.

3.8.1.2. The donor should be observed closely during the procedure. A qualified healthcare professional familiar with all aspects of apheresis should be available to provide assistance and emergency medical care procedures in case of an adverse reaction.

3.8.1.3. Collection of adequate granulocyte yields by apheresis requires pre-medication of the donor. The potential risk to the donor should be evaluated against the anticipated benefit to the intended recipient.

3.9. Repository of archive samples

Archived donor samples are useful for lookback investigations. These samples can be tested to ascertain if the index donation had been collected during a test 'window-period' or whether it was infected with a pathogen for which the blood service does not routinely screen (e.g. chikungunya, hepatitis E virus).

3.9.1. General requirements

Standard

3.9.1.1. If archive samples from donations are kept, then procedures should be in place prescribing their use and final disposal.

3.10. Management of adverse reactions in donors

The management of adverse reactions related to blood donation should be described in standard operating procedures. Prospective donors should be informed of the possible adverse reactions of blood donation and how they can be prevented. Prompt attention should be given to all donors experiencing adverse reactions. The donor should be referred as soon as possible to the responsible healthcare worker/physician in charge. The source of the adverse reaction should be identified, and corrective and preventive measures considered. Severe adverse reactions in donors should be reported to the nationally established haemovigilance system.

3.10.1. General requirements

Standard

3.10.1.1. All serious adverse reactions, including their management, should be documented in the record of the donor.

3.10.2. Prevention and treatment of adverse reactions in donors

Standards

3.10.2.1. A physician in charge should be identified for the overall medical supervision of blood collection and donor care.

3.10.2.2. Prospective donors should be informed of the possible adverse reactions of blood donation and how they can be prevented, and of the method for informing the blood establishment of delayed reactions.

3.10.2.3. The treatment of adverse reactions related to blood donation should be described in standard operating procedures.

3.10.2.4. Training of the personnel collecting blood should include preventing and recognising the signs of adverse reactions and their rapid treatment.

3.10.2.5. All serious adverse reactions and events should be promptly reported to a designated healthcare professional.

In each collection facility, a specific space should be available for dealing with donors who have an adverse reaction.

The donor should be observed until fully recovered and, in the event of a serious adverse reaction, the blood establishment should remain in contact with the donor until the complication has disappeared or the donor is in a stable condition.

3.10.3. Information for a donor with adverse reactions

Standards

3.10.3.1. When an adverse reaction occurs, the donor should be informed about the reaction, its treatment and the expected outcome.

3.10.3.2. The donor should be provided with advice as to whom to contact in the event that subsequent concerns arise.

A donor who has experienced a vasovagal reaction should be informed about the risk of delayed fainting.

Information on donor adverse reactions is provided in Chapter 10 of this *Guide*.

Chapter 4

Processing, storage and distribution of blood and blood components

4.0. Overview

Components are those therapeutic constituents of blood that can be prepared by centrifugation, separation filtration and freezing. Whole blood may be indicated in limited clinical settings. In general, patients should receive the component required to correct their specific deficiency.

Storage conditions and shelf life are specific for each component type Red cells maintain optimal functional capability when they are refrigerated. The quality of plasma constituents is best maintained in the frozen state while platelet viability is optimal at room temperature, although storage is possible both at room temperature (between + 20 °C and + 24 °C with continuous agitation) and refrigerated. The use of multiple plastic bag systems facilitates the preparation of high-quality components.

4.1. Processing

4.1.1. General considerations

Blood components are prepared either from whole blood donations using post-donation processing or by apheresis technology.

Labile blood components require optimal storage conditions and defined processing times to ensure quality. Due to the potential deterioration of activity and functionality of labile blood components, the conditions of storage and time before and during processing are vital to preparation of high-quality blood components. Delays in preparation or unsuitable storage conditions may affect the quality of the final components adversely.

Standards

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

4.1.1.2. The processing of blood and 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).

4.1.1.3. The premises used for the processing of blood and blood components should be kept in a clean and hygienic condition. The microbial contamination load on critical equipment surfaces and in the environment of the processing areas should be minimised using validated cleaning and / or monitoring procedures.

4.1.1.4. Procedures should detail the specifications for any materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary packaging material (bags) and equipment.

4.1.1.5. Procedures should be developed and validated for all processing activities. These should include time and temperature limits for the processing of blood components.

4.1.2. Choice of bag system

Disposables for blood and blood component collection and processing are medical devices that should comply with the requirements of the relevant regulations (such as EU Directives, European Pharmacopoeia and ISO standards).

Polyvinylchloride (PVC) with an adequate plasticiser is satisfactory for red blood cell storage.

Platelets, stored between + 20 °C and + 24 °C, require a plastic with increased oxygen permeability, such as special polyolefins or PVC with butyryl trihexyl citrate (BTHC) plasticiser.

Leaching of plasticisers and other substances into blood and blood components is known to occur from blood bag systems, labels and as a result of sterilisation of the system. Acceptable substances and limits are regulated in medical device legislation and CE marking.

When the use of a new plastic is considered, an adequate study of component preparation and/or storage should be conducted.

Assessment of the following parameters may be considered:

- Red cells: glucose, pH, haematocrit, haemolysis, ATP, lactate, extracellular potassium ions, and 2,3 DPG;
- Platelets: pH, pO2, pCO2, bicarbonate ions, glucose, lactate, ATP, P-selectin, LDH release, beta thromboglobulin release, response to hypotonic shock and swirling phenomenon, morphology score and extent of shape change;
- Plasma: factor VIII and signs of coagulation activation (e.g. thrombin anti-thrombin complexes).

The suitability of new plastics may also involve the evaluation of post-transfusion *in vivo* recovery and survival of red cells after 24 hours and the assessment of platelet recovery, survival and corrected count increments.

413 Red cell and platelet preservation

The preservation solutions used in blood collection have been developed to prevent coagulation and to permit storage of red cells. All such solutions contain sodium citrate, citric acid and glucose. Some may also contain adenine and phosphate.

A mix of citric acid and sodium citrate is used to adjust the pH of the anticoagulant to below pH 6 to prevent caramelisation of glucose during heat sterilisation of the blood bag system. Citrate binds to calcium and prevents clotting of the blood.

During refrigerated storage red cells undergo numerous physicochemical changes, which affect the quality, function and in vivo survival of the transfused red cells. A red cell additive solution supports maintenance of red cell viability, even if more than 90 per cent of the plasma is removed. Glucose is consumed by red cells during storage, hence the availability of glucose helps to maintain red cell viability during storage and following transfusion. The pH decreases during storage with a consequent reduction in the rate of glycolysis. In addition, the content of adenosine nucleotides (ATP, ADP, AMP) decreases during storage. The addition of adenine compensates for this decrease.

Phosphate may be used to enhance glycolysis. Other substances (e.g. mannitol, citrate) may be used to prevent in vitro haemolysis. Sodium chloride or disodium phosphate may be used to give the additive solution a suitable osmotic strength and/or buffering capacity.

When red cell concentrates are prepared without additive solution, the average haematocrit should be less than 0.70 in order to maintain red cell viability and ensure that the viscosity is sufficiently low to permit transfusion of the concentrate without further dilution before administration.

Microaggregates of platelets, leukocytes and fibrin are present in significant amounts from 3 - 4 days of storage of whole blood and red cells. Removal of platelets and/or leucocytes during component preparation reduces micro-aggregate formation and use of standard transfusion filters are now considered adequate.

Platelets are stored in either 100% plasma or a proportion of plasma and a platelet additive solution (PAS). PAS contains ingredients that maintain platelet quality and improve platelet metabolism. Most current PAS require storage with around 30-40% residual plasma to ensure sufficient glucose availability at the end of shelf life. Platelets stored in PAS exhibit improved platelet quality and metabolism, when compared to platelets stored in plasma. The lower plasma content and less cytokine accumulation, leads to a reduced risk of allergic transfusion reactions.

Platelet quality is impaired when the platelet pH falls below 6.4 and if there is inadequate glucose available. PAS helps to maintain platelet quality by preventing the lowering of the pH. The key ingredient of PAS is acetate which, through the process of oxidative phosphorylation, reduces the amount of glucose that is oxidised into lactic acid. Decreased lactic acid production prevents

lowering of the platelet pH. In addition, the production of bicarbonate following acetate oxidation and the addition of buffering salts such as phosphate, potassium and magnesium further prevents decrease in pH. However glucose depletion may still occur and may compromise quality, even when the pH is maintained above 6.4. Therefore, pH is not a good indicator of quality for platelets stored in PAS. (Evidence level, C)

4.1.4 Centrifugation of whole blood-derived blood components

The mean density of whole blood is 1.055 g/mL. The mean density of principle blood constituents is shown in Table 4-1. The sedimentation behaviour of blood cells is determined primarily by their size as well as the difference of their density from that of the surrounding fluid (see Table 4-1 below). Other factors are the viscosity of the medium and flexibility of the cells (which is temperature- dependent). The optimal temperature for centrifugation with respect to these factors is between + 20 °C and + 24 °C

Table 4-1. **Volume and density of principal blood constituents**

	Mean density (g/mL)	Mean corpuscle volume (fL)
Plasma	1.026	N/A
Platelets	1.058	9
Monocytes	1.062	470
Lymphocytes	1.070	230
Neutrophils	1.082	450
Red cells	1.100	87
Additive Solution	1.003	N/A

The conditions of centrifugation, such as g-force, acceleration, time, deceleration, etc., determine the composition of the desired component. For example, if platelet-rich plasma is desired, centrifugation should stop prior to the phase where platelet sedimentation commences. A low centrifugation speed allows for some variation in centrifugation time. If cell-free plasma is required, fast centrifugation for an adequate time allows separation into cell-poor plasma and densely packed cells. Slow braking is recommended to avoid cell contamination in plasma. It is important that the optimal conditions for good separation be carefully standardised for each centrifuge. A number of options exist for the selection of a procedure for centrifugation for the preparation of components from whole blood.

4.15. Leucocyte depletion

Leucocytes play no therapeutic role in blood components (except granulocyte preparations) and may cause adverse transfusion reactions. Leucocyte depletion involves the removal of leucocytes from blood components using filtration or apheresis technology. This is usually undertaken prior to storage of the component (pre-storage leucodepletion) using filters, which are incorporated in the blood bag system. This is considered superior to alternative approaches such as post-storage or bedside filtration.

The blood establishment should determine the most appropriate blood bag and filter system for the desired component.

To enable a comparison of the filters that can be used for leucocyte depletion and to facilitate selection, Manufacturers should provide data to the blood establishment on the performance of leucocyte depletion filters within each system, under defined conditions, including any effect on storage parameters. Manufacturers should also provide performance data to the blood establishment on variations between different filter types or modifications and between batches Performance data should be updated when the filter or system is modified and for each new batch.

Inadequate leucocyte depletion, slow filtration or filter blockage may occur with donations from donors with red cell abnormalities (e.g. sickle-cell traits). Follow-up of the donor to exclude a red cell abnormality may be considered if repeated filter blockage occurs and more detailed quality control procedures are necessary (e.g. leucocyte counting of every donation).

Standards

4.1.5.1. Processes used for leucocyte depletion should be validated. The validation should be carried out by the blood establishment using the manufacturer's instructions and against the requirements for leucocyte depletion and other quality aspects of the components (including those for plasma for fractionation).

4.1.5.2. For quality control, an appropriate validated method should be used for counting leucocytes.

4.1.6. Freezing and thawing of plasma for direct transfusion

Freezing is a critical step in the preservation of some plasma proteins, including coagulation factors (in particular factor VIII). To achieve the highest yield of factor VIII, the rate of cooling should be as rapid as possible. Optimally the core temperature of the plasma unit should be reduced to − 25 °C or lower within 60 minutes of commencing the freezing step. This normally requires the use of a blast-freezer.

Frozen units should be handled with care since the bags may be brittle. The integrity of the blood container should be verified before and after thawing to exclude any defects and leakages. Leaking containers should be discarded. The plasma component should be thawed immediately after removal from storage, using a validated procedure, in an environment that does not raise the plasma temperature above + 37 °C. After thawing of frozen plasma, the content should be inspected to ensure that no insoluble cryoprecipitate is visible. The component should not be used if insoluble material is present. To preserve labile factors, plasma should be used as soon as possible after thawing. Post-thaw shelf life may be extended for a validated period to facilitate urgent transfusion for some indications.

Thawed plasma should not be refrozen unless thawing is required for further manufacture, such as for pathogen inactivation and production of cryoprecipitate, and the thaw-freeze steps are performed in accordance with the manufacturing requirements.

4.1.7. Cryoprecipitation

The isolation of some plasma proteins, most importantly factor VIII, von Willebrand factor, fibronectin and fibrinogen, can be achieved by making use of their reduced solubility at low temperatures. In practice, this is done by freezing the plasma component, and then both thawing and centrifuging at low temperature, and then freezing the plasma component again.

Details regarding the freezing, thawing and centrifugation conditions required for cryoprecipitate production are given in Chapter 5, Blood component monographs.

4.1.8. Open and closed systems and sterile connection devices

The use of closed systems is strongly recommended for all steps in component processing (G.P.G 6.6.3) In order to maintain a closed system throughout processing, a sterile multiple bag configuration (either ready-made or sterile-docked) should be used. Open systems may exceptionally be necessary due to local constraints and should be undertaken in an environment specifically designed to minimise the risk of bacterial contamination (G.P.G 6.6.3)

Red cells prepared in open systems and stored at +4 °C should be transfused within 24 hours of processing. Platelets prepared in open systems should be transfused within 6 hours of processing.

It is recommended that any new developments in component preparation involving an open system should be subjected to intensive testing during the developmental phase to ensure maintenance of sterility.

Standards

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

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

4.1.9. Component labelling and information

Information about the composition, clinical indications, storage and transfusion requirements of blood components should be made available to clinicians through written or electronic communications. This includes the proviso that the blood component should not be transfused if there is any visual abnormality, e.g. haemolysis in red cell components or loss of swirling in platelet components, and that all blood components should be administered through an approved transfusion set (CE-marked within the EU).

The blood component label should contain the information (in eye-readable format) necessary for safe transfusion. This includes a unique identity number (preferably consisting of a code for the blood-collection organisation, the year of donation and a serial number), ABO and RhD blood groups, name of the blood component, essential information about the properties and handling of the blood component and the expiry date (see also labelling requirements in Chapter 5, Blood component monographs).

Standards

4.1.9.1. At all stages, all containers must be labelled with relevant information of 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).

4.1.9.2. 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).

4.1.9.3. For autologous blood and blood components, the label also must 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).

4.1.9.4. The type of label to be used, as well as the labelling methodology, should be established in written procedures. Critical information should be provided in machine-readable format to eliminate transcription errors.

4.1.9.5. The blood establishment responsible for the preparation of blood components should provide clinical users of blood components with information on their use, composition and any special conditions that do not appear on the component label.

4.1.10. Release of blood components

Standards

4.1.10.1. There must be a safe and secure system to prevent each single blood and blood component from being released until 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 is released, all current declaration forms, relevant medical records and test results meet all acceptance criteria (Directive 2005/62/EC Annex 6.6.1).

4.1.10.2. 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 clearly distinguish released from non-released units of blood and blood components (Directive 2005/62/EC Annex 6.5.1 and 6.6.2).

4.1.10.3. Each blood establishment should be able to demonstrate that a blood component has been approved for release by an authorised person, preferably assisted by validated information technology systems. The specifications for release of blood and blood components should be defined, validated and documented.

4.1.10.4. Where release is subject to computer-derived information, the following requirements should be met:

- The computer system should be validated to be fully secure against the possibility of blood and blood components being released that do not fulfil all test or donor selection criteria;

- The manual entry of critical data, such as laboratory test results, should require independent verification by a second authorised person.
- The computer system should block the release of all blood or blood components considered not acceptable for release. There should also be a means to block the release of any future donations from the donor.

4.1.10.5. In the absence of a computerised system for component status control, or in the event of computer system failure, the following requirements should be met:

- The label of a blood component should identify the component status and should clearly distinguish a released from a non-released (quarantined) component;
- Records should demonstrate that before a component is released, all current donor declaration forms, relevant medical records and test results have been verified by an authorised person;
- Before final component release, if blood or blood component(s) have been prepared from a donor who has donated on previous occasions, a comparison with previous records should be made to ensure that current records accurately reflect the donor history;
- There should be a system of administrative and physical quarantine for blood and blood components to ensure that they cannot be released until all mandatory requirements have been satisfied.

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

4.1.10.7. In the event that the final component fails release due to a confirmed positive infection test result for hepatitis B virus, hepatitis C virus or HIV 1/2 (Directive 2002/98/EC Annex IV), 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 and blocked for release and/or distribution. There must be an immediate update of the donor record (Directive 2005/62/EC Annex 6.6.3, 6.3.2 and 6.3.3).

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

4.1.11. Component recall and traceability (see also Chapter 10)

Standards

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

4.1.11.2. There should be a documented system, available in each blood establishment, whereby adverse effects caused by the administration of any component, or the identification of a component quality problem, can enable the recall, if appropriate, of all unused components derived from that donation, or all donations which are a constituent of a component pool, or donations/components implicated in a medical device recall.

4.1.11.3. A system should be in place that ensures that any recalled components, including those transfused or discarded, can be linked to the original donation and donor from which it was derived.

Any recall of a component due to a process failure should lead to a thorough investigation, with a view to preventing a recurrence.

4.2. Storage and distribution

4.2.1. General requirements

Storage conditions for blood components are designed to preserve optimal viability and functionality during the entire storage period. The risk of bacterial contamination is reduced if closed separation and storage systems are used.

There should be a system in place to maintain and control the storage of blood components throughout their shelf-life, including any transportation that may be required. Temperature should be continuously monitored. Warning systems should be used where applicable. A system should be in place to ensure

hygienic conditions are maintained in storage areas.

Standards

4.2.1.1. 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 comply with Directive 2003/94/EC (Directive 2005/62/EC Annex 7.1).

4.2.1.2. 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).

4.2.1.3. Storage and distribution routines should take place in a safe and controlled way, in order to ensure component quality during the entire storage period and to avoid any risk of identification error and mix-up of blood components.

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

4.2.1.5. Storage conditions should be controlled, monitored and checked. Appropriate alarms should be present and regularly checked, and these checks should be recorded. Appropriate actions on alarms should be defined.

4.2.1.6. Intermediate storage and transport should be carried out under defined conditions to ensure that the specified requirements are met.

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

4.2.1.8. Prior to distribution, blood components should be visually inspected. There should be a record identifying the person distributing the components and the institution receiving them.

4.2.1.9. 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).

4.2.1.10. Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for storage of rejected components and materials.

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

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

4.2.1.13. Return of blood and blood components into inventory for subsequent reissue can only be accepted 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).

4.2.1.14. Blood components should 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 there is documented evidence for each returned blood component that the agreed storage conditions have been met. Before subsequent distribution, the records should identify that the blood component has been inspected before re-issue.

4.2.1.15. Records should be kept of the distribution of blood components between blood establishments, blood establishments and hospital blood banks and between hospital blood banks. These records should show the date of supply, unique component identifier and name of the blood component, the quantity received or supplied, name and address of the supplier or consignee.

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

422. Equipment

The following points should be considered before purchase of any storage device:

- Identification of user requirements, specifications and quality criteria;
- Storage devices should have surplus capacity;
- The space should be easy to inspect;
- The operation should be reliable and temperature distribution should be uniform within the unit;
- The equipment should have temperature recording and alarm devices;
- The equipment should be easy to clean and should withstand strong detergents;
- The equipment should conform to local safety requirements.

The space for each of the component types should be clearly indicated. Autologous blood and blood components should be stored separately.

The temperature within the storage device should be continuously monitored and recorded. The number and position of temperature sensors should be determined by temperature mapping. These should be placed in the part of the space that represent the worst conditions.

The alarm system should have both acoustic and optical signals and should be regularly tested.

Equipment should be connected to a reserve power unit, as well as to the main supply.

423. Storage of red cell components

The maximum duration of storage (expiry date) should be noted on each container. This duration may vary with the type of preparation (concentration of cells, formula of anticoagulant, use of additive solution) and should ensure a mean 24-hour post-transfusion survival of no less than 75 per cent of transfused red cells.

Red cells are stored in a fluid state at a controlled temperature between + 2 °C and + 6 °C.

Frozen red cells should be stored at < − 60 °C in a validated suspension medium in order to produce satisfactory post-transfusion survival figures.

424. Storage of platelet components

The maximum duration of storage (expiry date) should be noted on each container

Platelets should be stored under conditions that ensure that their viability and haemostatic activities are optimally preserved.

Plastic bags intended for platelet storage should be sufficiently permeable to gases to guarantee oxygen availability to platelets and diffusion of carbon dioxide. The amount of oxygen required is dependent on the number of platelets and their concentration in the component. Lack of oxygen increases anaerobic glycolysis and lactic acid production and results in a fall in pH and glucose depletion. The quality of platelets is preserved if the pH remains above 6.4 throughout the storage period.

Agitation of platelets during storage should be sufficient to guarantee oxygen availability but as gentle as possible to prevent induction of activation and storage lesions. Platelets are normally stored between + 20 °C and + 24 °C.

A closed device that permits temperature control is recommended. If such a device is unavailable, the storage location chosen should be capable of maintaining the required temperature.

Platelets should be stored in agitators that:

- Enable satisfactory mixing in the bag, as well as gas exchange through the wall of the bag;
- Avoid folding of the bag;
- Have a set speed which avoids foaming.

425. Storage of frozen plasma components

The maximum duration of storage (expiry date) should be noted on each container

Freezers with automatic defrosting should be avoided, unless it can be guaranteed that the low temperature

is maintained during defrosting.

Information on storage conditions for fresh frozen plasma and cryoprecipitate and for cryoprecipitate-depleted plasma are provided in Chapter 5 of this *Guide*.

4.2.6. Storage of granulocyte preparations

Typically, granulocyte suspensions are prepared for a specific patient and administered immediately. If storage is unavoidable then this should be for the shortest possible period at between + 20 °C and + 24 °C and for no longer than 24 hours and without agitation.

4.2.7. Transportation of Blood Components – General Requirements

Blood components should be transported by a system that has been validated to maintain the integrity of the component over the pro- posed maximum time and extremes of ambient temperature of transport.

The temperature on receipt can be monitored as in the following example:

- Take two bags from the container;
- Place a thermometer between the bags and fix them together with rubber bands;
- Quickly place them back into the container and close the lid;
- Read the temperature after 5 minutes.

Alternatively an electronic sensing device may be used to take immediate measurements from the surface of a pack.

On receipt, if not intended for immediate transfusion, the component should be transferred to storage under the recommended conditions.

Standards

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

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

4.2.8. Transport of red cell components

Red cell components should be kept between + 2 °C and + 6 °C. The temperature of red cell components should not go below + 1 °C nor exceed + 10 °C. A maximum transit time of 24 hours at temperatures not above + 10 °C is recommended. Otherwise, transport conditions should be validated to ensure maintenance of the quality of the red blood cells.

4.2.9. Transport of platelet components

Platelet components are usually not agitated during transport and, therefore, oxygen delivery to platelets is reduced. Agitation of platelets can be interrupted (simulating transportation conditions) for up to 24 hours of the total shelf life of the component with no single interruption lasting longer than 8 hours without a major impact on the *in vitro* quality of the platelets at the end of a storage time of up to 7 days. The pH of the platelet components is better preserved when agitation is interrupted for several short periods compared to one long period.

Platelet components should be transported in an insulated container with temperature-stabilising elements that ensure transport temperature is maintained as close as possible to the recommended storage temperature.

The impact of transport conditions on the quality of platelet components should be validated by quality control tests, e.g. swirling tests and pH or glucose measurements of components at the end of the storage period.

4.2.10. Transport of frozen plasma components

Frozen plasma components should be transported in the frozen state as close as possible to the recommended storage temperature.

4.3. Additional processes

4.3.1. Irradiation of cellular blood components

Viable lymphocytes in blood components can cause fatal transfusion- associated graft versus host disease, particularly in severely immune-compromised patients, e.g. patients undergoing haematopoietic stem cell transplantation, children with inherited cellular immunodeficiency syndromes and some low birth weight neonates. Other clinical settings with an increased risk of this rare complication include intrauterine transfusion, transfusion between family members and transfusion of HLA-matched components.

Lymphocytes can be rendered non-viable by exposure to irradiation. Irradiation using processes identified below does not cause significant harm to other blood cells. Therefore, an irradiated component can be given safely to most patients. The *in vitro* quality of irradiated red cells deteriorates faster during storage than that of non-irradiated red cell components. Therefore, irradiation leads to a reduced shelf-life of red cell components.

Standards

4.3.1.1. The irradiation process should ensure that no part of the component receives a dose less than 25 Gy or more than 50 Gy. The exposure time should be set to ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose.

4.3.1.2. Regular dose-mapping of equipment should be undertaken. Exposure time should be standardised for each irradiation source and re-validated at suitable intervals. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated blood and blood components. A defined procedure should ensure the segregation of components that have not been irradiated from those that have been irradiated.

4.3.1.3. Red cell components may be irradiated up to 28 days after collection. Irradiated cells should be transfused as soon as possible, but no later than 14 days after irradiation and, in any case, no later than 28 days after collection. More stringent requirements are included in specific component monographs (see Chapter 6 in this *Guide*).

4.3.2. Bacterial safety

Bacterial contamination may still occur despite careful blood collection and processing procedures. Bacterial cultures of platelet components provide the best indication of the overall rate of contamination of whole blood donation provided that the sample for culture is obtained in a suitable volume and at a suitable time after collection. Bacterial screening of platelets also allows the extension of their shelf-life to 7 days, leading to reduced wastage Surveillance studies have found rates of contamination as high as 0.4 per cent in single donor platelets, although rates at or below 0.2 per cent are more often reported.

The causes of bacterial contamination include occult bacteraemia in the donor, inadequate or contaminated skin preparation at the phlebotomy site, coring of a skin plug by the phlebotomy needle and breaches of the closed system from equipment defects or mishandling.
Platelet components are more likely than other blood components to be associated with bacterial contamination due to their storage at room temperature, which facilitates bacterial growth.

A variety of procedures may be used to obtain a valid platelet sample for bacterial culture. Closed systems are required in order to minimise the risk of false positive cultures due to contamination at the time of sampling. Aseptic techniques should be used for inoculation in culture. Large volume samples (8 to 16 mL) can be cultured any time post-collection; however delaying sampling will decrease the likelihood of false negative results. Delayed sampling permits bacterial growth to a level that subsequent assays can detect reliably, thereby overcoming sampling errors at low contamination level. A quarantine period after sampling and inoculation could be considered to decrease the risk of transfusion of contaminated blood components.

Validated and approved pathogen inactivation technologies or a rapid test shortly before transfusion may

offer alternative approaches to assuring the bacterial safety of platelet components.

Data on routine bacterial monitoring should be analysed using statistical process control techniques to ensure that the process remains in control.

If routine bacterial monitoring of platelet components is not performed, e.g. when pathogen inactivation technologies for platelet components are in place, other methods for monitoring aseptic collection and processing should be considered.

Standard

4.3.2.1. A systematic programme to assure the bacterial safety of blood collection and processing procedures should be in place.

4.3.3. Prevention of cytomegalovirus transmission

Cytomegalovirus (CMV) is a common infectious agent that can be transmitted via the transfusion of blood components. The risk of disease transmission is highest with fresh components containing leucocytes.

CMV infection is often asymptomatic in healthy persons. Antibodies usually appear 4 to 8 weeks after infection and can be demonstrated in standard screening tests. Since the infection is common, the test has to be repeated on each donation from a previously seronegative donor.

Infection caused by this virus is usually not clinically significant in immunocompetent recipients, but can cause severe, even fatal, disease in certain immunosuppressed patients. These patients should receive components selected or processed to minimise the risk of CMV infectivity.

The use of components from anti-CMV-negative donors or leucocyte- depleted components significantly reduces the risk of CMV transmission and CMV disease in immunocompromised patients. However, neither method nor a combination of them can completely prevent transmission due to occasional cases of CMV viraemia in the early stage of acute infection.

There is no consensus on the requirement for CMV screening in blood services that undertake universal leucocyte depletion of blood components. Some services (especially in areas that have a high seroprevalence of CMV) have ceased antibody screening, but others believe that the combination of antibody screening and leucocyte depletion may confer additional safety. Use of pathogen inactivation technologies can also decrease the risk of CMV transmission.

4.3.4. Pathogen inactivation technologies

The aim of pathogen inactivation technologies (PIT) is to remove or inactivate bacteria and/or other pathogens (viruses, parasites) using physical and/or chemical methods. Components produced by these systems are referred to as ‘pathogen reduced’.

PIT systems for red cells and whole blood are in development but are not currently in use in Europe.

Several PIT systems are CE-marked for plasma and platelets and have subsequently been licensed for routine use in Europe and elsewhere. Currently available systems have been demonstrated to inactivate a wide range of viruses, bacteria, parasites and leucocytes. They do not reduce infectivity associated with prion proteins and, hence, vCJD risk.

With regard to the efficacy of pathogen reduced platelet components, there is some loss of platelets in the process. Most clinical studies have demonstrated a reduced corrected count increment compared to untreated control platelets. One study found an increase in bleeding risk associated with this phenomenon, not found in several other studies. Potential risks include toxicity and neo-antigen formation; neither has been observed in haemovigilance studies of short duration, but longer-term surveillance studies will be required to confirm the absence of long-term toxicity. Platelet PIT potentially allows the extension of their shelf-life to 7 days, leading to reduced wastage. A further advantage of some PIT systems is inactivation of lymphocytes, which obviates the need for irradiation of platelets and whole blood.

The value of implementation of PIT for blood components should be assessed in conjunction with current and alternative methods for risk reduction.

Chapter 5

Blood component monographs

D-2. Plasma, Fresh Frozen, Pathogen-Reduced

D-3. Cryoprecipitate

D-4. Cryoprecipitate, Pathogen-Reduced

D-5. Plasma, Fresh Frozen, Cryoprecipitate-Depleted

Part E. White cell components

E-1. Granulocytes, Apheresis

E-2. Granulocytes, Pooled

5.0 Overview

The blood components described in these monographs are components that are currently in use in Europe and of which there is considerable experience in their use.

New developments, however, may be proposed. Any novel component, significant change to an existing component, or novel or significantly changed processing technique should be validated to ensure the safety and efficacy of the component and offer at least equivalence or an advantage over components currently in use.

Current examples under investigation include whole blood for trauma (with or without platelets), freeze-dried plasma, 'universal' (suitable for all blood groups) plasma, and refrigerated platelets. Some may be useful in specific clinical situations; others may offer benefit to all recipients.

A novel or significantly changed component or processing technique can be considered for inclusion in the Guide when there is sufficient evidence to demonstrate its safety and efficacy, and inclusion has been agreed by the CD-P-TS following the Guide consultation.

Reversely, components may in a similar way be considered for removal from these monographs, where there is sufficient evidence that confirms the components to be inferior, clinically unjustifiable or too rarely used. An example of this may be non-leucodepleted components, the use of which is decreasing.

The component monographs have a standardised structure, which encompasses the headings as listed below.

Definition and properties

Here, information is given about the component, including its origin, the active constituents and contaminating cells (if appropriate).

Preparation

Here, a short description is given about the method(s) of preparation. More detailed information about preparation processes is described in Chapter 4 of this Guide.

Requirements and quality control

Typical component-specific testing parameters for quality control are given in tables, which are formatted as follows:

Parameter to be checked	Requirements	Frequency of control

If appropriate, the requirements may be met by performing the test on the donation sample that was taken as part of the donor screening process in place of individual component testing.

The monographs provide advice on frequency of control. An alternative approach to identify the number of units to be tested is statistical process control (SPC) (see Appendix 4).

Quality control may be carried out either as a separate quality control procedure for the given component or as a routine part of the preparation of all components.

Storage and transport

Mandatory storage and transport conditions for each blood component are given. Detailed and descriptive information about the processes of storage and transport are given in Chapter 4 of this Guide.

Labelling

The labelling should comply with relevant legislation and where in place, international agreements. The required information should be shown on the label or contained in the component information leaflet.

Warnings

Typical warnings and adverse reactions are described that should be communicated to the physician in written form, such as in a component information leaflet.

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Whole blood and red cell components

	Component	Technical information	Volume (mL per unit)	Hb content (g per unit)	Haematocrit	Other
A-1.	Whole blood (WB)	Undergone no primary processing after collection	450 ± 50	≥ 45	Not specified	Volume specified excludes anticoagulant
A-2.	Whole blood, leucocyte-depleted	WB with leucocyte removal	450 ± 50	≥ 43	Not specified	
B-1.	Red cells, leucocyte-depleted	WB with leucocyte removal and removal of a proportion of plasma	Depends on process	≥ 40	0.65–0.75	
B-2.	Red cells, leucocyte-depleted in additive solution	WB with leucocyte removal, removal of majority of plasma and resuspended in additive solution	Depends on process	≥ 40	0.50–0.70	
B-3.	Red cells	WB with removal of a major part of the plasma	280 ± 50	≥ 45	0.65–0.75	
B-4.	Red cells, buffy coat removed	WB with removal of a major part of the plasma and the buffy coat	250 ± 50	≥ 43	0.65–0.75	
B-5.	Red cells, in additive solution	WB with removal of plasma and addition of additive solution	Depends on process	≥ 45	0.50–0.70	
B-6.	Red cells, buffy coat removed, in additive solution	WB with removal of plasma and buffy coat and addition of additive solution	Depends on process	≥ 43	0.50–0.70	
B-7.	Red cells, apheresis	Red cells collected using automated apheresis equipment	Depends on process	≥ 40	0.65–0.75 0.50–0.70 if in additive solution	Can be leucocyte-depleted and/or suspended in additive solution
B-8.	Red cells, washed	Secondarily processed by sequential washing and resuspension in additive solution	Depends on process	≥ 40	0.40–0.70	Shelf-life reduced to 24 hours if processed in an open system

B-9.	Red cells, cryopreserved	Red cells frozen in cryoprotectant and later thawed and reconstituted	> 185	≥ 36	0.35–0.70	Hb (supernatant) < 0.2 g per unit Shelf-life reduced to 24 hours if processed in an open system

Component monographs

Part A. Whole blood components

A-1. Whole blood

Definition and properties

Whole blood is blood taken from a suitable donor using a sterile and pyrogen-free anticoagulant and container. *Whole blood* is a source material for *Whole blood, Leucocyte-Depleted* and component preparation, which is its major use. *Whole blood* for transfusion is used without further processing.

Whole blood for transfusion should not contain irregular antibodies of clinical significance.

Preparation

By definition, no (post-donation) preparation is required to produce a unit of *Whole blood*.

Requirements and quality control

Table 5A-1 lists the requirements for *Whole blood* for direct transfusion. Additional testing might be required to comply with national requirements (see also Chapter 9, Screening for markers of transfusion-transmissible infection).

Table 5A-1

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	450 mL ± 50 mL volume (excluding anticoagulant) A non-standard donation should be labelled accordingly	as determined by SPC
Haemoglobin per final unit [a]	Minimum 45 g	as determined by SPC
Haemolysis at the end of storage [a]	< 0.8 % of red cell mass	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

Whole blood for transfusion must be kept at a controlled temperature, i.e. between + 2°C and + 6°C (Directive 2004/33/EC Annex IV). The storage time depends on the anticoagulant/preservative solution used. For example, the storage time is up to 35 days if stored in CPDA-1. Validated transport systems should ensure that the temperature is maintained within the range of + 1°C to + 10°C at any time during a maximum transit time of 24 hours.

Whole blood for preparation of blood components may be kept between +2°C and + 6°C or for up to 24 hours in conditions validated to maintain a temperature between + 20°C and + 24 °C, which is a prerequisite for the production of platelet preparations from *Whole blood*.

Labelling

The labelling should comply with relevant legislation and where in place, international agreements. The following information on *Whole blood* for transfusion must be shown on the label or contained in the component information leaflet, as appropriate (Directive 2002/98/EC Annex III):

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;
- The unique identity number;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry
- The storage temperature
- The name of the anticoagulant solution

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- Blood group phenotypes other than ABO and RhD (optional);
- Additional component information: irradiated, etc. (if appropriate);
- That the component should not be used for transfusion if there is abnormal haemolysis or other deterioration;
- That the component should be administered through an approved blood administration set.

Warnings

Compatibility of *Whole blood* for transfusion with the intended recipient should be verified by suitable pre-transfusion testing.

RhD-negative female recipients of child-bearing age or younger should not be transfused with *Whole blood* from RhD-positive donors.

Micro-aggregates may form on storage.

Whole blood for transfusion is not recommended in cases of:

- Anaemia without blood volume loss;
- Plasma intolerance;
- Intolerance due to allo-immunisation against leucocyte antigens.

Adverse reactions include:

- Haemolytic transfusion reaction;
- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Anaphylaxis;

- Allo-immunisation against red cell and HLA antigens;
- Transfusion-related acute lung injury (TRALI);
- Post-transfusion purpura;
- Transfusion-associated graft versus host disease (TA-GvHD);
- Sepsis due to inadvertent bacterial contamination;
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;
- Syphilis can be transmitted if components are stored for less than 96 hours at + 4 °C;
- Protozoal transmission (e.g. malaria) may occur in rare instances;
- Transmission of other pathogens that are not tested for or recognised;
- Citrate toxicity in neonates and in patients with impaired liver function;
- Metabolic imbalance in massive transfusion (e.g. hyperkalaemia);
- Transfusion-associated circulatory overload (TACO);
- Iron overload.

A-2. Whole blood, Leucocyte-Depleted

Definition and properties

Whole blood, Leucocyte-Depleted (LD) is a component for transfusion or a source material for component preparation derived from *Whole blood* by removing the leucocytes to a minimum residual content.

Whole blood, LD contains a minimum haemoglobin content of 43 g.

Whole blood, LD contains less than 1.0×10^6 leucocytes.

Whole blood, LD for transfusion should not contain irregular antibodies of clinical significance.

Preparation

Generally a filtration technique is used to produce *Whole blood, LD*. Pre-storage leucocyte depletion within 48 hours after donation is the standard.

Requirements and quality control

Table 5A-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9, Screening for markers of transfusion-transmissible infection).

Table 5A-2

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	450 ± 50 mL volume (excluding anticoagulant) A non-standard donation should be labelled accordingly	as determined by SPC
Haemoglobin per final unit [a]	Minimum 43 g	as determined by SPC
Residual leucocytes per final unit [a]	$< 1 \times 10^6$	as determined by SPC
Haemolysis at the end of storage [a]	< 0.8 % of red cell mass	as determined by SPC

a A minimum of 90 % of units tested should meet the required value.

Storage and transport

Whole blood, LD must be kept at a controlled temperature between + 2°C and +6°C (Directive 2004/33/EC Annex IV). The storage time depends on the processing system and anticoagulant/preservative solution used and should be validated.

Validated transport systems should ensure that the temperature is maintained within the range of + 1°C to +10°C at all times during a maximum transit time of 24 hours.

Labelling

The labelling should comply with relevant legislation and where in place, international agreements. The following information on *Whole blood* for transfusion must be shown on the label or contained in the component information leaflet, as appropriate (Directive 2002/98/EC Annex III):

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;

- The unique identity number;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry
- The storage temperature
- The name of the anticoagulant solution

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- Blood group phenotypes other than ABO and RhD (optional);
- Additional component information: irradiated, etc. (if appropriate);
- That the component should not be used for transfusion if there is abnormal haemolysis or other deterioration;
- That the component should be administered through an approved blood administration set.

Warnings

Compatibility of *Whole blood, LD* with the intended recipient should be verified by suitable pre-transfusion testing.

RhD-negative female recipients of child-bearing age or younger should not be transfused with red cells from RhD-positive donors.

Whole blood, LD is not recommended in cases of:

- Anaemia without blood volume loss;
- Plasma intolerance.

Adverse reactions include:

- Haemolytic transfusion reaction;
- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Anaphylaxis;
- Allo-immunisation against red cell antigens;
- Transfusion-related acute lung injury (TRALI);
- Post-transfusion purpura;
- Graft versus host disease (TA-GvHD);
- Sepsis due to inadvertent bacterial contamination;
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;
- Syphilis can be transmitted if components are stored for less than 96 hours at +4°C;

- Protozoal transmission (e.g. malaria) may occur in rare instances;
- Transmission of other pathogens that are not tested for or recognised;
- Citrate toxicity in neonates and in patients with impaired liver function;
- Metabolic imbalance in massive transfusion (e.g. hyperkalaemia);
- Transfusion-associated circulatory overload (TACO);
- Iron overload.

Part B. Red cell components

B-1. Red Cells, Leucocyte-Depleted

Definition and properties

Red Cells, Leucocyte-Depleted (LD) is a red cell component derived from a non-leucodepleted red cell component or *Whole blood* donation by removing the leucocytes and a proportion of the plasma.

Red Cells, LD contains a minimum haemoglobin content of 40 g. The haematocrit is 0.65 to 0.75.

Red Cells, LD contains less than 1.0×10^6 leucocytes.

Preparation

Generally a filtration technique is used to produce *Red Cells, LD*. Processing and leucocyte depletion within 48 hours after donation is the standard.

Red Cells, LD can be produced:

- From *Whole blood*, *Leucocyte-Depleted*;
- By leucocyte filtration of a red cell component.

Requirements and quality control

As indicated for *Whole blood, LD* except for the parameters specified in Table 5B-1.

Table 5B-1

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.65–0.75	as determined by SPC
Haemoglobin per final unit[a]	Minimum 40 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Whole blood, LD*.

Labelling

As indicated for *Whole blood, LD*.

Warnings

As indicated for *Whole blood, LD*.

B-2. Red Cells, Leucocyte-Depleted in Additive Solution

Definition and properties

Red Cells, Leucocyte-Depleted in Additive Solution (LD-AS) is a red cell component derived from *Whole blood* by removing the leucocytes, removing the majority of the plasma and adding an additive solution, or from leucocyte filtration of *Red Cells, AS* or *Red Cells, Buffy Coat Removed-AS (BCR-AS).*

Red Cells, LD-AS contains a minimum haemoglobin content of 40 g. The haematocrit is 0.50 to 0.70.

Red Cells, LD-AS contains less than 1.0×10^6 leucocytes.

Preparation

Generally, a filtration technique is used to produce *Red Cells, LD-AS*. Leucocyte depletion within 48 hours after donation is the standard.

Red Cells, LD-AS can be produced:

- By leucocyte filtration of *Whole blood*, with subsequent centrifugation and removal of the plasma and immediate addition of the additive solution, followed by careful mixing;
- By leucocyte filtration of *Red Cells, AS* or *Red Cells BCR-AS*.

Requirements and quality control

As indicated for *Whole blood, LD* except for the parameters specified in Table 5B-2.

Table 5B-2

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.50–0.70	as determined by SPC
Haemoglobin per final unit[a]	Minimum 40 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value

Storage and transport

As indicated for *Whole blood, LD*.

Labelling

As indicated for *Whole blood, LD*.

Warnings

As indicated for *Whole blood, LD* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if the additive solution is replaced by fresh frozen plasma on the day of use.

B-3. Red Cells

Definition and properties

Red Cells is a component obtained by removal of a major part of the plasma from *Whole blood*.

Red Cells also contains the greater part of the *Whole blood* leucocytes (about 2.5 to 3.0 × 10^9 cells) and a variable content of platelets, depending on the method of processing.

Preparation

For the preparation of *Red Cells*, plasma is removed from *Whole blood* by centrifugation.

Requirements and quality control

As indicated for *Whole blood,* except for the parameters specified in Table 5B-3.

Table 5B-3

Parameter to be checked	Requirements	Frequency of control
Volume [a]	280 mL ± 50 mL	as determined by SPC
Haematocrit [a]	0.65–0.75	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value

Storage and transport

As indicated for *Whole blood*.

Labelling

As indicated for *Whole blood*.

Warnings

As indicated for *Whole blood,* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if fresh frozen plasma is added on the day of use.

B-4. Red Cells, Buffy Coat Removed

Definition and properties

Red Cells, Buffy Coat Removed (BCR) is a red cell component prepared by the removal of a major part of the plasma and the buffy coat layer from *Whole blood*.

Red Cells, BCR contains a minimum haemoglobin content of 43g. The haematocrit is 0.65 to 0.75.

Red Cells, BCR normally contains less than 1.2 × 10^9 leucocytes and a variable content of platelets, depending on the method of processing.

Preparation

Red Cells, BCR is derived from *Whole blood* by centrifugation. The plasma and 20 to 60 mL of the buffy coat layer are removed from *Whole blood* after centrifugation, resulting in the loss of 10 to 30 mL of the red cells from the donated *Whole blood*. Sufficient plasma is retained to give a haematocrit of 0.65 to 0.75.

Requirements and quality control

As indicated for *Whole blood*, except for the parameters specified in Table 5B-4.

Table 5B-4

Parameter to be checked	Requirements	Frequency of control
Volume [a]	250 mL ± 50 mL	as determined by SPC
Haematocrit [a]	0.65–0.75	as determined by SPC
Haemoglobin per final unit [a]	Minimum 43 g	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1.2 \times 10^9$	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Whole blood*.

Labelling

As indicated for *Whole blood*.

Warnings

As indicated for *Whole blood,* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if fresh frozen plasma is added on the day of use.

B-5. Red Cells, in Additive Solution

Definition and properties

Red Cells, in Additive Solution (AS) is a red cell component prepared by the removal of the plasma from *Whole blood* with subsequent addition of an appropriate additive solution.

Red Cells, AS contains a minimum haemoglobin content of 45 g. The haematocrit is 0.50 to 0.70.

Red Cells, AS also contains the greater part of the *Whole blood* leucocytes (about 2.5 to 3.0×10^9 cells) and a variable content of platelets, depending on the method of processing.

Preparation

Whole blood is collected, using CPD as the anticoagulant solution. After centrifugation of *Whole blood*, plasma is removed and the additive solution containing adenine is added immediately to the red cells and mixed carefully.

Requirements and quality control

As indicated for *Whole blood,* except for the parameters specified in table 5B-5.

Table 5B-5

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.50–0.70	as determined by SPC
Haemoglobin per final unit [a]	Minimum 45 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Whole blood*.

Labelling

As indicated for *Whole blood*.

Warnings

As indicated for *Whole blood* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if the additive solution is replaced by fresh frozen plasma on the day of use.

B-6. Red Cells, Buffy Coat Removed, in Additive Solution

Definition and properties

Red Cells, Buffy Coat Removed, in Additive Solution (BCR-AS) is a red cell component prepared by the removal of a major part of the plasma and the buffy coat layer from *Whole blood*, with subsequent addition of an appropriate nutrient solution.

Red Cells, BCR-AS contains a minimum haemoglobin content of 43 g. The haematocrit is 0.50 to 0.70.

Red Cells, BCR-AS contains less than 1.2×10^9 leucocytes and a variable platelet content, depending on the method of processing.

Preparation

Red Cells, BCR-AS is derived from *Whole blood* by centrifugation. For preparation, the plasma and 20 to 60 mL of the buffy coat layer are removed, resulting in the loss of 10 to 30 mL of the red cells from the donated *Whole blood*. The additive solution is immediately added to the red cells and carefully mixed.

Requirements and quality control

As indicated for *Whole blood,* except for the parameters specified in Table 5B-6.

Table 5B-6

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.50–0.70	as determined by SPC
Haemoglobin per final unit [a]	Minimum 43 g	as determined by SPC
Residual leucocyte content per final unit [a]	$< 1.2 \times 10^9$	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Whole blood*.

Labelling

As indicated for *Whole blood*.

Warnings

As indicated for *Whole blood* with the following addition:

- Not for exchange transfusion in newborns, unless used within 5 days of donation and only if the additive solution is replaced by fresh frozen plasma on the day of use.

B-7. Red Cells, Apheresis

Definition and properties

Red Cells, Apheresis (Aph) is a red cell component obtained by apheresis of a single donor using automated cell-separation equipment.

Red Cells, Aph contains a minimum haemoglobin content of 40 g. The haematocrit is 0.65 to 0.75 (0.50 to 0.70 if an additive solution is used).

The leucocyte content of *Red Cells, Aph* can vary. When leucocyte-depleted, *Red Cells, Aph* normally contains less than 1.0×10^6 leucocytes.

Preparation

For preparation of *Red Cells, Aph*, whole blood is removed by an appropriate apheresis machine from the donor and anticoagulated with a citrate-containing solution. The plasma is returned to the donor. Either one or two units of *Red Cells, Aph* can be collected during a single procedure.

Red Cells, Aph can be used either unmodified or can undergo further processing, e.g. leucocyte depletion or addition of an additive solution.

Requirements and quality control

As indicated for *Whole blood,* or *Whole blood, LD* (depending on whether leucodepleted or not) except for the parameters specified in Table 5B-7.

Storage and transport

As indicated for *Whole blood* if *Red Cells, Aph* is collected and prepared in a functionally closed system. If prepared or filtered by methods under an open system, the storage time is limited to 24 hours at between +2°C and +6°C.

Labelling

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether leucodepleted or not).

Table 5B-7

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.65–0.75	as determined by SPC
Haematocrit [a] (if additive solution)	0.50–0.70	as determined by SPC
Haemoglobin per final unit[a]	Minimum 40 g	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

In addition, if two or more units are collected from the donor in one session, each component should have a unique component identity number.

Warnings

As for *Red Cells* or *Red Cells, AS* depending on whether an additive solution is used.

B-8. Red Cells, Washed

Definition and properties

Red Cells, Washed (W) is derived from secondary processing of a red cell component or *Whole blood* involving sequential washing and re-suspension of red cells in an additive solution.

Most of the plasma, leucocytes and platelets are removed. The amount of residual plasma depends upon the washing protocol. The haematocrit can be varied according to clinical need.

Preparation

After centrifugation of the primary component and removal of the plasma or additive solution (and, if applicable, the buffy coat layer), the red cells are washed by sequential addition and removal of an additive solution. Centrifugation should be performed at a controlled temperature.

Requirements and quality control

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether the starting component is leucodepleted) except for the parameters specified in Table 5B-8.

Table 5B-8

Parameter to be checked	Requirements	Frequency of control
Volume [a]	To be defined for the system used	as determined by SPC
Haematocrit [a]	0.40-0.70	as determined by SPC
Haemoglobin per final unit [a]	Minimum 40 g	as determined by SPC
Protein content in supernatant per final unit [a]	< 0.5 g	as determined by SPC

[a] A minimum of 90 per cent of units tested should meet the required value

Storage and transport

As indicated for *Whole blood*. In addition, when an open system is used for washing, the storage time should be as short as possible after washing and should never exceed 24 hours.

If a closed system and a suitable additive solution are used, storage times may be prolonged, subject to validation.

Labelling

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether leucodepleted or not).

Warnings

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether leucodepleted or not).

B-9. Red Cells, Cryopreserved

Definition and properties

Red Cells, Cryopreserved (Cryo) is a red cell component derived by secondary processing of a red cell component or *Whole blood* or *Whole blood, LD*. Red cells are frozen (preferably within 7 days of collection) using a cryoprotectant and stored at −60°C or below, depending on the method of cryopreservation.

A reconstituted unit of *Red Cells, Cryo* contains low amounts of protein, leucocytes and platelets. Each unit of *Red Cells, Cryo* contains a minimum haemoglobin content of 36 g. The haematocrit is 0.35 to 0.70.

Preparation

Two methods are generally used for the preparation of *Red Cells, Cryo*. One is a high-glycerol, the other a low-glycerol technique. Both methods require a washing/de-glycerolisation

procedure following thawing and resuspension in an appropriate additive solution prior to issue.

Requirements and quality control

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether the starting component is leucodepleted) except for the parameters specified in Table 5B-9.

Since cryopreservation allows prolonged storage, serum and/or plasma samples obtained at collection should also be stored to enable future testing for newly discovered markers of transmissible diseases when components are thawed for use.

Storage and transport

Red Cells, Cryo in frozen state

Red Cells, Cryo in the frozen state should be constantly maintained between:

- −60°C and −80°C if stored in an electric freezer and when a high-glycerol method is used;
- −140°C and −150°C if stored in vapour-phase liquid nitrogen and when a low-glycerol method is used.

Table 5B-9

Parameter to be checked	Requirements	Frequency of control
Volume [a]	> 185 mL	as determined by SPC
Haemoglobin in supernatant of final unit [a, b]	< 0.2 g	as determined by SPC
Haematocrit [a]	0.35–0.70	as determined by SPC
Haemoglobin per final unit [a]	Minimum 36 g	as determined by SPC
Osmolarity [a]	Maximum 20 mOsm/L above osmolarity of resuspending fluid	as determined by SPC
Microbial control	No growth	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] final suspending solution

Red cells, Cryo in the frozen state can be stored for 30 years.

Thawed reconstituted Red Cells, Cryo

Thawed and reconstituted *Red Cells, Cryo* should be stored between +2°C and +6°C. The storage time should be validated but should be as short as possible after washing, and should never exceed 24 hours when an open system is used.

If transport in the frozen state is unavoidable, storage conditions should be maintained. Transport of thawed, reconstituted red cells is limited by the short storage time. Storage conditions should be maintained during transport.

Labelling

As indicated for *Whole blood* or *Whole blood, LD* (depending on whether the starting component is leucodepleted).

In addition, the following information should be traceable for each frozen unit:

- The producer's identification;
- The unique identity number;
- The date of donation;
- The date of expiry;
- The name and volume of the cryoprotective solution;
- Additional component information (if appropriate);
- The volume or weight of the blood component;
- The storage temperature.

Labelling of reconstituted components

After thawing and reconstitution (washing), the date of expiry should be changed to the date (and time) of expiry of the thawed component. In addition, the name and volume of the cryoprotective solution should be changed to the name and volume of the additive solution (if any).

Warnings

As indicated for *Whole blood* or *Whole blood, LD.*

In addition, when *Red Cells, Cryo* is processed in an open system, the risk of bacterial contamination is increased and therefore extra vigilance is required during transfusion.

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Platelet components

	Component	Technical information	Platelet content	Leucocyte content
C-1	Platelets, Recovered, Single Unit (SU)	Derived from a single whole blood donation, suspended in plasma	> 0.6×10^{11}	≤ 0.05×10^9 when prepared from buffy coat ≤ 0.2×10^9 when prepared from PRP or by single centrifugation method
C-2	Platelets, Recovered, Pooled	Pool of Platelets, Recovered SU, suspended in plasma, the number of which is determined by national regulations and the system used	≥ 2×10^{11}	≤ 0.3×10^9 per final unit when prepared from buffy coat ≤ 1×10^9 per final unit when prepared from PRP
C-3	Platelets, Recovered, Pooled, Leucocyte-Depleted	Pool of Platelets, Recovered, SU, leucocyte-depleted, suspended in plasma, the number of which is determined by national regulations and the system used	≥ 2×10^{11}	< 1×10^6
C-4	Platelets, Recovered, Pooled, in Additive Solution	Pool of Platelets, Recovered, SU, suspended in 30–40 % plasma and 60–70 % additive solution, the number of which is determined by national regulations and the system used	≥ 2×10^{11}	< 1×10^9
C-5	Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution	Pool of Platelets, Recovered, SU, leucocyte-depleted, suspended in 30–40 % plasma and 60–70 % additive solution, the number of which is determined by national regulations and the system used	≥ 2×10^{11}	< 1×10^6
C-6	Platelets, Recovered, Pooled, Pathogen-Reduced	Pool of Platelets, Recovered, SU, leucocyte-depleted, treated with pathogen inactivation technology, the number of which is determined by national regulations and the system used. May be suspended in plasma or mixture of plasma and additive solution	≥ 2×10^{11}	< 1×10^6

C-7	Platelets, Apheresis	Obtained by platelet apheresis of a single donor, suspended in plasma	≥ 2×10^{11} standard unit ≥ 0.5×10^{11} for neonates and infants	< 1×10^{9}
C-8	Platelets, Apheresis, Leucocyte-Depleted	Obtained by platelet apheresis of a single donor, leucocyte-depleted, suspended in plasma	≥ 2×10^{11} standard unit ≥ 0.5×10^{11} for neonates and infants	< 1×10^{6}
C-9	Platelets, Apheresis, in Additive Solution	Obtained by platelet apheresis of a single donor, suspended in 30–40 % plasma and 60–70 % additive solution	≥ 2×10^{11} standard unit ≥ 0.5×10^{11} for neonates and infants	< 1×10^{9}
C-10	Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution	Obtained by platelet apheresis of a single donor, leucocyte-depleted, suspended in 30–40 % plasma and 60–70 % additive solution	≥ 2×10^{11} standard unit ≥ 0.5×10^{11} for neonates and infants	< 1×10^{6}
C-11	Platelets, Apheresis, Pathogen-Reduced	Obtained by platelet apheresis of a single donor, leucocyte-depleted, treated with pathogen inactivation technology. May be suspended in plasma or mixture of plasma and additive solution	≥ 2×10^{11}	< 1×10^{6}
C-12	Platelets, washed	Secondarily processed by sequential washing of a standard platelet component and resuspension in saline or platelet additive solution	≥ 2×10^{11}	< 1×10^{6}
C-13	Platelets, Cryopreserved	Platelets frozen within 24 hours of collection using a cryoprotectant	≥ 50 % of pre-freeze content	Depends on original component

Part C. Platelet components

C-1. Platelets, Recovered, Single Unit, in Plasma

Definition and properties

Platelets, Recovered, Single Unit (Rec, SU) is a platelet component derived from a single *Whole blood* donation. It contains the majority of the original *Whole blood* platelet content, suspended in plasma.

Platelets, Rec, SU contains more than 0.6×10^{11} platelets.

Platelets, Rec, SU contains up to 0.2×10^{9} leucocytes if prepared by the platelet-rich plasma method or by the single centrifugation method, and up to 0.05×10^{9} leucocytes if prepared by the buffy coat method.

Platelets, Rec, SU can be transfused as single units, usually for neonatal and infant recipients, while a typical adult dose comprises 4 to 6 units of *Platelets, Rec, SU.*

Preparation

Preparation from platelet-rich plasma (PRP)

A unit of *Whole blood*, stored for up to 24 hours in conditions validated to maintain the temperature between +20°C and +24°C, is centrifuged so that an optimal number of platelets remain in the plasma and the numbers of leucocytes and red cells are reduced to a defined level. Platelets from PRP are sedimented by hard-spin centrifugation; the supernatant platelet-poor plasma is removed using a closed system, leaving 50 to 70 mL of it with the platelets. The platelets are allowed to disaggregate and are then re-suspended in the remnant plasma forming the final component.

Preparation from buffy coat

A *Whole blood* unit, stored for up to 24 hours in conditions validated to maintain the temperature between +20°C and +24°C, is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with the leucocytes. The buffy coat is separated and processed further to obtain a platelet concentrate. Single buffy coats diluted with plasma are centrifuged so that the platelets remain in the supernatant, but red cells and leucocytes are sedimented to the bottom of the bag. The platelet-containing supernatant is immediately transferred into an approved platelet storage bag using a closed system.

Preparation by the single centrifugation method

A Whole Blood unit, stored for up to 24 hours in conditions validated to maintain the temperature between + 20 and + 24 °C, is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with the leucocytes. While still spinning in the centrifuge, the upper part of the buffy coat containing the platelets is expressed into a satellite bag using a closed system together with an appropriate volume of plasma.

Requirements and quality control

Table 5C-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Screening for markers of transfusion-transmissible infection).

Demonstration of the swirling phenomenon, which is based on light scattering by platelets in motion and of normal morphology, should be carried out prior to issuing this component. This is best done as close as possible to the time of transfusion.

Table 5C-1

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
Volume [a]	As validated per 0.6×10^{11} platelets	as determined by SPC
Platelet content per final unit [a]	$> 0.6 \times 10^{11}$	as determined by SPC
Residual leucocytes per final unit [a]		as determined by SPC
a. prepared from buffy coat	a. $\leq 0.05 \times 10^{9}$	
b. prepared from PRP or by single centrifugation method	b. $\leq 0.2 \times 10^{9}$	
pH measured (+ 22 °C) at the end of the recommended shelf-life [b]	> 6.4	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] All tested units should comply. Measurement of the pH should be under conditions which prevent CO_2 escape. Measurement may be made at another temperature and then corrected.

Storage and transport

Platelets, Rec, SU should be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

The storage temperature must be between +20°C and +24°C (Directive 2004/33/EC Annex IV), under constant agitation.

The maximum storage time for *Platelets, Rec, SU* is 5 days. Storage may be extended to 7 days, in conjunction with appropriate detection or reduction of bacterial contamination.

During transportation, the temperature of *Platelets, Rec, SU* should be kept as close as possible to the recommended storage temperature and, upon receipt, unless intended for immediate therapeutic use, they should be transferred to storage under the recommended conditions.

Labelling

The labelling should comply with relevant legislation and where in place, international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate (Directive 2002/98/EC Annex III):

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;
- The unique identity number; if platelets are pooled the original donations should be traceable;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry
- The storage temperature
- The name of the anticoagulant solution

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- The number of platelets (average or actual, as appropriate)
- Blood group phenotypes other than ABO and RhD (optional);
- Additional component information: irradiated, etc. (if appropriate);
- That the component should not be used for transfusion if there is abnormal haemolysis or other deterioration;
- That the component should be administered through an approved blood administration set.

Warnings

RhD-negative female recipients of child-bearing age or younger should preferably not be transfused with platelets from RhD-positive donors. If this is unavoidable, administration of anti-D immunoglobulin should be considered.

Platelets, Rec, SU is not recommended in cases of:

- Plasma intolerance.

Adverse reactions include:

- Haemolytic reaction due to transfusion of ABO-incompatible plasma in the component;
- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Anaphylaxis;
- Allo-immunisation against HLA and red cell antigens;
- Allo-immunisation against HPA antigens;
- Transfusion-related acute lung injury (TRALI);
- Post-transfusion purpura;
- Graft versus host disease (TA-GvHD);
- Sepsis due to inadvertent bacterial contamination;
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;
- Syphilis transmission;
- Protozoal transmission (e.g. malaria) may occur in rare instances;
- Transmission of other pathogens that are not tested for or recognised;
- Citrate toxicity in neonates and in patients with impaired liver function;
- Transfusion-associated circulatory overload.

C-2. Platelets, Recovered, Pooled, in Plasma

Definition and properties

Platelets, Recovered, Pooled (Rec, Pool) is a platelet component derived from-fresh *Whole blood* donations, the number of which is determined by national regulations and the system used, which contains the majority of the original platelet content in a therapeutically effective adult dose, suspended in plasma.

Platelets, Rec, Pool contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool contains a maximum of 1×10^{9} leucocytes.

Preparation

Platelets, Rec, Pool can be produced:

- Directly from pooled *Whole blood*-derived buffy coats,
- By secondary processing involving pooling of *Platelets, Rec, SU,* prepared by PRP or single centrifugation method.

Preparation from buffy coat

A *Whole blood* unit, stored in conditions validated to maintain the temperature between +20°C and +24°C for up to 24 hours, is centrifuged so that the platelets are primarily sedimented to the buffy coat layer, together with the leucocytes. The buffy coat is separated and further processed so that, blood group-compatible buffy coats, the number of which is determined by national regulations and the system used, are pooled in a sterile manner and re-suspended with plasma. After careful mixing, the buffy coat pool is centrifuged (soft-spin) so that the platelets remain in the supernatant but the red cells and leucocytes are effectively sedimented to the bottom of the

bag. The platelet-containing supernatant is immediately transferred into an approved platelet storage bag using a closed system. This second processing step can either be done manually (separation of buffy coat pool by centrifugation, transfer, semi-automated expression) or automated (separation and expression of buffy coat pool during centrifugation).

Preparation from Platelets, Recovered, Single Units (PRP or single centrifugation method)

Units of *Platelets, Rec, SU*, the number of which is determined by national regulations and the system used, prepared by the PRP or single centrifugation method are connected and pooled. If storage for longer than 6 hours is intended, pooling should be undertaken in a sterile manner using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-2.

Table 5C-2

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	≥ 2×10^{11}	as determined by SPC
Residual leucocyte content [a]		as determined by SPC
a. prepared from buffy coat per final unit	a. ≤ 0.3×10^{9}	
b. prepared from PRP or by single centrifugation method per final unit	b. ≤ 1×10^{9}	

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- When an open system has been used for the preparation of *Platelets, Rec, Pool*, the storage time should not exceed 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following addition:

- The number of donations combined to make the pool.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-3. Platelets, Recovered, Pooled, Leucocyte-Depleted, in Plasma

Definition and properties

Platelets, Recovered, Pooled, Leucocyte-Depleted (Rec, Pool, LD) is a leucocyte-depleted platelet component derived from fresh *Whole blood,* the number of which is determined by national

regulations and the system used, which contains most of the original platelet content in a therapeutically effective adult dose suspended in plasma.

Platelets, Rec, Pool, LD contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool, LD contains less than 1.0×10^{6} leucocytes.

Preparation

Platelets, Rec, Pool, LD is leucocyte-depleted by filtration. Pre-storage leucocyte filtration is recommended in preference to filtration during or shortly before transfusion.

Platelets, Rec, Pool, LD can be produced:

- Directly from pooled *Whole blood*-derived buffy coats,
- By secondary processing, after pooling of *Platelets, Rec, SU,* prepared by PRP or single centrifugation method.

Preparation from buffy coat

A *Whole blood* unit, stored in conditions validated to maintain a temperature between +20°C and +24°C for up to 24 hours, is centrifuged so that the platelets are primarily sedimented to the buffy coat layer together with the leucocytes. The buffy coat is separated and further processed so that, blood group-compatible buffy coats, the number of which is determined by national regulations and the system used, are pooled in a sterile manner and re-suspended with plasma. After careful mixing, the buffy coat pool is centrifuged (soft-spin) so that the platelets remain in the supernatant, but the red cells and leucocytes are sedimented to the bottom of the bag. The platelet-containing supernatant is usually immediately filtered and transferred into an approved platelet storage bag using a closed system. This second processing step can either be done manually (separation of buffy coat pool by centrifugation, transfer, semi-automated expression) or automated (separation and expression of buffy coat pool during centrifugation).

Preparation from Platelets, Recovered, Single Units (PRP or single centrifugation method)

Units of *Platelets, Rec, SU*, the number of which is determined by national regulations and the system used, prepared by the PRP or single centrifugation method, are connected, pooled, immediately filtered and transferred into an approved platelet storage bag. If storage for longer than 6 hours is intended, preparation should be undertaken using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-3.

Table 5C-3

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	≥ 2×10^{11}	as determined by SPC
Residual leucocytes per final unit [a]	< 1×10^{6}	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- When an open system has been used for the preparation of *Platelets, Rec, Pool, LD*, the storage time should not exceed 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- Leucocyte-depleted;
- The number of donations combined to make the pool.

Warnings

As indicated for *Platelets, Recovered, SU*.

C-4. Platelets, Recovered, Pooled, in Additive Solution and Plasma

Definition and properties

Platelets, Recovered, Pooled, in Additive Solution (Rec, Pool, AS) is a platelet component derived from donations of fresh *Whole blood*, the number of which is determined by national regulations and the system used, which contains most of the original platelet content in a therapeutically effective adult dose suspended in a mixture of plasma (30 to 40 per cent) and an additive solution (60 to 70 per cent).

Platelets, Rec, Pool, AS contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool, AS contains less than 1×10^{9} leucocytes.

Preparation

Platelets, Rec, Pool, AS is prepared from either pooled *Whole blood*-derived buffy coats or Platelets, Rec, SU prepared by the single centrifugation method.

Preparation from pooled Whole blood-derived buffy coats

A *Whole blood* unit, stored in conditions validated to maintain a temperature between +20°C and +24°C for up to 24 hours, is centrifuged so that the platelets are primarily sedimented to the buffy coat layer together with the leucocytes. The buffy coat is separated and further processed

so that, blood group-compatible buffy coats, the number of which is determined by national regulations and the system used, are pooled using a closed system and suspended in an additive solution. After careful mixing, the buffy coat pool is centrifuged (soft-spin) so that the platelets remain in the supernatant, but the red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet-containing supernatant is immediately transferred into an approved platelet storage bag using a closed system. This second processing step can either be done manually (separation of buffy coat pool by centrifugation, transfer, semi-automated expression) or automated (separation and expression of buffy coat pool during centrifugation).

Preparation from Platelets, Recovered, Single Units (single centrifugation method)

Blood group-compatible units of Platelets, Rec, SU, the number of which is determined by national regulations and the system used, prepared by the single centrifugation method, are pooled together with a bag of additive solution in a sterile manner into an approved platelet storage bag using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-4.

Table 5C-4

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	≥ 2×10^{11}	as determined by SPC
Residual leucocyte content per final unit [a]	< 1×10^{9}	as determined by SPC
Glucose measured at the end of the recommended shelf-life [b], or pH	Above Limit of Quantification (LoQ) [c]	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] Preferred replacement for pH measurement in table 5C-1, see Chapter 4.1.3 (Evidence level C)
[c] LoQ has to be determined per analytical method used

Storage and transport

As indicated for *Platelets, Recovered, SU.*

Labelling

As indicated for *Platelets, Recovered, SU* with the following addition:

- The number of donations combined to make the pool.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-5. Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution and Plasma

Definition and properties

Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution (Rec, Pool, LD-AS) is a leucocyte-depleted platelet component derived from fresh *Whole blood* donations, the number of which is determined by national regulations and the system used, which contains the majority of the original platelet content in a therapeutically effective adult dose, suspended in a mixture of plasma (30 to 40 per cent) and an additive solution (60 to 70 per cent).

Platelets, Rec, Pool, LD-AS contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool, LD-AS contains less than 1.0×10^{6} leucocytes.

Preparation

Platelets, Rec, Pool, LD-AS is prepared from either *Whole blood*-derived buffy coats or Platelets, Rec, SU prepared by the single centrifugation method, and is then leucocyte depleted by filtration. Pre-storage leucocyte filtration within 6 hours of preparation is recommended.

Preparation from pooled Whole blood-derived buffy coats

A whole blood unit, stored in conditions validated to maintain a temperature between +20°C and +24°C for up to 24 hours, is centrifuged so that the platelets are primarily sedimented to the buffy coat layer together with the leucocytes. The buffy coat is separated and further processed so that, blood group-compatible buffy coats, the number of which is determined by national regulations and the system used, are pooled in a sterile manner and suspended in an additive solution. After careful mixing, the buffy coat pool is centrifuged (soft-spin) so that the platelets remain in the supernatant, but the red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet-containing supernatant is filtered and transferred into an approved platelet storage bag using a closed system. This second processing step can either be done manually (separation of buffy coat pool by centrifugation, transfer, semi-automated expression) or automated (separation and expression of buffy coat pool during centrifugation).

Preparation from Platelets, Recovered, Single Units (single centrifugation method)

Blood group-compatible units of Platelets, Rec, SU, the number of which is determined by national regulations and the system used, prepared by the single centrifugation method, are pooled together with a bag of additive solution and immediately filtered in a sterile manner into an approved platelet storage bag using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-5.

Table 5C-5

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	≥ 2×10^{11}	as determined by SPC
Residual leucocyte content per final unit [a]	< 1×10^{6}	as determined by SPC
Glucose measured at the end of the recommended shelf-life [b], or pH	Above Limit of Quantification (LoQ) [c]	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] Preferred replacement for pH measurement in table 5C-1, see Chapter 4.1.3 (Evidence level C)
[c] LoQ has to be determined per analytical method used

Storage and transport

As indicated for *Platelets, Recovered, SU.*

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- Leucocyte-depleted;
- The number of donations combined to make the pool.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-6. Platelets, Recovered, Pooled, Pathogen-Reduced

Definition and properties

Platelets, Recovered, Pooled, Pathogen-Reduced (Pool, PR) is a leucocyte-depleted platelet component derived from fresh *Whole blood* donations, the number of which is determined by national regulations and the system used, which contains the majority of the original platelet content in a therapeutically effective adult dose suspended in plasma or a mixture of plasma (30 to 50 per cent) and an additive solution (50 to 70 per cent). Subsequently, the component is subjected to treatment with an approved and validated pathogen inactivation technology (PIT) before storage. Pools of up to 3 standard adult doses can be produced prior to PIT if validated.

Platelets, Pool, PR contains a minimum of 2×10^{11} platelets.

Platelets, Pool, PR contains less than 1.0×10^{6} leucocytes.

The PIT typically reduces the risk of infection with enveloped viruses (e.g. HBV, HCV, HIV) and with most bacteria (with the exception of bacterial spores) by at least one-thousand-fold.

Depending on the procedure, some PITs have been shown to inactivate lymphocytes and, if this is the case, irradiation to prevent transfusion-associated TA-GvHD is not required.

Preparation

Platelets, Pool, PR is prepared by pooling buffy coats or Platelets, Rec, SU prepared by the single centrifugation method from several *Whole blood* donations as described for *Platelets, Recovered, Pooled, Leucocyte-Depleted* and *Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution*.

The PIT is undertaken in accordance with the manufacturer's instructions.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-6.

In addition, a technical procedure should be in place to ensure that the PIT method has been performed correctly.

Measurement of the residual content of photosensitisers should be performed as part of the (re)validation of the component.

Table 5C-6

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	≥ 2×10^{11}	as determined by SPC
Residual leucocyte content per final unit [a]	< 1×10^{6}	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- The maximum storage time for *Platelets, Pool, PR* may be extended to 7 days depending on the PIT and on the type of additive solution.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- The unique identity number (the original donations contributing to the pool should be traceable and if multiple units are pooled prior to PIT each final component should have a unique component identity number).

Warnings

As indicated for *Platelets, Recovered, SU* with the following additions:

- Viral transmission of lipid-enveloped viruses (e.g. HBV HCV, HIV) is highly unlikely after PIT but transmission of non-lipid-enveloped viruses (such as HAV, Parvovirus B19) is possible depending on the technology used, despite careful donor selection and screening procedures.

Platelets, Pool, PR should not be used:

- When prepared by amotosalen treatment in for neonates undergoing phototherapy with devices that emit a peak energy wavelength less than 425 nm, and/or have a lower bound of the emission bandwidth <375 nm;
- For patients with a known allergy to the compounds used for, or generated by, the PIT.

Adverse reactions include:

- Anaphylaxis and allergic reactions, including allergy to the compounds used for, or generated by, the PIT.

C-7. Platelets, Apheresis

Definition and properties

Platelets, Apheresis (Aph) is a component obtained by platelet apheresis of a single donor using automated cell separation equipment, which contains platelets in a therapeutically effective adult dose suspended in plasma.

Platelets, Aph contains a minimum of 2×10^{11} platelets.

Platelets, Aph contains less than 1×10^{9} leucocytes.

Preparation

For preparation of Platelets, *Aph*, *Whole blood* is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and then the platelets are harvested.

For use in neonates and infants, *Platelets, Aph* can be divided into satellite units using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in table 5C-7.

Table 5C-7

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	Standard unit: $\geq 2 \times 10^{11}$ For use in neonates or infants: $\geq 0.5 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{9}$	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- *Platelets, Aph* should be collected and prepared in a functionally closed system if stored for more than 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- If two or more units are collected from the donor in one session, each component should have a unique component identity number;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-8. Platelets, Apheresis, Leucocyte-Depleted

Definition and properties

Platelets, Apheresis, Leucocyte-Depleted (Aph, LD) is a leucocyte-depleted platelet component obtained by platelet apheresis of a single donor using automated cell separation equipment, which contains platelets in a therapeutically effective adult dose suspended in plasma.

Platelets, Aph, LD contains a minimum of 2×10^{11} platelets.

Platelets, Aph, LD contains less than 1.0×10^{6} leucocytes.

Preparation

To prepare *Platelets, Aph, LD*, *Whole blood* is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and the platelets are then harvested. Centrifugation, filtration or other in-process steps are included in the process to reduce the number of contaminating leucocytes. Pre-storage leucocyte depletion is recommended (within 6 hours after preparation if performed by filtration).

For use in neonates and infants, *Platelets, Aph, LD* can be divided into satellite units using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-8.

Table 5C-8

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit [a]	Standard unit: $\geq 2 \times 10^{11}$ For use in neonates or infants: $\geq 0.5 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{9}$	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- *Platelets, Aph, LD* should be collected and prepared in a functionally closed system if stored for more than 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- If two or more units are collected from the donor in one session, each component should have a unique component identity number;
- Leucocyte-depleted;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-9. Platelets, Apheresis, in Additive Solution

Definition and properties

Platelets, Apheresis, in Additive Solution (Aph, AS) is a component obtained by platelet apheresis of a single donor using automated cell separation equipment, which contains platelets in a therapeutically effective adult dose suspended in a mixture of plasma (30 to 40 per cent) and an additive solution (60 to 70 per cent).

Platelets, Aph, AS contains a minimum of 2×10^{11} platelets.

Platelets, Aph, AS contains less than 1×10^{9} leucocytes.

Preparation

To prepare *Platelets, Aph, AS*, *Whole blood* is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and then the platelets are harvested. Platelets are stored in a combination of plasma and an appropriate additive solution.

For use in neonates and infants, *Platelets, Aph, AS* can be divided into satellite units using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-9.

Table 5C-9

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit[a]	Standard unit: ≥ 2×10^{11} For use in neonates or infants: ≥ 0.5×10^{11}	as determined by SPC
Residual leucocyte content per final unit [a]	< 1×10^{9}	as determined by SPC
Glucose measured at the end of the recommended shelf-life [b], or pH	Above Limit of Quantification (LoQ) [c]	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] Preferred replacement for pH measurement in table 5C-1, see Chapter 4.1.3 (Evidence level C)
[c] LoQ has to be determined per analytical method used

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- *Platelets, Aph, AS* should be collected and prepared in a functionally closed system if stored for more than 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- If two or more units are collected from the donor in one session, each component should have a unique component identity number;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU.*

C-10. Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution

Definition and properties

Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution (Aph, LD-AS) is a leucocyte-depleted platelet component obtained by platelet apheresis of a single donor using automated cell-separation equipment, which contains platelets in a therapeutically effective adult dose suspended in a mixture of plasma (30 to 40 per cent) and an additive solution (60 to 70 per cent).

Platelets, Aph, LD-AS contains a minimum of 2×10^{11} platelets.

Platelets, Aph, LD-AS contains less than 1.0×10^{6} leucocytes.

Preparation

To prepare *Platelets, Aph, LD-AS*, *Whole blood* is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and then the platelets are harvested. Platelets are stored in a combination of plasma and an appropriate nutrient solution. Centrifugation, filtration or other in-process steps are included in the process to reduce the number of contaminating leucocytes. Pre-storage leucocyte depletion is recommended (within 6 hours after preparation if performed by filtration).

For use in neonates and infants, *Platelets, Aph, LD-AS* can be divided into satellite units using a closed system.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in Table 5C-10.

Table 5C-10

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit[a]	Standard unit: $\geq 2 \times 10^{11}$ For use in neonates or infants: $\geq 0.5 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{6}$ per unit	as determined by SPC
Glucose measured at the end of the recommended shelf-life [b], or pH	Above Limit of Quantification (LoQ) [c]	as determined by SPC

[a] A minimum of 90 % of units tested should meet the required value.
[b] Preferred replacement for pH measurement in table 5C-1, see Chapter 4.1.3 (Evidence level C)
[c] LoQ has to be determined per analytical method used

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- *Platelets, Aph, LD-AS* should be collected and prepared in a functionally closed system if stored for more than 6 hours.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- If two or more units are collected from the donor in one session, each component should have a unique component identity number, leucocyte depleted;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU*.

C-11. Platelets, Apheresis, Pathogen-Reduced

Definition and properties

Platelets, Apheresis, Pathogen-Reduced (Aph, PR) is a platelet component obtained by platelet apheresis of a single donor using automated cell separation equipment, which contains platelets in a therapeutically effective adult dose suspended in plasma or a mixture of plasma (30 to 50 per cent) and an additive solution (50 to 70 per cent). Subsequently, the component is subjected to treatment with an approved and validated PIT before storage. Double or triple doses can be treated with PIT before being split.

Platelets, Aph, PR contains a minimum of 2×10^{11} platelets.

Platelets, Aph, PR contains less than 1.0×10^{6} leucocytes.

The PIT typically reduces the risk of infection by enveloped viruses (e.g. HBV, HCV, HIV) and most bacteria (with the exception of bacterial spores) by at least one-thousand-fold depending on the technology used.

Depending on the procedure, some PITs have been shown to inactivate lymphocytes and, if so, irradiation to prevent transfusion-associated TA-GvHD is not required.

Preparation

To prepare *Platelets, Aph, PR*, whole blood is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and then the platelets are harvested. Platelets are stored in plasma or a mixture of plasma (30 to 50 per cent) and an additive solution (50 to 70 per cent). Centrifugation, filtration or other in-process steps are included in the process to reduce the number of contaminating leucocytes.

The PIT is undertaken in accordance with the manufacturer's instructions.

Requirements and quality control

As indicated for *Platelets, Recovered, SU* except for the parameters specified in table 5C-11. In addition, a technical procedure should be in place to ensure that the PIT method has been performed correctly.

Measurement of the residual content of photosensitisers should be performed as part of the (re)validation of the component.

Table 5C-11

Parameter to be checked	Requirements	Frequency of control
Platelet content per final unit[a]	≥ 2×10^{11}	as determined by SPC
Residual leucocyte content per final unit[a]	< 1×10^{6}	as determined by SPC
Glucose measured at the end of the recommended shelf-life, or pH [b]	Above Limit of Quantification (LoQ) [c]	as determined by SPC

a A minimum of 90 % of units tested should meet the required value.

b Preferred replacement for pH measurement in table 5C-1, see Chapter 4.1.3 (Evidence level C)

c LoQ has to be determined per analytical method used

Storage and transport

As indicated for *Platelets, Recovered, SU* with the following addition:

- The maximum storage time for *Platelets, Aph, PR* may be extended to 7 days depending on the type of additive solution and the PIT.

Labelling

As indicated for *Platelets, Recovered, SU* with the following additions:

- If two or more units are collected from the donor in one session, each component should have a unique component identity number, leucocyte-depleted;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU* with the following additions:

- Viral transmission of lipid-enveloped viruses (e.g. HBV, HCV, HIV) is highly unlikely after the use of PIT but transmission of non-lipid-enveloped viruses (such as HAV, Parvovirus B19) is possible depending on the technology used, despite careful donor selection and screening procedures.

Platelets, Aph, PR should not be used:

- When prepared by amotosalen treatment for neonates undergoing phototherapy with devices that emit a peak energy wavelength less than 425 nm, and/or have a lower bound of the emission bandwidth <375 nm;
- For patients with a known allergy to the compounds used for, or generated by, the PIT.

Viral transmission and bacterial contamination (other than bacterial spores) is highly unlikely. Transmission of other pathogens that are not sensitive to PIT is possible.

C-12. Platelets, washed

Definition and properties

Platelets, washed, is derived from secondary processing of a platelet component involving sequential washing and re-suspension of platelets in saline or a platelet additive solution.

Most of the plasma and leucocytes are removed. The amount of residual plasma depends on the washing protocol.

Preparation

After centrifugation of the primary component and removal of the plasma the platelets are washed by sequential addition and removal of saline or an additive solution.

Requirements and quality control

As indicated for the starting component except that a reduction in platelet count of approximately 15 per cent is to be expected.

Storage and transport

As indicated for the starting component with the following change and addition:

- *Platelets, washed,* should be used within 24 hours of production. When an open system is used for washing, the storage time should be as short as possible after washing and should not exceed 6 hours.

Labelling

As indicated for the starting component with the following additions:

- Washed;
- Name of suspending or additive solution.

Warnings

As for the starting component with the removal of the statement not recommending use in plasma intolerance.

C-13. Platelets, Cryopreserved

Definition and properties

Platelets, Cryopreserved (Cryo) is a component prepared by the freezing of *platelet components* within 24 hours of collection, using a cryoprotectant.

Reconstituted *Platelets, Cryo* contains more than 50 per cent of the platelets contained in the original component.

The method facilitates extended storage of platelets from selected donors and of autologous platelets.

Preparation

Platelets, Cryo is prepared by secondary processing of *Platelets, Aph*, or *Platelets, Recovered*. The component is cryopreserved within 24 hours of collection using a cryoprotectant. *Platelets, Cryo* is usually prepared using DMSO (6 per cent *w*/*v*).

Before use, the platelets are thawed, washed (when appropriate) and resuspended in (autologous) plasma or in a suitable additive solution.

Requirements and quality control

As indicated for *Platelets, Aph* except for the parameters specified in Table 5C-12:

Table 5C-12

Parameter to be checked	Requirements	Frequency of control
Volume	50–200 mL	All units
Platelet content	> 50 % of the pre-freeze platelet content	All units

Platelets, Cryo when thawed will not swirl.

Storage and transport

Platelets in the frozen state should be constantly maintained at:

- ≤ −80°C, if stored in an electric freezer;
- ≤ −150°C, if stored in vapour-phase liquid nitrogen.

If storage will be extended for more than one year, storage at −150°C is preferred.

If transport in the frozen state is unavoidable, storage conditions should be maintained during transportation.

Thawed platelets should be used as soon as possible after thawing. If short-to-intermediate storage is required, the component should be kept between +20°C and +24°C.

Transportation of thawed platelets is limited by the short shelf-life of this component. During transportation, the temperature of thawed *Platelets, Cryo* should be kept as close as possible between +20°C and +24°C.

Labelling

As indicated for the starting component.

In addition, the following information should be shown on the label or contained in the component information leaflet, as appropriate and should be traceable for each frozen unit:

- The name and volume of the cryoprotective solution.

Labelling of the reconstituted component

After thawing and reconstitution, the previous date of expiry should be changed to the date (and time) of expiry of the thawed component, and the name and volume of the cryoprotective solution should be changed to the name and volume of the additive solution (if any).

Warnings

As indicated for the starting component with the following addition:

- Residual cryoprotectant (e.g. DMSO) can be toxic.

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Plasma components

	Component	Technical Information	Volume	Factor VIII	Fibrinogen	Other
D-1	Plasma, Fresh Frozen	Derived from Whole blood or Apheresis for transfusion or fractionation, frozen to maintain coagulation factor content	Stated volume ± 10 %	Average after freezing and thawing, ≥ 70 IU per 100 mL	Not stated	May be leucocyte-depleted
D-2	Plasma, Fresh Frozen, Pathogen-Reduced	Plasma, Fresh Frozen, treated with pathogen inactivation technology	Stated volume ± 10 %	Average after freezing and thawing, ≥ 50 IU per 100 mL	Average after processing, ≥60% of freshly collected unit	May be leucocyte-depleted
D-3	Cryoprecipitate	Contains cryoglobulin fraction of plasma by further processing and concentration of Plasma, Fresh Frozen	30–40 mL	≥ 70 IU per unit	≥ 140 mg per unit	May be leucocyte-depleted Factor VIII ≥ 70 IU and vWF > 100 IU per unit only required if using for treatment of haemophiliac or vWD patients
D-4	Cryoprecipitate, Pathogen-Reduced	Cryoprecipitate treated with pathogen inactivation technology	Depends on system used	≥ 50 IU per single unit	≥ 140 mg per single unit	Factor VIII ≥ 50 IU and vWF ≥ 100 IU per unit only required if using for treatment of haemophiliac or vWD patients
D-5	Plasma, Fresh Frozen, Cryoprecipitate-Depleted	Residual component following removal of cryoprecipitate	Stated volume ± 10 %	Not stated	Not stated	Levels of labile factors V and VIII and fibrinogen reduced

Part D. Plasma components

D-1. Plasma, Fresh Frozen

Definition and properties

Plasma, Fresh Frozen (FFP) is a component for transfusion or for fractionation, prepared either from *Whole blood* or from plasma collected by apheresis, frozen within a period of time and to a temperature that adequately maintains the labile coagulation factors in a functional state.

FFP used as human plasma for fractionation must comply with the specifications of the European Pharmacopoeia monograph *Human plasma for fractionation (0853)*.

FFP used for clinical transfusion should comply with the specifications as given in this section (Chapter 5, Part D).

It must contain, on average, 70 per cent or more of the content of factor VIII of the freshly collected plasma unit (Directive 2004/33/EC Annex V) and at least similar quantities of the other labile coagulation factors and naturally occurring inhibitors.

It should not contain irregular antibodies of clinical significance. If leucocyte-depleted, the component should contain less than 1×10^6 leucocytes.

Preparation

From Whole blood

Plasma is separated from *Whole blood* that has been collected using a blood bag with integral transfer packs employing hard-spin centrifugation with freezing commenced within 6 hours of collection or within a timeframe validated to result in a component meeting specification. An intermediate step involving preparation of platelet-rich plasma is also permissible.

Alternatively, plasma may be separated from *Whole blood* that, immediately after donation, has been cooled rapidly to maintain the temperature between +20°C and +24°C and is held at that temperature for up to 24 hours.

Freezing should take place in a system that allows complete freezing within one hour to a temperature below −25 °C. If FFP is to be prepared from a single-pack *Whole blood* donation, adequate precautions should be adopted to avoid microbial contamination.

By apheresis

FFP may be collected by apheresis. Freezing should commence either within 6 hours of collection or within a timeframe validated to result in a component meeting specification. Freezing should take place in a system that allows complete freezing within one hour to a temperature below −25°C.

Leucocyte depletion of the starting material and/or virus inactivation and/or quarantine is a requirement in some countries.

Quarantine FFP

Quarantine FFP can be released once the donor has been re-tested, at least for HBsAg, anti-HIV and anti-HCV, with negative results after a defined period of time that is designed to exclude the risk associated with the window period. A period of six months is generally applied. This may be reduced if NAT testing is performed.

Requirements and quality control

Table 5D-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9, Screening for markers of transfusion-transmissible infection).

Table 5D-1

Parameter to be checked	Requirements	Frequency of control
ABO, RhD [a, b]	Grouping only for clinical FFP	All units
Anti-HIV 1 & 2 [a]	Negative by approved screening test	All units
HBsAg [a]	Negative by approved screening test	All units
Anti-HCV [c]	Negative by approved screening test	All units
Volume [c]	Stated volume ± 10 %	as determined by SPC
Factor VIII [c]	Average (after freezing and thawing): not less than 70 IU factor VIII per 100 mL	as determined by SPC on units in the first month of storage
Residual cells [c]	Red cells: < 6.0×10^9/L Leucocytes: < 0.1×10^9/L Platelets: < 50×10^9/L	as determined by SPC
	If leucocyte-depleted: < 1×10^6 per final unit	as determined by SPC
Leakage	No leakage in any part of container. Requires visual inspection after pressure in a plasma extractor before freezing	All units
Visual changes	No abnormal colour or visible clots	All units

[a] Unless performed on the source whole blood.
[b] Not required if plasma for fractionation.
[c] A minimum of 90 % of units tested should meet the required value.

Storage and transport

The following storage times and temperatures are permitted:

- 36 months at −25°C or below;
- 3 months at between −18°C and −25°C.

The storage temperature should be maintained during transport and the receiving hospital blood bank should ensure that the component has remained frozen during transit.

Unless for immediate use, the packs should be transferred at once to storage at the recommended temperature.

Once thawed, the component should not be re-frozen and should be transfused as soon as possible. If delay is unavoidable, the component should be stored and should be used within 4 hours if maintained between +20°C and +24°C or 24 hours if stored between +2°C and +6 °C. For management of major bleeding, thawed FFP that has been stored between +2°C and +6 °C can be used for up to 5 days, but it should be borne in mind that extended post-thaw storage will result in a decline in the content of labile coagulation factors.

Labelling

The labelling should comply with relevant legislation and where in place international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate (Directive 2002/98/EC Annex III):

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;
- The unique identity number; if two or more units are collected from the donor in one session, each component should have a unique component identity number;
- The producer's identification;
- The ABO and RhD groups (only for clinical FFP);
- The date of expiry
- The storage temperature
- The name of the anticoagulant solution

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- Additional component information: leucodepleted, quarantined etc. (if appropriate);
- That the component should be administered through an approved blood administration set.

After thawing, the date of expiry should be changed to the appropriate date (and time) of expiry of the thawed component. The storage temperature should also be changed accordingly.

Warnings

Transfusion of ABO blood group-incompatible plasma may result in haemolytic transfusion reaction.

FFP should not be used in a patient with an intolerance to plasma proteins.

Before use, the component should be thawed in a properly controlled environment at +37°C and the integrity of the pack should be verified to exclude any defects or leakages. No insoluble cryoprecipitate should be visible on completion of the thaw procedure.

Adverse reactions include:

- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Transfusion-related acute lung injury (TRALI);
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;
- Sepsis due to inadvertent bacterial contamination;
- Transmission of other pathogens that are not tested for or recognised;
- Citrate toxicity in neonates and in patients with impaired liver function;
- Transfusion-associated circulatory overload;
- Anaphylaxis and allergic reactions.

D-2. Plasma, Fresh Frozen, Pathogen-Reduced

Definition and properties

Plasma, Fresh Frozen, Pathogen-Reduced (PR) is a component for transfusion prepared from plasma derived from *Whole blood* or apheresis plasma which is subjected to treatment with an approved and validated PIT and subsequent freezing within a period of time to a temperature that adequately maintains the labile coagulation factors in a functional state.

Plasma, Fresh Frozen, PR may be prepared from small pools of up to 12 individual donations if in accordance with national regulations and the specifications of the manufacturer of the PR system.

It contains, on average, about 50 to 70 per cent of the labile coagulation factors and naturally occurring inhibitors present in fresh unfrozen/thawed plasma.

The PIT typically reduces the risk of infection by enveloped viruses (e.g. HBV, HCV, HIV) by at least one-thousand-fold depending on the technology used.

Plasma, Fresh Frozen, PR should not contain irregular antibodies of clinical significance.

If leucocyte-depleted, the component should contain less than 1×10^6 leucocytes.

Preparation

Plasma, Fresh Frozen, PR is prepared from plasma obtained from *Whole blood* or collected by apheresis as described for *Plasma, Fresh Frozen*. The PIT can be applied either before or after freezing and thawing of the plasma.

The PIT should be undertaken in accordance with the manufacturer's instructions.

Requirements and quality control

As indicated for *Plasma, Fresh Frozen* except for the parameters specified in Table 5D-2.

Measurement of the residual content of photosensitisers should be performed as part of the (re)validation of the component.

Table 5D-2

Parameter to be checked	Requirements	Frequency of control
Factor VIII	Average: not less than 50 IU factor VIII per 100 mL	as determined by SPC on units in the first month of storage
Fibrinogen	Average (after-processing): ≥ 60 % of the potency of the freshly collected plasma unit	as determined by SPC on units in the first month of storage

Storage and transport

As for *Plasma, Fresh Frozen* with the following change:

- In order to preserve labile factors, *Plasma, Fresh Frozen, PR* should be used as soon as possible following thawing. It should not be re-frozen.

Labelling

As for *Plasma, Fresh Frozen* with the following addition:

- The name of the PIT used.

Warnings

As indicated for *Plasma, Fresh Frozen* with the following additions:

- Viral transmission of lipid-enveloped viruses (e.g. HBV, HCV, HIV) is highly unlikely after the use of PIT but transmission of non-lipid-enveloped viruses (such as HAV, Parvovirus B19) is possible depending on the technology used, despite careful donor selection and screening procedures.

Plasma, Fresh Frozen, PR should not be used:

- When prepared by amotosalen treatment for neonates undergoing phototherapy with devices that emit a peak energy wavelength less than 425 nm, and/or have a lower bound of the emission bandwidth < 375 nm;
- For patients with G6PD deficiency when the plasma is prepared by the methylene blue procedure;
- For patients with a known allergy to the compounds used for, or generated by, the PIT.

D-3. Cryoprecipitate

Definition and properties

Cryoprecipitate is a component containing the sedimented cryoglobulin fraction of plasma obtained by further processing of *Plasma, Fresh Frozen*.

It contains a major portion of the factor VIII, von Willebrand factor, fibrinogen, factor XIII and fibronectin present in freshly drawn and separated plasma.

Preparation

Plasma, Fresh Frozen is thawed, either overnight between +2°C and +6°C or by the rapid thaw-siphon thaw technique. After thawing, the component is re-centrifuged using a hard spin at the same temperature. The supernatant cryoprecipitate-poor plasma is then partially removed. The sedimented cryoprecipitate is then rapidly frozen.

When *Cryoprecipitate* is prepared from *Whole blood*-derived plasma, the maximal final volume of the component is 40 mL. Pools of cryoprecipitate may be prepared.

Alternatively, *Plasma, Fresh Frozen* obtained by apheresis may be used as the starting material and the final component can be prepared using the same freezing/thawing/re-freezing technique.

Leucocyte depletion of the starting material and/or virus inactivation, and/or quarantine is a requirement in some countries.

Requirements and quality control

As indicated for *Plasma, Fresh Frozen* except for the parameters specified in Table 5D-3.

Table 5D-3

Parameter to be checked	Requirements	Frequency of control
Volume [a]	30–40 mL	All units
Factor VIII per final unit [a, b]	≥ 70 IU	Every 2 months: a. pool of 6 units of mixed blood groups during their first month of storage b. pool of 6 units of mixed blood groups during their last month of storage
Fibrinogen per final unit [a]	≥ 140 mg	1 % of all units with a minimum of 4 units per month
Von Willebrand factor per final unit [a, b]	> 100 IU	Every 2 months: a. pool of 6 units of mixed blood groups during their first month of storage b. pool of 6 units of mixed blood groups during their last month of storage

[a] This table is designed for quality control of cryoprecipitate obtained from FFP derived from one unit of whole blood. In the event that apheresis FFP is used as a starting material, the values may be different.

[b] Only required if component used for treatment of haemophilia and/or vWD patients respectively.

Storage and transport

As for *Plasma, Fresh Frozen* with the following additions and changes:

- The receiving hospital blood bank should ensure that the *Cryoprecipitate* has remained frozen during transit;
- Before use, *Cryoprecipitate* should be thawed in a properly controlled environment at + 37 °C immediately after removal from storage. Dissolution of the precipitate should be encouraged by careful manipulation during the thawing procedure;
- In order to preserve labile factors, *Cryoprecipitate* should be used as soon as possible following thawing. It should not be re-frozen.

Labelling

As indicated for *Plasma, Fresh Frozen.*

Warnings

As indicated for *Plasma, Fresh Frozen.*

D-4. Cryoprecipitate, Pathogen-Reduced

Definition and properties

Cryoprecipitate, Pathogen-Reduced is a component containing the sedimented cryoglobulin fraction of plasma obtained by further processing of *Plasma, Fresh Frozen*.

It is subjected to treatment with an approved and validated PIT and subsequent freezing within a period of time to a temperature that adequately maintains the labile coagulation factors in a functional state. It contains a major portion of the factor VIII, von Willebrand factor, fibrinogen, factor XIII and fibronectin present in freshly drawn and separated plasma.

The PIT typically reduces the risk of infection by enveloped viruses (e.g. HBV, HCV, HIV) by at least one thousand-fold.

Cryoprecipitate, PR used for clinical transfusion should comply with the specifications given in this monograph.

Preparation

Plasma, Fresh Frozen is thawed, either overnight between +2°C and +6°C or by the rapid thaw-siphon thaw technique. After thawing, the component is re-centrifuged using a hard spin at the same temperature. The supernatant cryoprecipitate-poor plasma is then partially removed. The sedimented cryoprecipitate is then either rapidly frozen and kept at less than −25°C until processing by the pathogen reduction method or subjected to the PIT process and then frozen.

Cryoprecipitate, PR is prepared from *Whole blood*-derived plasma or from apheresis-derived plasma.

For the PR step, units may be treated singly or pooled.

The PIT is undertaken in accordance with the manufacturer's instructions.

Requirements and quality control

As indicated for *Plasma, Fresh Frozen* except for the parameters specified in Table 5D-4.

Measurement of the residual content of photosensitisers should be performed as part of the (re)validation of the component.

Table 5D-4

Parameter to be checked	Requirements	Frequency of control
Volume	as per system used	All units
Factor VIII per final unit [a, b]	≥ 50 IU	Every 2 months a. pool of 6 units of mixed blood groups during their first month of storage b. pool of 6 units of mixed blood groups during their last month of storage
Fibrinogen per final unit [a]	≥ 140 mg	1 % of all units with a minimum of 4 units per month
Von Willebrand factor per final unit [a, b]	≥ 100 IU	Every batch for accurate labelling Every 2 months a. 4 units of small bags during their first month of storage b. 4 units of small bags during their last month of storage

The exact number of units to be tested could be determined by statistical process control.

[a] This table is designed for quality control of cryoprecipitate obtained from FFP derived from one unit of whole blood. In the event that apheresis FFP is used as a starting material, the values may be different.

[b] Only required if component used for treatment of haemophilia and/or vWD patients respectively.

Storage and transport

As indicated for *Plasma, Fresh Frozen* with the following additions and changes:

- Before use, *Cryoprecipitate, PR* should be thawed in a properly controlled environment at +37 °C immediately after removal from storage. Dissolution of the precipitate should be encouraged by careful manipulation during the thawing procedure;

- In order to preserve labile factors, *Cryoprecipitate, PR* should be used as soon as possible following thawing. It should not be re-frozen.

Labelling

As indicated for *Plasma, Fresh Frozen* with the following addition:

- Pathogen-reduced (indicating the name of the PIT used).

Warnings

As for *Plasma, Fresh Frozen* with the following addition:

- Viral transmission of lipid-enveloped viruses (e.g. HBV, HCV, HIV) is highly unlikely after the use of PIT but transmission of non-lipid-enveloped viruses (such as HAV, Parvovirus B19) is possible depending on the technology used, despite careful donor selection and screening procedures.

Cryoprecipitate, PR should not be used:

- When prepared by amotosalen treatment for neonates undergoing phototherapy with devices that emit a peak energy wavelength less than 425 nm, and/or have a lower bound of the emission bandwidth < 375 nm;
- For patients with G6PD deficiency when the plasma is prepared by the methylene blue procedure;
- For patients with a known allergy to the compounds used for, or generated by, the PIT.

D-5. Plasma, Fresh Frozen, Cryoprecipitate-Depleted

Definition and properties

Plasma, Fresh Frozen, Cryoprecipitate-Depleted is a component prepared from *Plasma, Fresh Frozen* by the removal of the cryoprecipitate.

Its content of albumin, immunoglobulins and coagulation factors is the same as that of *Plasma, Fresh Frozen*, except that the levels of the labile factors V and VIII are markedly reduced. The fibrinogen concentration is also reduced in comparison to *Plasma, Fresh Frozen*.

Preparation

Plasma, Fresh Frozen, Cryoprecipitate-Depleted is the by-product of the preparation of *Cryoprecipitate* from *Plasma, Fresh Frozen*.

Leucocyte depletion of the starting material and/or virus inactivation and/or quarantine is a requirement in some countries.

Requirements and quality control

As indicated for *Plasma, Fresh Frozen* (see Table 5D-1 above), with the exception of factor VIII.

Storage and transport

As for *Plasma, Fresh Frozen.*

Labelling

As for *Plasma, Fresh Frozen.*

Warnings

As for *Plasma, Fresh Frozen.*

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White cell components

	Component	Technical information	Volume	Granulocyte content	Other
E-1	Granulocytes, apheresis	Contains granulocytes suspended in plasma, obtained by apheresis of a single donor using automated cell separator	< 500 mL	At least 1.5–3.0 × 10^8 granulocytes/kg body weight of recipient	Significant content of red cells and platelets. should be irradiated
E-2	Granulocytes, pooled	Pool of buffy coats, the number of which is determined by national regulations and the system used, suspended in plasma or mixture of platelet additive solution and plasma	As defined locally	> 5 × 10^9 per unit	Significant content of red cells and platelets. should be irradiated

Part E. White cell components

E-1. Granulocytes, Apheresis

Definition and properties

Granulocytes, Apheresis is a component that contains granulocytes suspended in plasma and is obtained by apheresis of a single donor using automated cell separation equipment.

An adult therapeutic dose of *Granulocytes, Apheresis* contains between 1.5×10^8 and 3.0×10^8 granulocytes/kg body weight of the designated recipient.

Granulocytes, Apheresis has a significant content of red blood cells, lymphocytes and platelets.

Granulocytes, Apheresis should be irradiated.

Important notice

The clinical efficacy, indication and dosage of granulocyte transfusions have not been established. See concerns regarding risks to donor health in Chapter 2, Donor selection.

Preparation

Donors of *Granulocytes, Apheresis* require pre-treatment with corticosteroids and/or growth factors. *Granulocytes, Apheresis* is collected from a single donor by apheresis. Optimal collection yields require the use of a sedimenting agent, such as hydroxyethyl starch (HES), low molecular weight dextran or modified fluid gelatin.

Requirements and quality control

Table 5E-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9, Screening for markers of transfusion-transmissible infection).

Table 5E-1

Parameter to be checked	Requirements	Frequency of control
ABO, RhD	Grouping	All units
Anti-HIV 1 & 2	Negative by approved screening test	All units
HBsAg	Negative by approved screening test	All units
Anti-HCV	Negative by approved screening test	All units
HLA (when required)	Typing	As required
Volume	< 500 mL	All units

Granulocyte content per final unit	Achieve clinical dose: e.g. adult patient of 60 kg = 0.9–1.8 × 10^{10} granulocytes	All units

Storage and transport

Granulocytes, Apheresis is not suitable for storage and should be transfused as soon as possible after collection. If unavoidable, storage should be limited to the shortest possible period.

The unit should be transported to the user in a suitable container at between +20°C and +24°C, but without agitation.

Labelling

The labelling should comply with relevant legislation and where in place international agreements. The following information should be shown on the label or contained in the component information leaflet, as appropriate (Directive 2002/98/EC Annex III):

- The name of the blood component and the applicable product code;
- The volume or weight of the blood component;
- The unique identity number;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry (and time of expiry when required)
- The storage temperature
- The name of the anticoagulant solution, additive solutions and/or other agents

The following additional information should be shown on the label or contained in the component information leaflet, as appropriate:

- The date of donation;
- Additional component information: irradiated, etc. (if appropriate);
- Additional component information: CMV antibody negative etc. (as appropriate);
- The number of granulocytes;
- HLA type, if determined;
- That the component should be administered through an approved blood administration set.

Warnings

Because of the possibility of severe adverse effects associated with the collection (donor side-effects) and transfusion (recipient side-effects) of granulocytes, the goals of granulocyte transfusion should be defined clearly before a course of therapy is initiated.

As there is a significant content of red blood cells, compatibility of donor red cells with the designated recipient should be verified by suitable pre-transfusion testing. RhD-negative female recipients of child-bearing potential should not be transfused with granulocyte concentrates

from RhD-positive donors; if RhD-positive concentrates have to be used, the prevention of RhD immunisation by use of RhD-immunoglobulin should be considered.

Attention to HLA compatibility is also required for allo-immunised recipients.

Granulocytes, Apheresis should be irradiated.

CMV-seronegative components for CMV-seronegative recipients should be considered.

Administration through a micro-aggregate or leucocyte-reduction filter is contraindicated.

The risk of adverse reactions is increased with concomitant administration of amphotericin B.

Adverse reactions include:

- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Allo-immunisation against red cell antigens, HLA, HPA and HNA;
- Transfusion-related acute lung injury (TRALI);
- Post-transfusion purpura;
- Sepsis due to inadvertent bacterial contamination;
- Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures;
- Syphilis transmission;
- Protozoal transmission (e.g. malaria, toxoplasmosis) may occur in rare instances;
- Transmission of other pathogens that are not tested for or recognised;
- Citrate intoxication in neonates and in patients with impaired liver function;
- Accumulation of HES in multi-exposed patients.

E-2. Granulocytes, Pooled

Definition and properties

Granulocytes, Pooled is a component that contains granulocytes obtained by pooling of buffy coats, the number of which is determined by national regulations and the system used, suspended in either plasma or a mixture of platelet additive solution and plasma. *Granulocytes, Pooled* contains on average 11.0×10^9 granulocytes per unit. The recommended dose for an adult is 1-2 units daily and for a child 0.3×10^9 granulocytes/kg.

Granulocytes, Pooled has a significant content of red blood cells, lymphocytes and platelets.

Granulocytes, Pooled should be irradiated.

Preparation

One method of preparation involves pooling of up to 12 ABO matched buffy coats within 18 hours of donation with platelet additive solution added prior to centrifugation. The red cell residue, supernatant and granulocyte-rich layer (buffy coat) are separated. The buffy coat is then mixed with 70 mL of ABO-matched plasma from one of the donations.

An alternate method of preparation involves the use of the remaining cellular residue after preparation of *Platelets, Recovered, Pooled* from buffy coats. Two ABO-matched residues are

combined and diluted with saline prior to centrifugation. The red cell residue, supernatant and granulocyte rich layer (buffy coat) are separated. The buffy coat is used as such.

The component should be stored in a pack that allows gas exchange (i.e. a platelet pack).

Requirements and quality control

As indicated for *Granulocytes, Apheresis* except for the parameters specified in Table 5E-2.

Table 5E-2

Parameter to be checked	Requirements	Frequency of control
Volume	As defined locally	All units
Granulocyte content per final unit	> 5×10^9	All units

Storage and transport

As for *Granulocytes, Apheresis* with the following addition:

- At the very latest, transfusion should commence by midnight on the day following donation (day 1).

Labelling

As for *Granulocytes, Apheresis* with the following addition:

- The number of donations combined to make the pool.

Warnings

As for *Granulocytes, Apheresis*.

Chapter 6

Component monographs for intrauterine, neonatal and infant use

Part A. Components for intrauterine transfusions

A-1. Red Cells, Leucocyte-Depleted for Intrauterine Transfusion

A-2. Platelets, Leucocyte-Depleted for Intrauterine Transfusion

Part B. Components for neonatal exchange transfusion

B-1. Whole Blood, Leucocyte-Depleted for Exchange Transfusion

B-2. Whole Blood, Leucocyte-Depleted, Plasma Reduced for Exchange Transfusion

B-3. Red Cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma, for Exchange Transfusion

Part C. Components (small volume) for neonatal and infant transfusion

C-1. Red Cells for Neonatal and Infant Small-Volume Transfusion

6.0. Overview

Specially designed blood components are required for intrauterine and infant transfusions. The following factors should be considered when transfusing neonates: (1) smaller blood volume, (2) reduced metabolic capacity, (3) higher haematocrit and (4) an immature immunological system. All these aspects are particularly important in foetal transfusions and for small premature infants.

The components used should be fresh enough so that metabolic and haemostatic disturbances can be minimised. In particular, methods of preparation, administration of red cell components should be validated to ensure that the delivered potassium ion load is within acceptable limits.

ABO and Rh groups, as well as other antigens to which the mother has become sensitised, have to be taken into account when selecting components for intrauterine and neonatal use.

There is a significant risk of transfusion-associated graft versus host disease (TA-GvHD) and cytomegalovirus (CMV) transmission when a foetus or small infant is transfused. At-risk patients should receive cellular components selected or processed to minimise the risk of CMV transmission and, when appropriate, the components should also be irradiated. Pathogen inactivation technologies are an alternative to irradiation in prevention of TA-GvHD (see Chapter 4 Subsection 4.3.4).

The rate of transfusion should be carefully controlled to avoid excessive fluctuations in blood volume or potassium ion overload.

Exchange transfusion is a special type of massive transfusion. Components produced for this are also suitable for large-volume (massive) transfusion of neonates and small infants.

Consideration should be given to producing red cell components for these patients from donors who have screened negative for haemoglobin S.

There are specific national regulations or guidelines for pre-transfusion blood grouping and compatibility testing of neonates.

Preterm infants are amongst the most intensively transfused of all hospital patients and have potentially the longest post-transfusion survival. Therefore consideration should be given to minimising the number of donors that such infants are exposed to.

For top-up and small-volume red cell transfusions it is good practice to divide a component unit into several sub-batches. Many centres dedicate all the satellite units from one donation to a single patient. Except when irradiated and provided that transfusion rates are carefully controlled, there is no scientific or clinical evidence to restrict the shelf-life of these components.

For use in infants and neonates a standard fresh frozen plasma (FFP) component can be divided into approximately equal volumes in satellite packs, prior to freezing, by using a closed or functionally closed system. Otherwise, the monograph for Plasma, Fresh Frozen (Chapter 5, Section D-1) is applicable for neonatal FFP components and clinical indications for use of FFP in neonates are the same as those in older patients.

Apheresis-derived platelet components can be divided into satellite packs by using a closed system as for red cells and FFP.

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Component monographs for intrauterine, neonatal and infant transfusion

Monograph	Technical information	Maximum storage period (days)	Hb content (g/unit)	Other
A-1. Red cells, leucocyte-depleted for intrauterine transfusion	Prepared by removing and/or exchanging a proportion of plasma with another appropriate solution. The component should be irradiated before use.	5 Within 24 hours of irradiation	Locally defined	Hct 0.70–0.85

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Monograph	Technical information	Storage period Volume	Platelet content	Other
A-2. Platelets, leucocyte-depleted for intrauterine use	Platelets obtained from a single donor, either by apheresis or from whole blood, for intrauterine use. The platelets may be hyperconcentrated. The component should be irradiated before use.	As for source component. Should be used within 6 hours of any secondary concentration process.	50–60 mL	$45–85 \times 10^9$ per unit

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Monograph	Technical information	Maximum storage period (days)	Hb content (g/unit)	Other
B-1. Whole blood, leucocyte-depleted for exchange transfusion	A component for exchange or large volume transfusion of neonates. The component should be irradiated unless delay would compromise the clinical outcome.	5 Within 24 hours of irradiation	40	Hct as for WB
B-2. Whole blood, leucocyte-depleted, plasma-reduced for exchange transfusion	Whole blood, leucocyte-depleted for exchange transfusion with a proportion of the plasma removed. The component should be irradiated unless delay would compromise the clinical outcome.	5 Within 24 hours of irradiation	40	Hct as clinically prescribed or locally defined
B-3. Red cells, leucocyte-depleted, suspended in fresh frozen plasma, for exchange transfusion	Prepared from red cells, leucocyte-depleted with additive solution/plasma being removed and thawed FFP added to reach the clinically required Hct.	5 from day of collection of red cells Within 24 hours of irradiation	40	Hct as clinically prescribed or locally defined

	The component should be irradiated unless delay would compromise the clinical outcome.			

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Monograph	Technical information	Maximum storage period (days)	Hb content (g/unit)	Other
C.-1. Red cells for neonatal and infant small volume transfusion	Prepared by secondary processing of desired red cell component with division into a number of small volume satellite packs using a closed system. May be irradiated when clinically indicated.	Up to that of original component Storage period after irradiation as specified	40 (pre-split)	Volume 25–100 mL per unit

Part A. Component monographs used for intrauterine transfusion

A-1. Red Cells, Leucocyte-Depleted for Intrauterine Transfusion

Definition and properties

Red Cells, Leucocyte-Depleted for Intrauterine Transfusion (IUT) is a red cell component for intrauterine transfusion used to treat severe foetal anaemia.

Red Cells, IUT has a haematocrit (Ht) of 0.70 to 0.85.

Red Cells, IUT contains less than 1×10^6 leucocytes per original source component.

Preparation

Red Cells IUT is prepared by the secondary processing of *Whole Blood LD*, *Red Cells LD* or *Red Cells LD-AS*. In order to achieve the required haematocrit, the storage medium is partly removed and/or exchanged for another appropriate solution.

Red Cells, IUT should be compatible with both mother and foetus. In the event that the foetal blood group is not known, a type O RhD-negative donation should be selected unless the mother has blood group antibodies that necessitate the use of another blood group. The red cells should be antigen-negative for any relevant maternal allo-antibodies.

The component should not contain irregular antibodies of clinical significance.

Red Cells, IUT should be used within 5 days of donation.

Red Cells, IUT should be irradiated and used within 24 hours of irradiation.

Requirements and quality control

As indicated for the source component with the following additional requirements given in Table 6A-1.

Table 6A-1

Parameter to be checked	Requirements	Frequency of control
Haematocrit	0.70–0.85	All units

Storage and transport

The storage and transport conditions are as for the source components. The storage time should not be longer than 24 hours after concentration and irradiation. The component should be used within 5 days of donation.

Labelling

The additional and/or amended labelling requirements to those of the source component are:

- The relevant blood group phenotype if the maternal antibody is other than anti-RhD;
- The modified date and time of preparation;
- The modified date and time of expiry;
- The name of the anticoagulant or additive solution;
- Additional component information, e.g. irradiated, etc. (as appropriate);

- The volume or weight of the blood component;
- The haematocrit of the blood component.

Warnings

Compatibility of this component with maternal serum/plasma should be verified by suitable pre-transfusion testing.

The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume.

As the foetus is at increased risk of graft versus host disease, the component should be irradiated.

Adverse reactions

Note: although the component is given to the foetus, because of placental transfer adverse reactions may also affect the mother.

The general adverse reactions are outlined in the relevant source component monograph.

In addition, the foetus is especially vulnerable to:

- Cytomegalovirus infection;
- Citrate toxicity;
- Metabolic imbalance (e.g. hyperkalaemia);
- Transfusion-associated circulatory overload.

A-2. Platelets, Leucocyte-Depleted for Intrauterine Transfusion

Definition and properties

Platelets, Leucocyte-Depleted for Intrauterine Transfusion (IUT) is a platelet component for intrauterine transfusion used for the correction of severe thrombocytopaenia. It is produced from a single donor either by apheresis or from whole blood.

Platelets, IUT should be leucocyte-depleted, irradiated and may be hyper-concentrated.

Platelets, IUT contains 45 to 85 × 10^9 platelets (on average, 70 × 10^9) in 50 to 60 mL of suspension medium.

Preparation

Platelets, IUT is prepared either from *Platelets, Apheresis, LD* or by leucocyte-depletion of *Platelets, Pooled, Recovered* and, where appropriate, the donation is from an HPA-compatible donor.

The component can be concentrated if necessary by removing part of the supernatant solution by centrifugation. This should be followed by a 1-hour rest period.

If platelets obtained from the mother are to be transfused, then these should be depleted of plasma and re-suspended in an additive solution.

Platelets, IUT should be irradiated.

Requirements and quality control

As indicated for the source component, with the following additional requirements given in Table 6A-2.

Table 6A-2

Parameter to be checked	Requirements	Frequency of control
HPA [a]	Typing	When required
Volume	50–60 mL	All units
Platelet content	45–85 × 10^9 per unit	All units

[a] HPA typing of the selected donor, not of the individual component.

Storage and transport

Storage and transport requirements are as defined for the source component, but *Platelets, IUT* should be used within 6 hours after any secondary concentration process.

Labelling

The additional and/or amended labelling requirements to those of the source component *Platelets, IUT* are:

- If components are split for use in neonates and infants, each split should have a unique unit identity number that allows traceability to the source donation and to other subunits prepared from the same component;
- Additional component information e.g. irradiated, plasma- or supernatant-reduced, etc. (if appropriate);
- The volume or weight of the blood component;
- The platelet count;
- The date and time of expiry.

Warnings

As the foetus is at increased risk of graft versus host disease, the component should be irradiated.

The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume and possible bleeding after puncture should be monitored.

Adverse reactions

Note: Although the component is given to the foetus, because of placental transfer adverse reactions may also affect the mother.

The general adverse reactions are outlined in the relevant source component monograph.

In addition, the foetus is especially vulnerable to:

- Cytomegalovirus infection;
- Citrate toxicity;
- Transfusion-associated circulatory overload.

Part B. Component monographs used for neonatal exchange transfusion

B-1. Whole Blood, Leucocyte-Depleted for Exchange Transfusion

Definition and properties

Whole Blood, Leucocyte-Depleted for Exchange Transfusion (ET) is a form of *Whole Blood, LD* with the properties as defined in the source monograph. *Whole blood, ET* should be transfused within 5 days of donation. Exchange transfusion is a special type of massive transfusion.

Preparation

If the maternal antibody is anti-RhD, the component is prepared from type O RhD-negative red cells. If the maternal antibody is other than anti-RhD, red cells are selected that are antigen-negative for any relevant maternal allo-antibodies.

Whole Blood, ET should be irradiated:

- If there is a prior history of intrauterine transfusion;
- For all other patients, unless compelling clinical circumstances indicate that delay would compromise the clinical outcome.

Whole Blood, ET should be used within 24 hours of irradiation.

Requirements and quality control

As indicated for *Whole Blood, LD*.

Storage and transport

The storage and transport of *Whole Blood, ET* is as described in the monograph for *Whole Blood, LD*.

The storage time should not be longer than 24 hours after irradiation and 5 days from donation.

Labelling

Additional and/or amended labelling requirements to those of *Whole Blood, LD* are:

- Blood group phenotype, if the antibody is other than anti-RhD;
- The modified date and time of expiry;
- Additional component information, e.g. irradiated, etc. (as appropriate).

Warnings

Blood group compatibility with any maternal allo-antibodies is essential. The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume.

Adverse reactions

In addition to the adverse reactions identified for *Whole Blood, LD*, particular concerns in the context of newborns undergoing exchange transfusion are:

- Metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
- Thrombocytopaenia;
- Cytomegalovirus infection;
- Graft versus host disease, unless irradiated;
- Transfusion-associated circulatory overload;

- Haemolytic transfusion reaction;
- Hypothermia.

B-2. Whole Blood, Leucocyte-Depleted, Plasma Reduced for Exchange Transfusion

Definition and properties

Whole Blood, Leucocyte-Depleted, Plasma Reduced for Exchange Transfusion (PR, ET) is *Whole Blood, ET* with a proportion of the plasma removed. *Whole Blood, PR, ET* should be transfused within 5 days of donation. Exchange transfusion is a special type of massive transfusion.

Preparation

Whole Blood, LD is selected within 5 days from donation and a proportion of the plasma is removed to achieve a clinically prescribed haematocrit.

If the maternal antibody is anti-RhD, the component is prepared from a type O RhD-negative donation. If the maternal antibody is other than anti-RhD, red cells are selected that are antigen negative for any relevant maternal allo-antibodies.

Whole Blood, PR, ET should be irradiated:

- If there is a prior history of intrauterine transfusion;
- For all other patients, unless compelling clinical circumstances indicate that delay would compromise the clinical outcome. *Whole Blood, PR, ET* should be used within 24 hours of irradiation.

Requirements and quality control

As indicated for *Whole Blood, LD*, with the following additional requirements given in Table 6B-2.

Table 6B-2

Parameter to be checked	Requirements	Frequency of control
Haematocrit	As clinically prescribed or locally defined	All units

Storage and transport

The storage and transport of *Whole Blood, PR, ET* is as described in the monograph for *Whole Blood, LD*.

The storage time should not be longer than 24 hours after irradiation and 5 days from donation.

Labelling

Additional and/or amended labelling requirements to those of *Whole Blood, LD* are:

- Blood group phenotype, if the antibody is other than anti-RhD;
- The modified date and time of expiry;
- Additional component information, e.g. irradiated, haematocrit, etc. (as appropriate).

Warnings

Blood group compatibility with any maternal allo-antibodies is essential. The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume.

Adverse reactions

In addition to the adverse reactions identified for *Whole Blood, LD*, particular concerns in the context of newborns undergoing exchange transfusion are:

- Metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
- Thrombocytopaenia;
- Cytomegalovirus infection;
- Graft versus host disease, unless irradiated;
- Transfusion-associated circulatory overload;
- Haemolytic transfusion reaction;
- Hypothermia.

B-3. Red Cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma, for Exchange Transfusion

Definition and properties

Red Cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma, for Exchange Transfusion (Red Cells, in FFP, ET) is a reconstituted component derived from *Red Cells, LD* or *Red Cells, LD-AS* to which *Plasma, Fresh Frozen* is added. Exchange transfusion is a special type of massive transfusion.

Preparation

Red Cells, LD or *Red Cells, LD-AS* is selected within 5 days from collection for secondary processing. The supernatant containing the additive solution and/or plasma is removed after centrifugation, and then thawed fresh frozen plasma is added to reach the clinically required haematocrit.

If the maternal antibody is anti-RhD, the component is prepared from type O RhD-negative red cells. If the maternal antibody is other than anti-RhD, red cells are selected that are antigen-negative for any relevant maternal allo-antibodies. The red cells and FFP should be ABO-compatible with both mother and infant.

Red Cells, in FFP, ET should be irradiated:

- If there is a history of prior intrauterine transfusion;
- For all other patients, unless compelling clinical circumstances indicate that delay would compromise the clinical outcome.

Red Cells, in FFP, ET should be used within 24 hours of irradiation.

Requirements and quality control

As indicated for the source components (*Red Cells, LD*; *Red Cells, LD-AS* and *FFP*), with the following additional requirements given in Table 6B-3.

Table 6B-3

Parameter to be checked	Requirement	Frequency of control
Haematocrit	As clinically prescribed or locally defined	All units

Storage and transport

The storage and transport of *Red Cells, in FFP, ET* is as described in the monograph for *Red Cells, LD* or *Red Cells, LD-AS*.

In addition, storage time should not be longer than 24 hours after reconstitution and irradiation and 5 days from the red cell donation.

Labelling

The additional and/or amended labelling requirements to those of the reconstituting components are:

- A new unique identity number by which the source donation identity numbers should be traceable;
- The name of the blood component;
- The ABO and RhD group of the red cells;
- Blood group phenotype, if the antibody is other than anti-RhD;
- The date and time of preparation;
- The new date and time of expiry;
- Additional component information, e.g. irradiated, haematocrit, etc. (as appropriate).

Warnings

Compatibility of *Red Cells, in FFP, ET* with the intended recipient should be verified by suitable pre-transfusion testing. Blood group compatibility with any maternal antibodies is essential.

The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume.

Adverse reactions

The side-effects correspond to those of the two constituent components.

Particular concerns in the context of newborns undergoing exchange transfusion are:

- Metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
- Thrombocytopaenia;
- Cytomegalovirus infection;
- Graft versus host disease, unless irradiated;
- Transfusion-associated circulatory overload;
- Haemolytic transfusion reaction;
- Hypothermia.

Part C. Component (small volume) monographs for neonatal and infant transfusion

C-1. Red Cells for Neonatal and Infant Small-Volume Transfusion

Definition and properties

Red Cells for Neonatal and Infant Small-Volume Transfusion is a red cell component derived from *Red Cells, BCR*; *Red Cells, BCR-AS*; *Red Cells, LD*; or *Red Cells, LD-AS*, which is divided into satellite units.

The properties are those of the source component.

Preparation

Red Cells for Neonatal and Infant Small-Volume Transfusion is prepared by the secondary processing of *Red Cells, BCR*; *Red Cells, BCR-AS*; *Red Cells, LD*; or *Red Cells, LD-AS*. The selected component is divided into 3 to 8 satellite packs by using a closed or functionally closed system.

The component may be irradiated where clinically indicated.

Requirements and quality control

As indicated for the source components (*Red Cells, BCR*; *Red Cells, BCR-AS*; *Red Cells, LD*; or *Red Cells, LD-AS*), with the following additional requirements given in Table 6C-1.

Table 6C-1

Parameter to be checked	Requirement	Frequency of control
Volume	25–100 mL per unit	All units

Storage and transport

Storage and transport requirements are as described for the primary source red cell component.

The storage time should not exceed that of the original component.

The component may be irradiated at any time up to 28 days following collection as long as the component is transfused immediately following irradiation. If the irradiated component is to be stored then irradiation may be undertaken up to 14 days following collection and the component stored for up to 48 hours. This period may be extended to 14 days when effective mechanisms are in place to avoid such units being transfused in large volume and/or rapid transfusion clinical settings.

Labelling

The additional and/or amended labelling requirements to those of the primary red cell component are:

- If components are split for use in neonates and infants, each satellite pack should have a unique unit identity number which allows traceability to the source donation and to other subunits prepared from the same component;
- The name of the blood component;
- Additional component information e.g. irradiated, etc. (if appropriate);
- The volume or weight of the component;
- The date and time of expiry.

Warnings

Transfusion rates should be carefully controlled.

Red Cells for Neonatal and Infant Small-Volume Transfusion should not be used for rapid transfusion or large-volume transfusion, unless used within 5 days from the source red cell donation.

Adverse reactions

Adverse reactions are those of the primary component selected for secondary processing. In addition, of particular concern for infants and neonates are:

- Metabolic imbalance (e.g. hyperkalaemia in massive transfusion or if rapidly transfused);
- Citrate toxicity;
- Transfusion-associated circulatory overload;
- Cytomegalovirus infection;
- Graft versus host disease, unless the component is irradiated.

Chapter 7

Pre-deposit autologous donation

7.0. Overview

Pre-deposit autologous donation (PAD) refers to the transfusion of blood or blood components collected from an individual and transfused back to the same individual.

Autologous transfusion techniques are used to avoid allo-immune complications of blood transfusion, and to reduce the risk of transfusion-associated infections. As with other clinical interventions, the risks and benefits of the various autologous transfusion procedures need to be carefully considered before deciding whether to proceed in an individual patient. PAD may be useful in rare circumstances where compatible allogeneic blood is not available, e.g. antibodies to high-incidence antigens. There are a number of disadvantages and risks associated with the use of PAD. For this reason, and as a consequence of the introduction of Patient Blood Management approaches, its use is increasingly restricted in other clinical settings.

PAD involves the collection, processing and storage of autologous blood components in the weeks preceding surgery for reinfusion in the peri-operative period. Either whole blood or components collected by apheresis may be used. The incidence of severe adverse reactions and severe adverse events associated with the collection of autologous blood components has been shown to be significantly increased com- pared with allogeneic blood donors.

7.1. Selection of patients for PAD and blood collection

7.1.1 Role of the physician in charge of the patient

The physician responsible for the overall care of the patient, usually the anaesthetist or surgeon, should request the pre-operative collection.

This request should identify:

- The indication for PAD;
- The underlying diagnosis;
- The type and number of components required;
- The date and location of scheduled surgery.

The physician should inform the patient of the anticipated benefits, risks and constraints of PAD and allogeneic transfusion and that allogeneic transfusion may still be required.

Standards

7.1.1.1. PAD should be performed in or under the control of a blood establishment.

7.1.1.2. PAD should only be considered when there is a clear indication for it and when there is a strong likelihood that blood will be needed.

7.1.2 Role of the blood establishment physician

In general, the same donor selection criteria used for allogeneic whole blood and component donation should also apply to PAD and derived components. Exceptions may however be made in particular for age, body weight, haemoglobin level and, where appropriate, platelet count.

Standards

7.1.2.1. The physician in charge of blood collection has ultimate responsibility for ensuring that the patient's clinical condition allows PAD.

7.1.2.2. When autologous donation is contraindicated, the physician in charge of blood collection should inform the patient and the physician in charge of the patient.

7.1.2.3. Written informed consent must be obtained from the patient by the physician in charge of the blood collection, who should provide the patient with the following information:

- The reasons for requiring a medical history;
- The nature of the procedure and its risks and benefits;
- The possibility of deferral and the reasons why this might occur;
- The tests that are performed and why, and that a reactive test for mandatory microbiological markers may result in the destruction of the collected unit;
- The significance of 'informed consent';
- The possibility that the PAD may not suffice and that allogeneic transfusion may be additionally required;
- That unused blood is not transfused to other patients and will be discarded;
- In the case of a paediatric patient or where the individual is not legally competent to consent, the information should be provided both to the child, or the individual, and the parents or legal guardians who should give written informed consent.

7.1.3. Contraindications and deferral criteria for PAD

Appropriate autologous pre-deposit collection may be carried out safely in elderly patients. However, more careful consideration may need to be given in the case of a patient aged more than 70 years.

Serious cardiac disease, depending on the clinical setting of blood col- lection, is a relative contraindication and assessment by a cardiologist may be required. Patients with unstable angina, severe aortic stenosis or uncontrolled hypertension should not be considered.

In patients with a haemoglobin concentration between 100 and 110 g/L, PAD may be considered taking into account the aetiology of the anaemia and the collection schedule. Autologous pre-deposit collection should not be undertaken in patients with a haemoglobin concentration below 100 g/L.

Standards

7.1.3.1. PAD should not be performed in a patient with an active bacterial infection.

7.1.3.2. Patients with significant blood-borne infections, such as HIV, HBV and HCV, should not be included in a PAD programme unless compatible allogeneic blood is not available.

7.1.3.3. Haemoglobin levels should be measured before each collection.

7.1.4. Blood collection

Surgical admission and the day of the surgical procedure should, as far as possible, be guaranteed. Sufficient time to enable optimal collection of blood should be allowed before surgery, but should not exceed the storage time of the collected blood component.

Sufficient time should be given from the date and time of the final blood collection prior to surgery for the patient to make a full circulatory and volaemic recovery. This should preferably be 7 days with a minimum of 72 hours.

Iron and/or erythropoietin should be considered to raise the patient's haemoglobin in conjunction with PAD.

For patients undergoing double-unit red cell apheresis, shorter collection intervals can be accepted at the discretion of the blood establishment physician.

7.1.5. PAD in children

Children under 10 kg should not be included in a PAD programme. For children between 10 and 20 kg, the use of volume compensation solutions is usually needed.

Pre-deposit autologous collection may be considered in children undergoing harvesting of bone marrow and in exceptional cases whereby suitable allogeneic blood is not available for elective surgery. The child should understand the nature of the procedure and be willing to co-operate.

The maximum volume that can be drawn at each collection is 10 mL/kg or 12 per cent of the estimated blood volume. The volume of anticoagulant in the pack should be adjusted as required to maintain an appropriate ratio of blood to anticoagulant. Paediatric packs of 200 mL or 250 mL (available with small-gauge needles) should be used wherever possible. Adverse reactions related to blood collection, such as haemodynamic disturbances, occur significantly more often in children. Volume replacement with crystalloid solutions

reduces the rate of these adverse reactions.

7.2. Testing, processing, storage and distribution of PAD blood components

7.2.1. Blood group testing and screening for infectious disease

Standard

7.2.1.1. Blood group testing and screening for infectious disease should be carried out according to the minimum requirements for the equivalent allogeneic components.

7.2.2. Processing

Standard

7.2.2.1. Autologous blood should be processed as for the equivalent allogeneic components.

7.2.3. Labelling

Standards

7.2.3.1. 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).

7.2.3.2. In addition to the labelling information described for allogeneic components, labels on PAD must have:

- The statement: autologous donation;
- The statement: strictly reserved for;
- Family name and first name;
- Date of birth;
- Unique identity number of the patient.

7.2.4. Storage and handling

Transfusion of allogeneic blood components should normally only proceed after the relevant available autologous components have been issued and transfused.

Standards

7.2.4.1. Pre-deposit autologous blood components should be stored, transported and distributed under the same conditions as, but clearly separated from, the equivalent allogeneic components.

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

7.2.4.3. Untransfused autologous blood components should not be used for allogeneic transfusion or for plasma for fractionation.

7.3. Record keeping

Hospitals and blood establishments should ensure that the following records are retained for every patient in a PAD programme:

- The date and type of surgery;
- The name of the prescribing physician;
- The time of transfusion, specifying whether blood was used during surgery or post-operatively;
- The actual use of the prepared pre-operative autologous blood components;
- The concurrent use of peri-operative autologous transfusion techniques;
- The use of allogeneic blood components;
- The occurrence of any adverse reactions.

7.4. Audit

Blood establishments should audit the use of PAD, where it is provided on a regular basis.

Chapter 8

Immunohaematology

8.0. Overview

The aim of any immunohaematology laboratory is to perform the appropriate tests on the correct blood sample and to obtain accurate results to ensure that a compatible blood component is issued to the right patient. It is essential to obtain accurate results for tests such as ABO/ RhD typing and antibody screening on the donor and patient, as well as compatibility testing. Antibody screening is performed to detect clinically significant non-ABO red cell antibodies. Positive results of screening tests should be investigated fully to identify antibody specificity.

Errors at any stage of the performance of such tests can lead to transfusion of incompatible blood with significant adverse health effects to patients. These errors can be due to inadequate procedures leading to misidentification of samples from donors or patients, technical failures in testing or misinterpretation of results and transcription errors. Haemovigilance data indicate that, in some cases, a combination of factors contributes to error, with the original error being perpetuated or compounded by the lack of adequate procedural controls within the laboratory or at the bedside.

The implementation of a quality management system helps to reduce the number of technical, and more often procedural, errors made in laboratories. These include quality assurance measures such as the use of standard operating procedures, staff training, periodic assessment of the technical competence of staff, documentation and validation of techniques, reagents and equipment, procedures that monitor day-to-day reproducibility of test results and methods to detect errors in analytical procedures.

8.1. Requirements for samples

8.1.1. Identity of donors and donations

Standard

8.1.1.1. The procedure for blood collection must be designed to ensure that the identity of the donor is verified and recorded surely, and that the link between the donor and blood, blood components and blood samples is established clearly (Directive 2005/62/EC Annex 6.2.1).

8.1.2. Identity of patients

Standard

8.1.2.1. Documented criteria for safe patient identification and labelling should be in place. Where available, these should comply with national requirements.

8.1.3. Sample handling, retention and storage

Standards

8.1.3.1. The handling and storage of samples should follow the manufacturer's instructions.

8.1.3.2. A sample of the patient's plasma/serum used for compatibility testing and/or antibody screening should be retained for a period of time after a transfusion.

8.2. Selection of reagents and validation of methods

8.2.1. General requirements

Standards

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

8.2.1.2. There must be data confirming the suitability of any laboratory re- agents used in the testing of donor samples and blood component samples (Directive 2005/62/EC Annex 6.3.4).

8.2.1.3. Only test reagents that have been licensed or evaluated and considered suitable by a responsible national health authority should be used. In the EU, such reagents are considered as *in vitro* diagnostic devices and should be CE-marked. In-house manufactured reagents may be used for rare occasions (e.g. blood

group genotyping of high- or low-frequency antigens where commercial CE-marked reagents are not available) (GPG 6.5.6).

8.2.1.4. Regulation (EU) 2017/746 classifies ABO, Rh (D, C, E, c, e), K, Jk^a, Jk^b, Fy^a, Fy^b reagents as class D in Annex VIII. The manufacturers of such reagents should have a full quality system certified by an authorised body and should submit an application containing all the control results for each lot (GPG 6.5.7).

8.2.1.5. The qualification of reagents should detect deviations from the established minimal quality requirements (specifications) (see GPG 6.3.3).

8.2.1.6. Prospective purchasers should require potential suppliers to provide them with a certificate of analysis or evidence that individual lots meet defined acceptance criteria for the intended purpose. Each lot of reagent should be qualified by the purchaser to demonstrate suitability for its intended purpose within the system used for testing (GPG 6.3.9)

8.2.1.7. All techniques and modifications to techniques in use should be validated.

8.3. Quality control and quality assurance

8.3.1. Quality control

Quality-control procedures for immunohaematology may be divided into internal quality control and external quality assurance. Procedures should be in place for the use of all reagents, techniques, methods and equipment. Nonetheless even when this occurs there is still a possibility of incorrect results being generated. Either this can arise because of inadequacy of the method or, more often, operational errors such as inaccurate test performance or incorrect interpretations.

Standard

8.3.1.1. Quality-control procedures should be implemented for the reagents, techniques and equipment used for ABO, RhD and other blood-group antigen typing and detection and identification of antibodies. The frequency of the control is dependent on the method used. (GPG 6.5.8)

The frequency of control should be informed by a risk-based assessment, taking into consideration all relevant factors including the manufacturer's recommendations.

8.3.2. Internal quality control

Quality control of reagents and techniques

Quality-control procedures recommended are applied to the reagents used for manual and automated techniques. However, reagents for automated instruments are generally specific for that instrument.

Each new lot should be tested for control against specifications.

For antigen testing quality controls should include positive, preferably heterozygous, and negative controls. For antibody testing, a positive, preferably weak, control is included.

The controls should be carried out with each test series or at least once on the day of use, provided the same reagents are used throughout.

Maintenance and Quality control of equipment

Equipment used (in particular centrifuges, automatic cell washers, incubators, refrigerators and freezers) should undergo regular maintenance and quality control in accordance with manufacturers' instructions.

Equipment for automated blood grouping should also be systematically controlled in accordance with the manufacturer's instructions.

8.3.3. External quality assurance (proficiency testing)

Standard

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

If no proficiency programme is available in a particular geographical area, the laboratory should arrange mutual proficiency testing with another laboratory. Although such external quality control is not as informative as participation in a comprehensive proficiency-testing programme, it is a valuable addition to the internal quality-control procedure.

8.4. Blood group testing

8.4.1. General requirements

Standards in this section apply to testing of donors, donations and patients, whether performed by serological or molecular methods. This includes both manual and automated testing.

Serological testing

Serological blood group testing involves the detection of red cell antigens and antibodies using specifically typed reagent red cells and antibodies. This is currently the standard procedure used in most immunohaematology laboratories.

Molecular testing

Molecular testing is becoming increasingly available and used as an alternate or supplemental technique to serological testing. In time, molecular testing may replace the need for routine serological testing. Current indications for molecular typing include (but not limited to) the following situations:

- Where serological testing renders unclear results;
- Where there is a suspicion of weak antigens or variants (within ABO, RHD, RHCE, JK, FY);
- Where serological reagents directed to specific antigens do not exist or are not readily available.
- Antenatal testing to identify pregnancies/foetuses at risk of haemolytic disease of the foetus and newborn (HDFN).

It can also be useful in chronically -transfused patients in order to determine their red cell phenotype and the selection of phenotyped red cell components.

Testing can be undertaken on samples from blood, amniocentesis, biopsy of chorionic villi, and plasma.

Molecular investigations may be carried out at regional, national or international laboratories. Before ordering such typing, information on how to handle and ship samples, material or prepared DNA should be requested.

Standards

8.4.1.1. Blood group testing should be undertaken in accordance with the instructions provided by the manufacturer of the reagents and kits.

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

8.4.2. Blood group testing of blood donors and donations

Standards

8.4.2.1. 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).

8.4.2.2. 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).

ABO and RhD typing

Standards

8.4.2.3. The ABO and RhD labelling of blood components of all first-time donors should be based upon the results of two independent ABO and RhD tests. At least one of the ABO tests should include reverse grouping.

8.4.2.4. A positive RhD test should lead to labelling of the unit as 'RhD positive'. Components should be labelled as 'RhD negative' only if the donor has tested negative for RhD using appropriate reagents or tests specifically selected to detect r e l e v a n t weak D and D variants.

8.4.2.5. ABO and RhD testing should be performed on all donations except for plasma intended only for fractionation.

Additional phenotyping

Standard

8.4.2.6. If additional typing for non-ABO and RhD antigens is performed then, before the result of the confirmed phenotype is printed on the label, a test should be done at least twice using two different samples collected from two different donations. The results should be linked to the donor record.

Unconfirmed results may be printed on the label, but should be clearly differentiated from confirmed results in order to avoid confusion. Such unconfirmed results should be used only to select red cell units for patients and the phenotype of the red cell unit should be confirmed prior to transfusion where the patient has the corresponding antibody. Typing may be determined by phenotyping or genotyping.

Reconfirmation

Standards

8.4.2.7. The ABO and RhD blood group should be verified on each subsequent donation and a comparison should be made with the historically determined blood group. This is not required for plasma intended only for fractionation.

8.4.2.8. If a discrepancy with the historical result is found, the applicable blood components should not be released until the discrepancy is unequivocally resolved.

Antibody screening and identification

Standard

8.4.2.9. All first-time donors as well as repeat and regular donors with a history of pregnancy or transfusions since the last donation should be tested for clinically significant irregular red cell antibodies.

Donors with antibodies

Blood establishments should have policies in place to investigate positive red cell antibody screening tests in donors in order to determine the management of the donation and the donor.

Positive direct antiglobulin test (DAT)

A positive DAT result will generate positive compatibility test results (when using antiglobulin technique) and possible shortened erythrocyte survival after transfusion. Therefore, red cell components identified during compatibility testing using an antiglobulin technique as having a positive DAT should be discarded.

8.4.3. Blood group testing of patients

ABO and RhD typing

Standard

8.4.3.1. The ABO and RhD blood group and, when needed, other blood types should be determined on the patient's blood sample before issuing components for transfusion. In an emergency, when a delay may be life-threatening, components may be issued before all results of grouping and antibody screening are completed. In these situations, testing should be completed as soon as possible.

Antibody screening and identification

Standards

8.4.3.2. The laboratory should have a reliable and validated procedure for blood grouping and antibody detection that includes an effective mechanism to verify the accuracy of the data at the time of issuing a report on the blood group and other test findings for inclusion in the patient's record.

8.4.3.3. Sufficiently sensitive techniques for the detection of clinically significant red cell allo-antibodies should be used, including reagent red cells that cover all appropriate antigens, preferably with homozygous expression for the most clinically significant allo-antibodies.

8.5. Pre-transfusion testing

8.5.1. General requirements

The purpose of pre-transfusion testing is to select compatible blood components that will survive normally in the circulation and to avoid clinically significant haemolysis of red blood cells during or after transfusion. Pre-transfusion testing involves ABO and RhD testing of the potential recipient along with screening for red cell antibodies and when necessary, identification of detected antibodies. For red cell components, a compatibility test will then be performed to ensure that the selected component is suitable for the intended recipient.

Compatibility might be assured by one of the following;

- Testing for compatibility between the component and the patient normally using an antiglobulin technique;
- An 'immediate spin' crossmatch which aims to exclude ABO incompatibility;
- Electronic release of the component whereby the compatibility is determined using dedicated and validated computer software.

The most appropriate method to achieve compatibility will be determined by the results of blood group and antibody testing on the current sample, the results of previous testing where available and the clinical urgency of the transfusion.

Antiglobulin crossmatch

The principle of antiglobulin crossmatch is to test donor red cells with the recipient's plasma/serum, with subsequent addition of anti-human globulin reagent to detect any antibody coating of the donor red cells. This test is the main component of a full serologic crossmatch and is typically performed in patients with clinically significant red cell antibodies.

Information on pre-transfusion control at the patient's bedside is provided in Chapter 11 of this *Guide*.

Standards

8.5.1.1. Compatibility between red cell components and the recipient's plasma/serum should be assured for transfusions. Sufficiently sensitive techniques for the detection of clinically significant red cell allo-antibodies should be used.

8.5.1.2. Sample validity rules should be defined to identify the acceptable age of a pre-transfusion sample that can be used for the purpose of compatibility testing and release of red cell components for transfusion.

8.5.1.3. Compatibility testing should be carried out on a sample taken no more than 3 days before the proposed transfusion for patients who have been transfused or have become pregnant during the last 3 months.

In patients with autoantibodies or on treatments that interfere with pre-transfusion testing (e.g. monoclonal antibody therapy), reduced frequency of antibody investigation may be considered if the patient is clinically stable and has formed no alloantibodies. The decision should be made in consultation between a transfusion medicine specialist, the laboratory director and the patient's clinician and be informed by a risk assessment.

8.5.1.4. An antiglobulin crossmatch should be performed if clinically significant red cell allo-antibodies are suspected or have been identified by current or previous testing.

8.5.1.5. Laboratories should maintain records of the tests performed and of the destination of all units handled (including the identity of the patient).

8.5.2. Type and screen procedure

The type and screen procedure tests for the ABO-RhD type of the patient and screens for clinically significant antibodies. A type and screen procedure is commonly performed for patients where there is an anticipation that blood might be transfused such that the pre-transfusion sample is received and tested in advance of the planned procedure. In the event that the red cell antibody screen is negative and

the patient has no known history of clinically significant antibodies, red cell components may be issued for transfusion on request using either an 'immediate spin' crossmatch or an electronic release system. If the patient has clinically significant antibodies, anti-globulin crossmatch testing should be completed before issuing red cell components.

8.5.3. Electronic release

Electronic release systems utilise computer technology to assure compatibility between the component and the recipient. Such systems need to be carefully designed and validated prior to introduction. An essential pre-requisite is that the system should not allow the issue of ABO-incompatible red cells.

Standards

8.5.3.1. A type and screen procedure may be used as a replacement for anti-globulin crossmatch testing if the patient has no known history of clinically significant antibodies and antibody screening has not detected clinically significant red cell antibodies.

8.5.3.2. The antibody screening procedure should include the use of reagent red cells that cover all appropriate, clinically significant antigens (preferably with homozygous expression).

8.5.3.3. Electronic release systems should utilise a reliable, computerised and validated procedure that ensures compatibility between the donor red blood cells and recipient plasma.

8.5.4. Selection of red cells

Transfusion support for patients with red cell allo-antibodies.

Standard

8.5.4.1. Whenever possible, red cell components that lack the corresponding antigens should be selected for transfusion, and an antiglobulin crossmatch, or equivalent procedure, between donor red cells and recipient plasma/serum should be undertaken before issuing red cell components for transfusion.

8.5.5. Additional considerations

Use of extended red cell antigen matching to avoid allo-immunisation

Chronically transfused patients are at increased risk of developing red cell allo-antibodies. Consideration might be given to providing red cell components matched for additional antigens to avoid this occurring. This might also apply to women of childbearing age when selection of red cell components lacking clinically important antigens could be considered to avoid the future risk of haemolytic disease of the foetus and newborn.

Neonates and Intrauterine Transfusion (IUT)

Red cell antigens to which the mother has been immunised have to be taken into account when selecting red cell components for the neonate or IUT.

Emergencies and requirement for matching

RhD matching in emergencies

Standard

8.5.5.1. Non-RhD-immunised RhD-negative men, and women that no longer have childbearing potential, may be transfused with RhD positive red cells if necessary. Hospital blood banks should have a policy in place to guide when this may occur.

Massive transfusion in immunised patients

In case of ongoing massive bleeding requiring repeated transfusion of red cells to immunised patients, red cells lacking corresponding antigens may become unavailable in requested numbers. Depending on the clinical status of the patient, transfusion of units positive for the corresponding antigens may be necessary.

Chapter 9

Screening for markers of transfusion- transmissible infection

9.0. Overview

In combination with donor education, judicious donor selection and pathogen inactivation technologies, effective testing of blood donations for markers of transfusion-transmissible infection (TTI) is a pivotal blood safety strategy. It is essential to obtain accurate and timely results for appropriate markers of infectious agents transmissible by transfused blood products, in order to safeguard the health of recipients of blood and blood components. Selection of licensed, appropriate, validated screening and confirmatory tests should meet the applicable national standards. Testing algorithms need to be designed in the context of the epidemiology of the local donor population, as this influences pre-test probability of an accurate result, and test performance.

Current tests for markers of transfusion-transmissible infection are based on the detection of relevant antigens and/or antibodies usually in a combined assay, and viral nucleic acid.

- Screening tests are usually easy to perform, suitable for testing many samples, and are selected to optimise sensitivity. These assays should have high enough specificity to avoid undue loss of donations, and potentially donors, due to non-specific reactivity.
- Supplementary tests can be performed in addition to screening tests. These tests usually have similar sensitivity and specificity to the screening tests, although often use different detection targets in order to maximise utility of the combined assays. When used in combination with the screening test, a supplemental test improves diagnostic certainty.
- Confirmatory tests should have high specificity and thereby further support diagnostic certainty. They are usually performed in specialised or referral laboratories. Ideally confirmatory tests should be as sensitive as, and more specific than, those used for screening, although this is not always the case. Some screening tests are more sensitive than the available confirmatory tests.
- A combination of screening and supplementary tests may be sufficient to exclude the majority of false positive results and hence be considered equivalent to a confirmatory test. Donations showing repeatedly reactive results in any screening test need to be subjected to confirmatory testing in order to determine the true status of the donor. A confirmed positive result means that it is highly likely that the sample is from someone who has the infectious disease.

It is recommended that algorithms be developed nationally to enable the appropriate and consistent investigation and resolution of reactivity on the screening assay. In the case of confirmed positive results, appropriate donor management should take place, including the provision of information to the donor and follow-up procedures.

Quality assurance for screening and confirmatory tests for infectious markers is particularly important and implies both general and specific approaches. Only tests that have been licensed or evaluated and considered suitable by the relevant authority(ies) should be used.

There should be special emphasis on training of staff, assessment of staff competency, maintenance and calibration of equipment, and the monitoring of the storage conditions of donor samples, test materials and reagents, together with documentation of all of these actions.

9.1. Selection of infectious marker tests and validation of methods

9.1.1. General requirements

Tests include both serological and molecular tests (using nucleic acid amplification techniques, i.e. NAT) which can be performed in a manual or automated manner. In general, tests are intended/validated to be applied as either screening or confirmatory assays, but not suitable for use in both settings.

Standards

9.1.1.1. Only tests that have been licensed or evaluated and considered suitable by the responsible health

authorities can be used. In the EU, these reagents are considered as *in vitro* diagnostic devices and must be in accordance with Regulation (EU) 2017/746.

9.1.1.2. There must be data confirming the suitability of any laboratory reagents used in the testing of donor samples and blood component samples (Directive 2005/62/EC Annex 6.3.4).

9.1.1.3. TTI screening tests should be performed in accordance with the instructions provided by the manufacturers of the reagents and test kits.

9.1.1.4. Serological testing should be routinely performed on samples transferred directly into the analyser from the original sample tube or aliquoted in a fully automated environment. Secondary aliquot samples may be used for NAT testing of mini-pools of individual samples (GPG 6.4.4).

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

9.1.1.6. All laboratory assays and test systems for TTI marker screening, including any upgrades from the manufacturer, used by blood establishments should be validated before introduction to ensure compliance with the intended use of the test.

9.1.1.7. Correct determination of negative and positive controls, as provided by and in accordance with the manufacturer's instructions, is a minimum requirement.

9.1.1.8. There must be clearly defined procedures to resolve discrepant results and ensure that 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 be stored separately in a dedicated environment (Directive 2005/62/EC Annex 6.3.3).

9.1.1.9. Initially reactive samples should be re-tested in duplicate. If any of the repeat tests are reactive, then the sample is deemed repeatedly reactive. The donation linked to the reactive sample should not be used for transfusion or the manufacture of medicinal products unless allowed by national regulations.

9.1.1.10. Algorithms to enable consistent resolution of repeatedly reactive samples and linked donations should be in place.

9.1.1.11. In the event that a repeatedly reactive sample is confirmed positive, the donor should be notified and a further sample should be obtained to reconfirm the results and the identity of the donor or alternatively the donor is referred to an external clinician for confirmation.

9.1.1.12. Appropriate confirmatory testing must take place. In case of con- firmed 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).

It is recommended that initial and repeat reactivity rates and confirmed positive results of screening for TTIs and epidemiological data be collected and monitored at least on a national level. This will allow international comparisons to be made.

9.2. Requirements for samples

921. Identity of donors and donations

Standard

9.2.1.1. The procedure for blood collection must be designed to ensure that the identity of the donor is verified and recorded surely, and that the link between the donor and blood, blood components and blood samples is established clearly (Directive 2005/62/EC Annex 6.2.1).

922. Sample handling and storage

Standards

9.2.2.1. The handling and storage of samples should follow the reagent and or device manufacturer's instructions.

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

When donor samples are archived for possible future lookback investigations, the storage conditions should preserve their integrity and the sample should be demonstrated to be suitable for the testing systems that will be used.

9.3. Quality control and quality assurance

The specific approach to the quality of the screening process should rely on the following categories of measures:

- Batch pre-acceptance testing (BPAT) of new manufacturer's lots of kits should be performed as an additional measure of quality control;
- Regular review of the results of the screening programme, taking into account results for individual batches of reagents, and assessing results of testing of control samples and of specificity;
- Process validation and revalidation should be undertaken using a panel of samples that has been established by comparison with available standards;
- External proficiency exercises, ideally as part of an external quality assurance programme, involving the testing of a panel of samples circulated to laboratories supplied by an approved proficiency testing provider.

The collection and review of these data should be used to monitor test performances.

9.3.1. Quality control

The quality control measures for TTI markers can be divided into internal quality control and external quality assurance programmes. Procedures should be in place for the use of all reagents, techniques, methods and equipment. Nonetheless even when this occurs there is still a possibility of incorrect results being generated. This can arise either because of inadequacy of the method or, more often, operational errors such as inaccurate test performance or incorrect interpretations.

9.3.2 Internal quality control

Quality control of reagents and techniques

Quality control procedures recommended are applied to TTI marker screening tests. For those performed on automated instruments, these are generally specific for that instrument. Each new lot should be tested for control against specifications. It is further recommended that the tests include an external weak positive control in order to allow for statistical process controls.

The controls should be carried out with each test series or at least once a day provided the same lot numbers of reagents are used throughout.

Standards

9.3.2.1. Appropriate quality control measures should be in place when screening for infectious markers. The frequency of testing of the controls is dependent on the method used. Where appropriate the blood establishment should define 'run' in procedures. These should at least meet requirements set by manufacturers of the instruments.

Quality Control testing should include a weak positive control for each plate or run. Where possible, the weak positive control should not be the one provided by the manufacturer.

Maintenance and Quality control of equipment

Equipment used (in particular centrifuges, refrigerators and freezers) should undergo regular maintenance and quality control in accordance with the manufacturers' instructions. Equipment for automated screening should also have system controls in accordance with the manufacturer's instructions.

9.3.3. External quality assurance (proficiency testing)

Standards

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

6.3.5).

9.4. Confirmatory testing, donor notification and lookback

9.4.1. General requirements

Standards

9.4.1.1. Repeat reactive samples in TTI screening tests require confirmatory testing performed by an authorised laboratory.

9.4.1.2. The results of confirmatory testing that present evidence of ongoing infection should be discussed with the donor and the donor should be deferred from donation and referred for appropriate care.

9.4.1.3. If a confirmed infection by HBV, HCV or HIV or, where appropriate another agent, is demonstrated on testing of a repeat donor, the blood establishment should undertake a look-back procedure to identify previous potentially infectious donations. The look-back procedure should ensure that:

- The blood establishment informs the hospital in writing about the incident and advises the hospital to trace the recipient(s) of the implicated blood component(s) and to inform the treating physician about the potentially infectious transfusion;
- The relevant organisation that carried out plasma fractionation is notified;
- If the recipient is confirmed to be positive for the given infection, the incident is reported to the national haemovigilance system and/or competent authority.

9.5. Classification of TTI testing

9.5.1. Mandatory testing requirements

Standards

9.5.1.1. 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).

9.5.1.2. The minimum mandatory serological blood donor screening tests are: antibody to HIV-1 (anti-HIV-1) and HIV-2 (anti-HIV-2) including outlying types (e.g. HIV-1 type O), antibody to hepatitis C virus (anti- HCV) and hepatitis B surface antigen (HBsAg).

9.5.1.3. Appropriate quality control measures should be in place for the mandatory serological blood donor screening tests (See 9.3.2.1 above)

The approaches currently used to confirm HIV or HCV infection consist of the use of a nationally established algorithm, which may include an alternative immunoassay (IA), western blot or recombinant immunoblots. Tests for antigens and the use of nucleic acid amplification techniques may be of value in the interpretation of uncertain screening test results. The positive confirmatory test should be repeated on an additional sample taken as soon as possible and not later than 4 weeks after the first sample. Confirmation of HBV infection is usually based on specific HBsAg neutralisation but anti-HBc and HBV NAT are also helpful in defining the infection status of the donor. The stage of infection of the donor may be determined using anti-HBc (total and IgM-specific) and HBe antigen/ antibody (HBeAg/anti-HBe) testing results. It should be noted that following hepatitis B immunisation, a transient positive HBsAg result may be obtained and this can be identified by follow-up HBsAg testing of the donor and/or use of HBV NAT on the donor.

9.5.2. Nucleic acid amplification techniques (NAT)

Standards

9.5.2.1. If screening of blood donations by NAT, either by testing individual donations or in mini-pools, is required by national authorities for the release of blood components, the NAT assays should be performed in accordance with the instructions provided by the manufacturers of the reagents and test kits. Where testing in mini-pools is performed, a risk assessment should be undertaken which takes into consideration the population prevalence of the TTI and other factors which impact residual risk. This information should be used in conjunction with the manufacturer's instructions to determine the size of the mini pool .

9.5.2.2. If NAT is performed by assembling various samples in mini-pools, a thoroughly validated system of labelling/identification of samples, a validated strategy and pooling process and a validated algorithm to re-assign pool results to individual donations should be in place.

9.5.2.3. Appropriate quality control measures should be in place for NAT testing (See 9.3.2.1 above)

9.5.3. Additional screening

National authorities may, taking into account the epidemiological situation in any given region or country, also require additional testing for other agents or markers. Such tests may include:

- *Treponema pallidum* haemagglutination assay (TPHA);
- IA ELISA for syphilis;
- Antibody to human T-cell lymphotropic virus types 1 (anti-HTLV 1) and 2 (anti-HTLV 2);
- Antibody to hepatitis B core antigen (anti-HBc);
- HEV RNA
- Malaria
- West Nile Virus

Standard

9.5.3.1. Appropriate quality control measures should be in place when screening for additional TTI markers (see 9.3.2.1 above)

Anti-HTLV 1/2

Anti-HTLV 1/2 testing should be undertaken either as a universal screening test of donations or on a first pass test basis (i.e. donors tested only once). This test is not required for plasma for fractionation.

The approach to anti-HTLV 1/2 confirmation testing is similar to that of HIV and involves nationally established algorithms as well as specific assays including immunoblot and NAT. Sensitive tests for genome detection (including typing) may be helpful in defining the infection status of the donor.

Anti-HBc

Donors or donations should be tested by an approved test that will detect antibodies to hepatitis B core antigen (anti-HBc). The approach to deferral or re-entry of an anti-HBc positive donor should be established in an algorithm.

Re-entry into the donor base of an anti-HBc positive donor and the subsequent release of his/her donations should only be considered when the donor has been shown to have anti-HBs with a titre of at least 100 IU/L and each subsequent donation should test negative for both HBsAg and HBV DNA using approved assays.

The requirements identified in standard 9.1.1.10 do not necessarily apply to all donations found repeatedly reactive for anti-HBc. Additional testing, e.g. for anti-HBs and/or HBV-DNA might enable some repeatedly reactive donations to be used clinically.

Syphilis

There is ongoing discussion over the need to test blood donors for syphilis. The tests may be used as an indicator of risk behaviours for sexually transmitted diseases and are still required by most European countries. Most blood establishments use a treponemal antibody test employing a variant of the *Treponema pallidum* particle agglutination assay (TPPA) or another IA. Reactive syphilis screening results should ideally be confirmed by an appropriate treponemal antibody test, including TPPA, fluorescent treponemal antibody test (FTA), IA or an immunoblot test. This test is not required for plasma for fractionation.

9.5.4. Selective screening

Selective screening of donations involves the application of a test to reduce the risk of TTIs from a donor population considered at higher risk for the infection (e.g. malaria, *T. cruzi* and WNV RNA), or screening of selected donations aimed at providing a safer component for recipients at increased risk of infection with a known TTI (e.g. CMV, HEV and parvovirus B19).

When such testing is undertaken, the assay and test system should be fully validated. Appropriate quality control measures should be in place when screening for infectious markers.

Standard

9.5.4.1. Appropriate quality control measures must be in place when screening for selective TTI markers (See 9.3.2.1 above)

CMV screening

Testing for CMV antibodies is most commonly performed using an IA. The screening of donations for anti-CMV antibodies enables the establishment of a panel of anti-CMV negative components for dedicated use in highly susceptible patients. This test is not required for plasma for fractionation.

Confirmation of reactive results and notification of reactive donors is not necessary when screening of selected donations for antibodies to CMV (anti-CMV) is undertaken.

Malaria screening

At present, only a few reliable and robust malaria antibody tests are commercially available. Any malarial antibody testing requirement necessitates integration within local approaches to the taking of donor histories. Users need to be aware that assays may depend on the detection of heterotypic antibodies. Users should ensure that the assay detects antibodies to the *Plasmodium* species prevalent in their donor panel. This test is not required for plasma for fractionation. Currently, NAT for malaria cannot be recommended for use in screening of blood donors because it may fail to detect the small number of parasites in a blood donation that can infect a transfusion recipient.

Standard

9.5.4.2. If malaria antibody testing is used to determine donor acceptance or rejection, the test employed should be shown to detect antibodies to the malaria parasite types that are likely to pose a risk of transfusion transmission and to the Plasmodium species prevalent in their donor panel.

Trypanosoma cruzi screening

Donors who were born or have been transfused in areas where trypanosomiasis is endemic can be selected to be tested for antibodies against *T. cruzi*. This test is not required for plasma for fractionation.

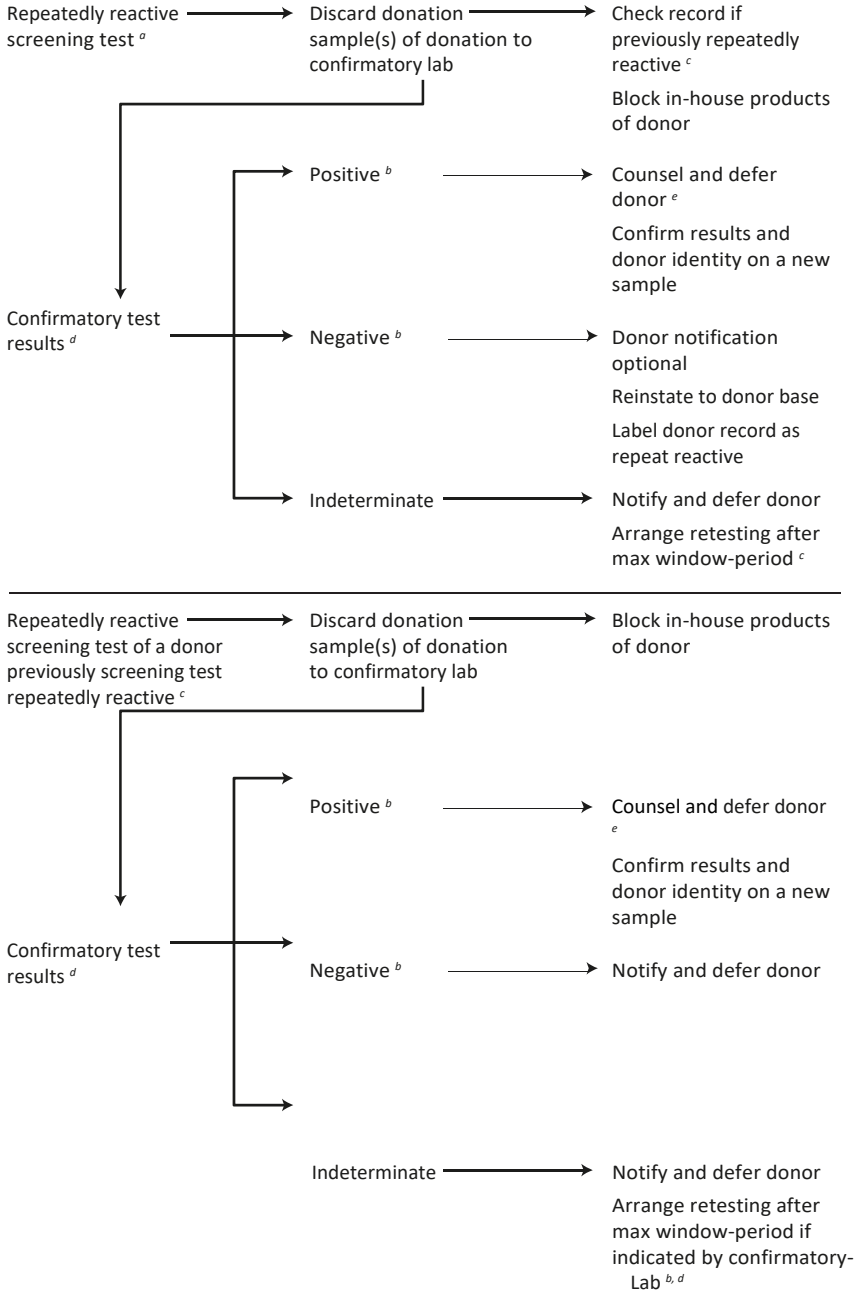
West Nile virus

NAT testing for West Nile virus RNA may be performed as an alternative to donor deferral for potential donors returning from areas with ongoing transmission of West Nile virus.

Algorithm for TTI marker screening and confirmatory testing

Figure 9-1 shows a widely used algorithm for TTI marker screening and confirmatory testing as an example.

Figure 9-1. **Algorithm for infectious marker screening and confirmatory testing**



[a] For example, a repeatedly reactive serological screening test or a positive NAT on a single donation. Confirmatory testing is performed by an authorised medical microbiology reference laboratory, which is responsible for results and may use tests at its discretion. The confirmatory laboratory should be kept informed about the type of screening test used by the blood establishment, and is contracted to use tests at least as sensitive as the screening test and, if feasible, based on other principles.

[b] The confirmatory laboratory is contracted to provide overall confirmatory test results or interpretations as follows: 'positive', which means infected; 'negative', which means not infected; or 'indeterminate', which means a diagnosis cannot be established (may include a demand for follow-up testing). If a confirmatory test(s) is less sensitive than the screening assay, the conclusion of confirmatory testing should read 'uncertain' (unless positive).

[c] The blood establishment keeps a donor record allowing longitudinal recording of confirmatory laboratory test results as: screening test positive; confirmatory lab positive; negative; or indeterminate.

[d] The confirmatory laboratory is contracted to keep longitudinal records of the unique donor ID, linked to laboratory test results.

[e] Refer donor to a medical doctor (general practitioner or specialist). Inform plasma fractionation centre(s) if plasma from earlier donation(s) has been issued. Inform hospital(s) to allow look back if component(s) from earlier donation(s) have been issued.

Chapter 10

Haemovigilance

10.0. Overview

Haemovigilance means a set of organised surveillance procedures relating to serious adverse or unexpected events or reactions in donors or recipients, and the epidemiological follow-up of donors (Directive 2002/98/EC).

Haemovigilance covers the transfusion chain from donation of blood to transfusion of blood components. It provides useful information on the morbidity arising from donation and transfusion of blood, and gives guidance on corrective measures to prevent recurrence of incidents. It should also incorporate an early alert/warning system.

The information provided contributes to improving the safety of blood donation and transfusion by:

- Providing the medical community with a reliable source of information about adverse events and reactions associated with blood collection and transfusion;
- Enabling identification of measures to reduce the recurrence of incidents or errors;
- Warning hospitals and blood establishments about adverse events and reactions that could involve more individuals than a single recipient, including:
  - those related to the transmission of infectious diseases;
  - those related to blood bags, solutions or blood processing.

The ultimate goal of haemovigilance is to prevent the occurrence and recurrence of adverse events and reactions. Therefore the results of data analyses should be fed back periodically to the providers of haemovigilance data and communicated to the competent authorities.

Standard

10.0.0.1. Haemovigilance procedures should be in place to ensure the organised surveillance of serious adverse or unexpected events or reactions in donors and in recipients of blood and blood components and for the epidemiological assessment of infections in donors.

10.1. Pre-requisites for implementation of a haemovigilance system

Haemovigilance is the shared responsibility of the professionals in the field and the competent authorities. It involves operational linkages between clinical departments, hospital blood banks, blood establishments and national authorities.

10.1.1. Traceability of blood components

Traceability is defined as the ability to trace, in all directions, every individual unit of blood and any blood components derived from it from the donor to its final destination, whether this is to a recipient, to a manufacturer of medicinal products or its disposal.

Traceability requires a unique identification number for each donation and an identifier for each component prepared from that donation. This information should be linked to data that identifies both the donor and the recipient. In this way, all recipients transfused with a particular donor's blood, or all donors who donated the blood components that a recipient received, may be traced.

Traceability is essential for:

- Tracing implicated donor(s) in the event of a report of possible transmission of an infectious agent to a recipient or non-infectious complication, e.g. transfusion-related acute lung injury (TRALI);
- Tracing implicated recipient(s) in the event of a donor subsequently being identified with a transfusion-transmissible infection or with a non-infectious risk;
- Tracing recipients in the event of systemic problems (e.g. blood pack defects) that put recipients at risk of serious adverse reactions or events.

The use of unique identifiers for donations and components also allows information to be collated on the total number of:

- Recipients who have been transfused;
- Blood units or components that have been issued or used;
- Blood donors who have donated the transfused blood units or components.

This information enables calculation of the rate of adverse events and reactions and supports the estimation of risks.

Confirmation is required that the blood component was transfused to the designated recipient for whom it was issued. Without this, proving the link between donor and recipient requires verification in the recipient's notes that the blood component was transfused. The document confirming the transfusion should also include information on the existence or non-existence of immediate adverse events or reactions.

In the case of blood components that have not been issued for transfusion, data should be available to identify the facility where the units have been used or disposed of.

Standards

10.1.1.1. There must be procedures in place to ensure full traceability, allowing the tracing of each individual unit of blood (or any blood components derived from it), from the donor to its final destination and vice versa. (Directive 2005/61/EC)

10.1.1.2. A procedure should be in place to verify that each unit has been transfused to the intended recipient or, if not transfused, to verify its sub- sequent disposition.

10.1.1.3. Traceability should also cover cases in which the blood unit or component is not transfused, but is used for the manufacturing of medicinal products, for research, for investigational purposes or disposed of.

10.1.2 Confidentiality of haemovigilance data

Standard

10.1.2.1. Any database of haemovigilance reports should operate in compliance with applicable regulations on the confidentiality of individual recipient and donor data. Individual reports should be anonymised.

10.1.3 Co-operation between blood establishments, hospital blood banks and clinical departments

Reporting and analysis of adverse events and reactions associated with transfusion requires close co-operation between the clinical department where transfusion took place, the hospital blood bank that issued the transfused blood component and the blood establishment that collected and distributed the blood unit (if different from the hospital blood bank).

If blood collection and processing is carried out in facilities located outside of hospitals, look-back, trace-back and recall procedures may also be described in the contract(s) between the blood establishment and the hospital(s).

Co-operation is essential to ensure complete investigation of any adverse event or reaction, including uneventful transfusion errors. Prompt reporting enables the blood establishment to take action, as required, including preventing the transfusion of blood components from implicated donor(s), donations or processes.

Standards

10.1.3.1. Hospitals should inform the blood establishment whenever a recipient of blood components has a serious adverse reaction, indicating that a blood component may have been the cause.

10.1.3.2. Facilities where transfusion occurs must have procedures in place to retain the record of transfusions and to notify blood establishments without delay of any serious adverse reactions observed in recipients during or after transfusion which may be attributable to the quality or safety of blood and blood components (Directive 2005/61/ EC).

10.1.3.3. Any serious adverse events (accidents and errors) related to the collection, testing, processing, storage

and distribution of blood and blood components which may have an influence on their quality and safety, as well as any serious adverse reaction observed during or after transfusion which may be attributed to the quality and the safety of blood and blood components must be notified to the competent authority (Directive 2002/98/EC).

10.1.3.4. The clinical outcome of serious adverse reactions, if known, in the recipients of blood components should be notified to the competent authority.

10.2. Types of adverse reactions and adverse events collected in a haemovigilance system

10.2.1. Adverse reactions in recipients

Adverse reactions in recipients include:

- Haemolytic transfusion reactions, e.g. acute or delayed;
- Delayed serological reactions as a result of allo-immunisation against red cell antigens;
- Non-haemolytic transfusion reactions, e.g. TRALI, transfusion-associated circulatory overload (TACO), graft versus host disease (GvHD), febrile transfusion reactions and allergic reactions;
- Other transfusion reactions, e.g. haemosiderosis and hyperkalaemia;
- Bacterial, viral, parasitical, fungal or transmissible spongiform encephalopathy (TSE) transmission.

Definitions of adverse reactions have been developed by the International Society of Blood Transfusion Working Party on Haemovigilance (ISBT WP HV) in partnership with other professional associations.

10.2.2. Adverse reactions in donors

Adverse reactions in donors are defined as any unintended response associated with the collection of blood or blood components. They should be documented in donor records and serious adverse reactions should also be documented in the records of the quality system.

Standards for the surveillance of complications related to blood donation have been developed by ISBT WP HV in partnership with other professional associations.

Analysis of reports of adverse reactions in donors will assist in the development of approaches to improve the overall safety of blood collection. Information should, where appropriate, be reported at least annually to the national haemovigilance system.

Information on the management of adverse reactions in donors is provided in Chapter 3 of this *Guide*.

10.2.3. Adverse events

An adverse event is defined as any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to an adverse reaction in blood recipients or blood donors. Adverse events related to donation may also have consequences for the safety and quality of the derived blood components.

Adverse events include incorrect, inappropriate or unsuitable blood component transfusions even if they did not lead to harm to the recipient. For example, administration of an ABO-compatible component to an unintended recipient or failure to provide irradiated components when indicated.

Adverse events related to blood donation can be associated with:

- Donor selection: the donor is inappropriately allowed to donate blood e.g. does not fulfil haemoglobin requirements, under-weight, fails to disclose risk factors;
- Blood collection: failure to follow procedure, e.g. overweight blood collection, inadequate volume of anticoagulant used for apheresis procedures.

Serious adverse events are those that might have led to death or life-threatening, disabling or incapacitating conditions for recipients or donors, or which might have resulted in prolonged hospitalisation or morbidity. Examples include:

- Failure to detect an infectious agent;
- Errors in ABO typing;
- Incorrect labelling of blood samples or blood components from donors.

'Near-miss' events are a subgroup of adverse events. A near-miss event is defined as any error which, if undetected, could result in determination of a wrong blood group or failure to detect a red cell antibody or the issuance, collection or administration of an incorrect, inappropriate or unsuitable component, but where the mistake was recognised before transfusion took place.

Notification of adverse events that do not cause an adverse reaction may help to identify weaknesses in the transfusion process and thereby reduce risk. Relevant staff should be informed of the importance of reporting of adverse events.

Data concerning adverse events in donors should be collected and evaluated within blood establishments and, where appropriate, should be reported at least annually to the national haemovigilance system.

Standard

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

10.3. Device defects

10.3.1. Reporting requirements

Standard

10.3.1.1. When a causality assessment suggests that a medical device (including *in vitro* diagnostics) had a possible role in causing an adverse reaction or event, the manufacturer or its authorised representative should be notified at the same time as the competent authorities, even if full causality has not yet been confirmed at the time of reporting. When haemovigilance and medical device vigilance are the responsibility of separate entities, both should be notified.

10.4. Post-transfusion infection reported to the blood establishment

10.4.1. General requirements

Hospitals should inform the blood establishment of a possible transfusion-associated infection without delay to allow further action to be taken regarding implicated donations and donors in order to prevent harm to other recipients.

Where feasible and appropriate, the blood establishment should temporarily defer all implicated donors from further donations and retrieve or quarantine all in-date components for transfusion collected from the implicated donors.

Investigation of reports may include re-analysis of tests performed on implicated donors or donations, or the use of additional tests performed on archived or new samples from the implicated donors. If such analyses exclude infection, the donors may be reinstated and quarantined components released.

If an implicated donor is found to be infectious the blood establishment should defer the donor, initiate a look-back procedure on previous potentially infectious donations and inform the hospital(s) concerned.

Standards

10.4.1.1. Hospitals should inform the blood establishment, without delay, whenever a recipient of blood components develops laboratory test results or disease symptoms, indicating that a blood component may have been infectious.

10.4.1.2. The blood establishment should request relevant information from the hospital about the infection and the course of disease in the recipient.

10.4.1.3. The blood establishment's physician should establish a plan of investigation, the results of which should be recorded.

10.4.1.4. Confirmed transfusion-transmitted infections should be reported to the competent authorities and the national haemovigilance system.

10.4.2. Tracing of recipients of potentially infectious blood donations (look-back)

Blood establishments should initiate a look-back to identify recipients of blood components from a potentially infectious blood donation.

Information on look-back of potentially infectious blood donations is provided in Chapter 9 of this *Guide*.

10.5. Post-donation information

Post-donation information includes information provided by the donor or other source and received by telephone or other means of communication following a donation, which may have consequences for the safety and quality of the donated components.

Information on post-donation information is provided in Chapter 2 of this *Guide*.

10.6. Reporting haemovigilance data

10.6.1. Standardisation of reporting

There should be standardisation of reporting throughout the haemovigilance network. This involves the use of common data elements and agreed definitions of the different types of adverse events and adverse reactions. A training programme that ensures consistency in the in the notification and interpretation of an incident is highly recommended.

Report forms should enable differentiation between adverse reactions in recipients and donors, as well as from adverse events. They should include a brief summary that describes the event, as well as the corrective actions taken.

10.6.2. Minimum information to be captured in the initial incident report at hospital level

Information about transfused patients should be managed according to the confidentiality requirements/legislation of individual countries.

Reported recipient identifiers should include at least date of birth, gender and a unique case number. Any clinical signs observed should be documented in a standardised fashion, either specific for a given adverse event or reaction or in the same format for every untoward effect. The clinical outcome of all adverse reactions should be stated.

10.6.3. Component information

This information should include a detailed description of the component involved:

- Unit number and appropriate codes for components;
- Description of the component, including:
  - the type of component, e. g. red cell, platelet or plasma;
  - the type of preparation, e. g. from whole blood or from apheresis;
  - other characteristics, e.g. leucocyte-depleted, irradiated, plasma-reduced;
- Conditions and duration of storage prior to transfusion.

10.6.4. Information about severity

The severity of adverse reactions and events should be determined.

Grading scales for assessment of severity of adverse reactions for both donors and recipients have been developed by the ISBT WP HV in partnership with other professional associations and is accessible via ISBT web page

10.6.5. Information about imputability

Standard

10.6.5.1. The possible relationship between the observed adverse reaction and the transfusion of blood components (imputability) should be determined.

Imputability grading, as identified in Directive 2005/61/EC is provided in the table below:

Imputability scale		Explanation
N/A	Not assessable	When there is insufficient data for imputability assessment.
0	Excluded	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to alternative causes.
0	Unlikely	When the evidence is clearly in favour of attributing the adverse reaction to causes other than the blood or blood
1	Possible	When the evidence is indeterminate for attributing the adverse reaction either to the blood or blood component or to alternative causes.
2	Likely, probable	When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.
3	Certain	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the blood or blood component.

Chapter 11

Elements for a quality system on the clinical use of blood

11.0. Overview

The clinical transfusion process encompasses the 'transfusion of the right blood component to the right patient at the right time, in the right condition and according to appropriate guidelines'. It is a chain of inter-related events beginning with the appropriate decision that the patient needs transfusion of one or more blood components and ending with the assessment of the clinical outcome of the transfusion.

11.1. Key measures for the safety of transfusion

The safety of transfusion of blood components is underpinned by several key measures:

- The decision to transfuse;
- The completion of the transfusion request form;
- The correct identification of the patient and obtaining an appropriately labelled pre-transfusion sample at the point of collection;
- The pre-transfusion testing within the laboratory
- The selection and issue of appropriate blood components;
- The prescription of the blood component including specific requirements, volume and rate of transfusion;
- The administration of the component to the right patient following appropriate bedside patient identification checks;
- The careful monitoring of the patient for any adverse reactions before, during and at the end of the transfusion.

For safe and appropriate use of blood in clinical transfusion practice, it is necessary to have in place a 'Quality System for Clinical Transfusion' involving different health professional. Structures and individuals that contribute to the governance of the process include the hospital management, the hospital transfusion committee (HTC), the hospital blood bank and/or the blood establishment providing blood components to the hospital or to the patient, and all hospital staff involved in the transfusion chain and in the haemovigilance system.

Elements of the quality system include:

- Adoption and regular updating of clear guidelines for appropriate use of blood and blood components;
- Adoption of standard operating procedures (SOPs) for the implementation and surveillance of appropriate blood utilisation;
- Thorough dissemination of guidelines and SOPs;
- Appropriate selection of suitable blood components for each clinical condition;
- Safe storage, issue and handling of blood components;
- Ensuring correct patient and blood component identification throughout the transfusion process;
- Safe administration of the component and monitoring of the patient;

- Recognition, management and prevention of adverse effects of transfusion;
- Constant monitoring of quality and revision of all transfusion medicine activities;
- Definition of staff responsibilities and needs for training and education.

11.2. Decision to transfuse

A transfusion should only be ordered when the anticipated benefits outweigh the risks.

Transfusion of blood components should follow appropriate evidence-based guidelines that are updated regularly.

11.2.1. Documentation of the indication for transfusion

Standard

11.2.1.1. The indication for transfusion should be documented in the patient clinical record.

When possible, informed consent should be obtained from the patient prior to transfusion. This is mandatory in some countries. It is the responsibility of the prescribing physician and the consent should be documented in the clinical record of the patient. Information could be delivered orally but is preferable in written form and should include appropriate information on the risks and benefits of transfusion therapy and its alternatives. The written information provided should be approved by the HTC.

Before ordering the transfusion, the treating doctor should be aware of the patient's transfusion history including any adverse reactions.

The decision to transfuse should be evidence-based. Therefore, professionals should be familiar with the recommendations of good quality and regularly updated transfusion guidelines that take into account the best available current evidence.

These specific internal guidelines should contain detailed instructions on appropriate use of blood components for the most important clinical conditions, guidance on the dosage, need for special requirement (e.g. irradiated, washed) and a maximum (or agreed) surgical blood ordering schedule.

It is strongly recommended that specific guidelines or recommendations are available, at least for management of:

- Critical/massive haemorrhage;
- Obstetric haemorrhage;
- Paediatrics;
- Intensive care patients;
- Cardiovascular surgery;
- Patients with haemoglobinopathies and other haematological- transfusion-dependent chronic disorders;
- Haematopoietic stem cell transplant;
- Patients with immune cytopaenias, thrombotic thrombocytopenic purpura, coagulation factor deficiencies and disseminated intra-vascular coagulation;
- Out of hospital patients receiving transfusions;
- Patients who refuse blood;
- Transfusion requests in times of blood shortage (emergency blood management plan or EBMP).

The HTC should plan and review the results of regular transfusion audits and make the audit reports available to prescribing clinicians so that when significant deviations from the guidelines are observed, corrective actions can be put in place.

It is recommended that clinical services develop clinical key performance indicators (KPIs) as part of their quality management programme. These might include blood component wastage, non-homologous red cell transfusion, crossmatch to transfusion ratios, using appropriate transfusion thresholds and meeting specific requirements.

The medical staff of the blood establishment and hospital blood bank should provide transfusion medicine clinical support and advice on all aspects of the process.

1122. Patient blood management

Blood transfusion medicine/therapy is a key part of patient blood management (PBM) programmes. These aim to provide the best clinical care, optimising the patient blood counts, reducing unnecessary blood losses and ensuring the judicious use of blood components. PBM is based on an interdisciplinary overview of the patient's needs.

Blood transfusion services and all blood establishment stakeholders should be directly involved in PBM programmes.

Medical schools, education institutes, hospitals and blood establishments should support education in safe transfusion practice and transfusion medicine, including a specific educational programme in PBM for all clinicians in training and updates for all clinical staff in practice.

1123. Alternatives to the transfusion of allogeneous blood components

Transfusion of blood components should be ordered when there are no better alternatives. When available, possible alternatives should be discussed with the patient and his/her opinion should be taken into account. Physicians should be aware of alternative treatments which can be less harmful or more specific, and could be used to avoid blood component transfusion: coagulation factor concentrates, erythropoietin, thrombopoietin receptor agonists, antifibrinolytic agents, blood recovering devices and autotransfusion modalities.

Red cell salvage (CS) during surgery is a means of autologous transfusion. Blood collected from the operation site may be given back to the patient either after a simple filtration or a washing procedure.

Acute normovolaemic haemodilution involves the collection of blood immediately before surgery, with blood volume compensation (leading to a haematocrit below 0.32), with subsequent re-infusion during or after surgery. These techniques do not allow storage of the collected blood. They are usually performed under the supervision of anaesthesiologists and/or surgeons.

CS covers a range of techniques that scavenge blood from operative fields or wound sites and re-infuse the blood back into the patient. CS can be performed during intraoperative and/or post-operative periods. The aim of CS is to reduce or eliminate the need for allogeneic blood transfusion. At least one allogeneic packed red cell unit should be saved. The blood salvage system comprises a collection and a processing system.

The collection system consists of:

- The suction line and suction tip used in the surgical field;
- The vacuum source;
- An anticoagulant;
- The collection reservoir.

During collection of red blood cells, an appropriate anticoagulant is added to salvaged blood.

Anticoagulated blood is then filtered and collected in a reservoir. When a sufficient amount of blood has been collected, separation by centrifugation and washing of red blood cells follows.

Various separation devices use centrifuge bowls for stepwise pro- cessing or a disc-shaped separation chamber enabling continuous processing of salvaged red cells. The washing procedure removes (to a large extent) free haemoglobin, plasma, platelets, white blood cells and anticoagulant. Remaining red blood cells are then resuspended in normal (0.9 per cent) saline. The resulting haematocrit should be between 0.60 and 0.80. Small washing volumes, fast washing rates and half-full bowls should be avoided. Salvaged red cells should be transfused immediately or at least within 6 hours. Blood filters and standard blood administration filters are required. Some manufacturers recommend micro-aggregate or leucodepletion filters to remove bacteria, cancer cells or amniotic-fluid contaminants depending on the different clinical settings.

Indications for the use of CS:

- Patients undergoing cardiothoracic, vascular, transplant or major orthopaedic surgery;
- Anticipated blood loss of 1 000 mL or 20 per cent of estimated blood volume;
- Patients with low haemoglobin levels or at an increased risk of bleeding;
- Patients with multiple antibodies or rare blood types;
- Patients with objections to receiving allogeneic blood.

Parameters for quality control of the component should be:

- Volume;
- Haematocrit;
- Haemolysis at the end of the process;
- Protein content of the supernatant.

Precautions for the use of CS

Some substances should not be aspirated with blood: antibiotics not licensed for intravenous use, iodine, hydrogen peroxide, alcohol, topical clotting factors, orthopaedic cement, sterile water.

Careful use of a large-bore suction tip under low vacuum pressure can reduce the risk of shear-induced haemolysis.

Colorectal surgery: salvaged blood can (under special preventive measures) be gained during colorectal surgery or other types of surgery if the blood has come into contact with bacteria. Use of leucodepletion filters and washing of salvaged blood reduces the risk of microbial contamination because these methods also help to minimise the risk of activation of coagulation factors or influx of cytokines and other biologically active substances. As an additional precaution, broad-spectrum antibiotics should be administered to the patient.

Haemorrhage in cancer patients: although the passing of blood through a leucodepletion filter significantly reduces the number of retransfused tumour cells, the salvaged cells should be irradiated.

Obstetric haemorrhage: use of leucodepletion filters in obstetric haemorrhage provides a significant reduction in contamination of cells from amniotic fluid. This is also true for caesarean section. There is also concern regarding reinfusion of foetal red cells from the operative field. If the mother is RhD-negative and the foetus RhD-positive, the extent of maternal exposure should be determined as soon as possible, and a suitable dose of human anti-D immunoglobulin should be administered.

11.3. Completion of the transfusion request form, identification of patient and blood sampling

11.3.1. General considerations

Standards

11.3.1.1. The transfusion request should be made by a medical doctor or, if permitted, by specially trained healthcare professionals.

11.3.1.2. Detailed instructions for the completion of the request form including minimum requirements for patient identification and the taking of pre-transfusion samples should be available and all staff permitted to make these requests should be trained and competent to under- take this role.

11.3.1.3. The number of units, type(s) of blood component(s) and associated special requirements (e.g. irradiation or washing), date and location of the transfusion and the urgency of the transfusion should be indicated on the request.

Clinical indication should also be communicated to the hospital blood bank, or if appropriate to the blood establishment.

Information on transfusion history, including previous adverse reactions, and recent pregnancy is necessary to determine the period of validity of the pre-transfusion sample.

A procedure for auditing transfusion requests should be in place in order to identify compliance with local clinical guidelines and to facilitate interventions to improve compliance and, where appropriate, to update the guidelines. Validated information technology tools which provide alerts or support clinicians in transfusion decision-making are useful.

11.4. Correct identification of the patient and obtaining a pre-transfusion sample

11.4.1. Collection of samples

Collection of blood samples from the intended recipient for pre-transfusion testing is a crucial point in the safety of the transfusion chain.

Standards

11.4.1.1. Where appropriate, the request form should be accompanied by the appropriate blood samples for pre-transfusion testing.

11.4.1.2. Procedures should be in place to ensure that samples have been drawn from the correct patient.

11.4.2. Minimum requirements for identification

Minimum requirements for patient identification are family name, given name(s) and date of birth. Where applicable, these data should be supplemented by a unique patient identity number.

Whenever possible, positive patient identification should be performed at the time of sampling. The patient should be asked to state his/her name and date of birth if conscious and/or these or other identifiers should be checked on a wristband securely attached to the patient.

The information on the request form, patient's wristband (when present) and sample tube label should be identical.

In newborn infants, the gender and the number on the identification wristband should also be recorded on the request form and the sample tube.

Standards

11.4.2.1. If it is not possible to establish a patient's identity, a procedure should be in place to otherwise uniquely identify the intended recipient and the respective sample.

11.4.2.2. Any patient identification discrepancy at any step of the process should be investigated and corrected.

11.5. Testing within the laboratory

Information on testing is provided in Chapter 8 of this *Guide*.

11.6. Selection and issue of appropriate blood components

11.6.1. Minimum requirements

Standards

11.6.1.1. Before issuing a blood component, the hospital blood bank, or if appropriate the blood establishment, should check that the correct component has been selected, special requirements have been fulfilled and the component(s) remains in date.

11.6.1.2. A check of the integrity of the unit has also to be made.

A compatibility/issuing label will then be attached to the component containing the patient identifiers obtained from the sample and/or request form.

11.7. Handling and storage of blood components in hospital clinical areas

11.7.1. Minimum requirements for systems and documentation

Standard

11.7.1.1. Transport should be undertaken using systems that maintain the integrity of blood components and ensure traceability.

Procedures should be in place to document receipt of the issued blood components in the clinical area.

11.7.2. Storage of blood components in hospital clinical areas

Standard

11.7.2.1. When stored for a longer time in a specifically designated blood refrigerator or platelet incubator on the ward/operating theatre validated procedures should be in place to assure that the right unit is provided for the right patient.

To avoid compromising clinical effectiveness and safety, blood components should be transfused within the time limits required by the current rules or local procedures. It is recommended that the blood component should not remain out of controlled storage for more than 60 minutes if it is not transfused and is to be returned to storage. This is subject to systems being in place to ensure this does not adversely impact the safety and quality of the components.

Relevant staff should be properly trained in the principles and practice of handling different types of blood components and written procedures should be available.

Standards

11.7.2.2. Return of blood and blood components into inventories for subsequent re-issue must be allowed only if all requirements and procedures relating to quality as laid down by the blood establishment to ensure the integrity of blood components are fulfilled (Directive 2005/62/EC/Annex 7.6).

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

11.8. Administration of blood components

11.8.1. General considerations

Standards

11.8.1.1. Only trained personnel should be allowed to administer blood components.

11.8.1.2. Procedures should be in place to verify the identity of the recipient at the bedside in order to ensure that the blood component will be transfused to the intended recipient.

This involves asking the patient to state his/her name and date of birth and/or by checking the identification details on the patient's wrist-band against the information provided on the compatibility label.

In addition, confirmation of compatibility between patient and blood component should be carried out by:

- Checking the written or electronic prescription (including special requirements);
- Checking the record of the patient's blood group against the blood group on the blood component label;
- Checking that the unique identification number on the blood component label matches that on the compatibility label and/or on the hospital blood bank report, where available.

Prior to commencing the transfusion a check should be made to verify that the expiry date of the blood component has not been passed and that there is no visible deterioration of the blood components (with particular emphasis on discolouration or detectable micro-perforations of the bag).

Where undertaken, the bedside confirmation of ABO group should then be performed and documented.

11.8.2. Administration of blood components

Standard

11.8.2.1. Blood components should be administered using an approved blood administration set that incorporates an integral mesh filter to filter out large clots and aggregates and ensure an effective flow rate.

This set and any other infusion equipment (e.g. infusion pumps) should be used in accordance with the manufacturer's recommendations. It is recommended that no transfusion sets be used for more than 6 hours.

Transfusion should be completed within 4 hours of removal from controlled storage.

To ensure traceability, all blood components administered should be recorded in the clinical patient record, including the component identification number and the start and end times of the transfusion.

11.9. Special precautions

11.9.1. Warming of blood

Hypothermia induced by rapid/massive transfusion (more than 50 mL/kg/hour in adults and 15 mL/kg/hour in children) increases the risks of organ failure and coagulopathy. If warming of blood is indicated, only validated and regularly controlled warming devices should be used in accordance with the manufacturer's instructions.

11.9.2. Addition of medicinal products or infusion

Because of the risk of damage to the blood components, addition of medicinal products or infusion solutions to blood units should be avoided unless their safety has been demonstrated.

11.10. Transfusion monitoring

11.10.1. Observation of the patient

Standard

11.10.1.1. The patient should be observed during and after the transfusion.

Observation during the first 15 minutes of the transfusion is especially important to allow early detection of signs of serious acute reactions. Requirements should be documented in procedures and personnel should be trained.

Vital signs such as blood pressure, pulse, respiratory rate and temperature should be measured before starting the transfusion, at 15 minutes after the start of the transfusion and at the end of the transfusion of every blood component transfused.

11.10.2. Documentation

The time when transfusion is started, interrupted and stopped should be clearly reported in patient records, as well as vital signs or any other symptoms that could indicate a transfusion reaction.

Confirmation of transfusion of the blood component should be sent back to the hospital blood bank, or if appropriate to the blood establishment.

An assessment of the effectiveness of the transfusion should be performed (by post-transfusion increment rates or improvements in patient symptoms and clinical signs) and documented in a clinical record, identifying whether the desired effect was obtained and the likely need for further transfusion.

11.11. Management and reporting of transfusion reactions

Complications may occur during or immediately after the transfusion, or after a delay of hours, days or months. Therefore, careful documentation of the transfusion as well as recording and reporting of transfusion complications is essential.

Patients should be encouraged to report any new or worsening symptoms during and after transfusion.

Transfusion complications include both adverse events and adverse reactions associated with transfusions and even failure of expected therapeutic response. Careful recording and reporting of any observed reaction is the responsibility of the attending physician/clinical team.

In the event of a suspected transfusion reaction, the transfusion should be stopped and the line should be maintained with normal saline. The patient should be assessed for severity of the reaction and treated accordingly. Where the reaction is a mild allergic or febrile reaction and settles with treatment, after medical consultation the transfusion may be restarted at a slower rate with more frequent observations. For severe reactions the key priority is resuscitating the patient and treating any specific symptoms or suspected causes of the reaction. As ABO-incompatible red cells can cause such a reaction, a clerical check of the documentation associated with the transfusion should be undertaken, including an identification check of the recipient and blood component and a check that the ABO and RhD blood group of the component is compatible with the patient's blood group. New samples should be taken from the patient and the transfusion packs and, together with a transfusion reaction report, these should be sent to the hospital blood bank, or if appropriate the blood establishment, for further investigation if clinically indicated. Before starting a further transfusion the assessment of the reaction has to be completed.

Respiratory complications of blood transfusion are increasingly recognised and have been shown by haemovigilance schemes to be associated with a high mortality in vulnerable patient groups. Any patient experiencing new or worsening breathlessness during or after a transfusion should be

fully assessed by a medical doctor to determine if there is an allergic reaction, transfusion-associated circulatory overload or transfusion-related acute lung injury which should then be investigated and managed accordingly. Air embolism is now a rare complication of blood transfusion.

When clinical symptoms and signs suggest the possibility of bacterial infection, blood cultures should be obtained from the patient as well as bacterial culture from the blood component bag. Care should be taken not to contaminate the content of the bag after disconnecting from the patient.

In countries where universal pre-storage leucocyte depletion has not been implemented, the use of leucocyte-depleted blood components for subsequent transfusions is recommended for patients with repeated, febrile non-haemolytic transfusion reactions.

Long-term complications may also occur. These mainly comprise immunological complications, e.g. allo-immunisation and transmission of infectious pathogens.

Haemosiderosis is a serious complication of chronic red cell transfusion affecting patients suffering from transfusion-dependent conditions. Unless patients undergo iron-chelation therapy to control iron overload in the liver and heart, this complication may lead to severe organ impairment and death before the third decade of life.

There should be co-operation between the clinician responsible for the patient and the hospital blood bank/blood establishment to facilitate investigation of possible transfusion-transmitted infections (TTI).
Suspected TTI may require investigation when the recipient develops a viral or bacterial infection after transfusion or a donor is found to have developed an infectious disease marker. Medical follow-up of recipients and donors will be required to determine causality.

Follow-up and patient counselling, where appropriate, is also necessary when significant allo-immunisation against transfused cells may have taken place.

11.12. Traceability and haemovigilance

11.12.1. General considerations

Standards

11.12.1.1. Facilities where transfusion occurs must have procedures in place to guarantee the retention of at least the following data: blood component supplier identification, issued blood component identification, transfused recipient identification, for blood units not transfused, confirmation of subsequent disposition, date of transfusion or disposition, lot number of the component, if relevant (Directive 2005/61/EC).

11.12.1.2. Any serious adverse reaction or event related to the transfusion must be investigated, recorded and notified to the haemovigilance system (Directive 2005/61/EC).

11.13. Hospital transfusion committees

Establishment of hospital transfusion committees is to be encouraged. The hospital chief executive and senior hospital management have the responsibility to support and resource the HTC.

A hospital blood transfusion committee should include representatives of the hospital blood bank, the blood establishment and the main clinical units with significant transfusion activity. It is recommended that physicians, nurses and administrative personnel be represented on these committees.

The main goals of HTCs are:

- To define blood transfusion policies adapted to local clinical activities;

- To perform regular evaluation of blood transfusion practices;
- To analyse adverse events and adverse reactions related to blood transfusion;
- To take any corrective and preventive measures if necessary;
- To ensure that all staff involved in transfusion practice receive adequate training;
- Audit systems for the clinical use of components further enhance the efficacy and safety of transfusion practices.

APPENDIX 1.
KEY CRITERIA FOR DONOR ELIGIBILITY

The Standards require medical assessment to be undertaken on all prospective donors using a combination of interview, questionnaire and, if necessary, further direct questions. The questionnaire must be designed to elicit information on the health and lifestyle of the donor that may adversely affect the safety of both the recipient and the donor.

Blood establishments should develop a questionnaire that is appropriate for local circumstances. Therefore, it is not possible to provide a generic questionnaire in this *Guide*.

Instead, key eligibility topics for donor inclusion in the questionnaire or direct questions in an interview have been developed and are included in the table below.

Key eligibility topics identified as being critical for the safety of donors and recipients are labelled as 'core'. It is recommended that countries include a question which meets the described intent of the core topics for donor eligibility in their donor questionnaire. Examples of such questions are included, but the wording may be changed provided the question still meets the described intent.

A number of key eligibility topics have also been identified that may be considered to be important for the safety of donors and recipients dependent on local arrangements and circumstances in blood establishments. These are labelled as 'optional'. The blood establishment may choose to include or not include such questions.

Core and optional sample questions have been categorised into those which apply only to first-time and repeat donors, and those which also apply to regular donors.

Blood establishments may also choose to include additional questions.

These recommendations are intended as a guide. Final responsibility for the content of the donor health questionnaire lies with the blood establishment and competent authorities.

Key evaluative topic for donor eligibility	**Intent of question**	**Core sample question**	**Optional sample question**	**First-time & repeat donors**	**Regular donors**
General – health	To assess general health and provide the donor with an opportunity to volunteer health issues that may not be addressed by specific questions.	Are you in good health?		Y	Y
General – previous donation history	A donor who has previously volunteered to donate should have a record, which may contain important information regarding their ongoing eligibility. Countries with more than 1 blood establishment could also have donors who present at different establishments.	Have you ever volunteered to donate blood before? If yes: where/when?		Y	N

General – previous deferral	To identify people who have been permanently deferred from donating blood previously.	Have you previously been told not to give blood?		Y	N
General – weight	Total blood volume is proportional to donor weight. Donors must weigh at least 50 kg to safely donate blood.		Is your weight over 50 kg?	Y	Y
General – donor comprehension	Efficacy of the donor interview process requires the donor to firstly understand the questions being asked of him/her and then to truthfully and accurately complete the questionnaire to the best of his/her knowledge. NOTE: If not included as an optional question, then Blood establishments should include as part of the donor declaration to assist gaining written informed consent.		Have you read and understood the above questions and do you affirm that you have answered the questions truthfully and to the best of your knowledge?	Y	Y
Serious illness – examples	To capture any history of serious illness, using examples of common and important serious illnesses that have implications for donor and/or recipient safety. Each example listed would require deferral or further assessment of eligibility.	Have you ever suffered from any serious illness? Examples include: • jaundice, malaria, tuberculosis, rheumatic fever? • heart disease, high or low blood pressure? • severe allergy, asthma? • convulsions or diseases of the nervous system? • chronic diseases such as diabetes or malignancies?		Y	N
Serious illness – physician and hospital visits	Illness that is serious enough to require medical consultation may be relevant to donor selection.	Since your last donation, have you been to see a doctor or to hospital?		N	Y

Hazardous occupations and hobbies	To identify donors with occupations or hobbies that may put them or other people at risk in the event of a delayed vasovagal reaction following blood donation.		Do you have a hazardous occupation or hobby such as driving public transport, operating heavy machinery, underwater diving and piloting a plane or other activities?	Y	Y
Pregnancy	To protect donors from iron depletion ± risk of vasovagal reaction in late pregnancy. Donors who have recently become pregnant should be deferred temporarily to allow time for iron stores to replenish.	For women: Are you or have you become pregnant in the previous 6 months?		Y	Y
	To identify donors whose blood donations may contain HLA or granulocyte antibodies and thereby pose a higher risk of TRALI. These antibodies may develop in response to exposure to foetal antigens during pregnancy.		Have you ever been pregnant?	Y	N
Medications – general	Medications may render blood donations partly or completely unsuitable for use. This question also serves as an additional prompt for underlying disease, and therefore the indications for each medication should also be determined.	Have you taken any medications recently?		Y	Y
Medications – platelet affecting drugs	Some medications affect platelet function. This question can also serve to capture chronic pain or inflammation.		In the last 48 hours have you taken any aspirin, pain killers or anti-inflammatory medications?	Y	Y
Medications – teratogenic	Medications with known teratogenic potential require donor deferral to cover the maximum	Have you ever had medication with:		Y	Y

	potential period that the drug will circulate in the donor's peripheral blood, with a subsequent risk if the donation is transfused to a pregnant recipient.	• isotretinoin (e.g. Accutane R) • etretinate (e.g. Tigason R) • acitretin (e.g. Neotigason R) • finasteride (e.g. Proscar R, Propecia R) • dutasteride (e.g. Avodart R)		
Medications – vaccinations	Recent vaccination may harm immuno-compromised blood recipients through the transmission of live/attenuated pathogens, and may also interfere with the interpretation of donor screening tests, such as HBsAg.	Have you had any vaccinations in the last 8 weeks?	Y	Y
Blood-borne risks – intravenous use of drugs	Injecting drug use is an important route of transmission for blood-borne infections including HIV, hepatitis B and C.	Have you ever used needles to take drugs, steroids, or anything not prescribed by your doctor?	Y	Y
Sexual activity – sex worker	In many countries, sex workers have a significantly higher prevalence of blood-borne and sexually transmitted infections than the general population.	Have you ever received payment (gifts, money or drugs) for sex?	Y	Y
Sexual activity – male to male sex	Male to male sex is associated with a higher risk of HIV. This group also has a higher risk of syphilis, gonorrhoea, as well as infection by hepatitis B and hepatitis A viruses.	For men: have you had male to male sex in the *[specified time period]*? *(For the purpose of this question, sex is defined as oral or anal intercourse with or without a condom.)*	Y	Y
Sexual activity – female partner of	Men who have sex with men have a higher risk of HIV infection and other sexually transmitted	For women: to the best of your knowledge, has any man with whom you have had sex in the *[specified*	Y	Y

man who has sex with men	diseases. Therefore, women who have sexual contact with men in this group have a higher risk of such diseases than other women.	*time period]* ever had sex with another man? *(For the purpose of this question, sex is defined as oral, vaginal or anal intercourse with or without a condom.)*			
Sexual activity – at-risk sexual partner	A donor with a known history of sexual contact with persons in these risk groups has a higher risk of infection by HIV and/or hepatitis.	In the past *[specified time period]* have you had sexual contact with someone who: • is HIV positive or has hepatitis? • has ever used needles to take drugs, steroids, or anything not prescribed by his/her doctor? • receives or has received payment (gifts, money or drugs) for sex?		Y	Y
	Donors who have had sex with a new sexual partner may be at higher risk of infection by HIV and other sexually transmitted diseases.		Have you had sex with a new partner within the past 4 months?	Y	Y
	Some countries have a high prevalence of HIV. Sexual contact with residents or former residents of those countries is a risk factor for HIV exposure.		Since your last donation (or, if a new donor, in the last 12 months) have you had sex with a new partner who currently lives or previously lived in another country?	Y	Y
Travel – entry question	Several infectious diseases relevant to blood safety are restricted to certain geographical regions. These include variant Creutzfeldt-Jakob disease (vCJD), malaria, Chagas disease, and other vector-borne diseases such as West Nile virus, dengue fever and chikungunya.	Were you born or have you lived and/or travelled abroad?		Y	Y

Travel – malaria semi-immunity	A country without endemic malaria can use this question to flag for possible malaria semi-immunity.	Have you ever spent a continuous period of 6 months or more abroad? If so, check whether the donor spent any continuous period of 6 months or more in a malaria-endemic area.		Y	Y
Travel – malaria exposure	A donor who visits a malaria risk area could harbour asymptomatic infection after returning to their country of residence.	Have you been abroad since your last donation (or, for new donors, in the last 12 months)? If so, check whether the donor visited any malaria-endemic areas.		Y	Y
Travel – unexplained fever	A donor who visits a malaria risk area could harbour asymptomatic infection after returning to their country of residence.		Have you ever had an unexplained fever after travelling abroad? If so, check whether it was within 6 months of visiting a malaria--endemic area.	Y	Y
Travel – Chagas exposure	To identify donors who were born in a Chagas-endemic country, and hence are suitable only for plasma derivative production.	What was your country of birth?		Y	N
Travel – vCJD exposure	The core geographical risk of variant Creutzfeldt–Jakob disease (vCJD) has been defined as extending from 1980 to 1996 in the United Kingdom. In each individual blood establishment, risk assessment should define the appropriate cumulative period and whether additional countries should be added to the risk zone.	From 1980 to 1996 inclusive, did you spend 6 months or more (cumulative) in the UK?		Y	N

Other blood-borne risks – hepatitis	To identify donors with occupational or household exposure to hepatitis, and trigger appropriate clearance/immunity testing.	Have you been exposed to hepatitis or jaundice (via family, household or occupation) in the past 6 months?		Y	Y
Other blood-borne risks – flexible endoscopy	Some countries have reported an association between procedures employing flexible endoscopy and hepatitis C infection.		Have you had an endoscopy or gastroscopy in the last 4 months? If so, was a flexible instrument used and was any biopsy performed?	Y	Y
Other blood-borne risks – dental	Tooth extraction and other dental procedures can be associated with transient bacteraemia, which can theoretically cause bacterial contamination of fresh blood components.	Have you had any dental treatment in the last week?		Y	Y
Other blood-borne risks – invasive procedures	Invasive procedures can be a source of blood-borne infection. The donor may require temporary deferral to exclude window period transmission of infectious disease.	Since your last donation or in the previous 6 months have you had: • an operation or medical investigations? • any body piercing and/or tattoo? • acupuncture treatment by anyone other than a registered practitioner? • an accidental injury involving a needle and/or mucous membrane exposure to human blood?		Y	Y
Other blood-borne risks – familial CJD	Classical Creutzfeldt–Jakob disease (CJD) may potentially be transmitted by blood transfusion.	Have you been told of a family history of Creutzfeldt-Jakob disease (CJD)?		Y	Y
Other blood-borne risks – pituitary extracts	Most reported cases of iatrogenic CJD have been associated with human-	Have you ever had treatment with human pituitary extracts?		Y	N

	derived pituitary hormone treatment.				
Other blood-borne risks – transplantation	Transplantation may result in the transmission of a range of infectious diseases, and corneal transplantation and *dura mater* grafts have been reported as causes of iatrogenic CJD.	Have you ever had a transplant or graft (organ, bone marrow, cornea, *dura mater*, bone, etc.)?		Y	Y
Other blood-borne risks – cuts and abrasions	Broken or inflamed skin is a potential source of bacterial contamination. A rash may be a sign of underlying disease.		Do you have any cuts, abrasions or sores?	Y	Y
Other blood-borne risks – gastrointestinal symptoms	Gastrointestinal symptoms could be associated with conditions which impact both recipient safety (e.g. Yersinia enterocolitica) and donor safety (e.g. hypokalaemia secondary to vomiting and diarrhoea).	In the past week, have you had any diarrhoea, abdominal pain or vomiting?		Y	Y
Other blood-borne risks – transfusion	Blood transfusion may cause transmission of blood-borne infections, including geographically restricted infections such as vCJD and Chagas disease.	Have you ever received a blood transfusion or injection of blood products? If so, where and when?		Y	Y
Other blood-borne risks – positive infectious disease testing	HIV, hepatitis B, hepatitis C and HTLV are transfusion-transmissible infectious agents, and all may be transmitted between partners by sexual or blood contact.	Are you or is your partner positive for HIV, hepatitis B, hepatitis C or HTLV?		Y	Y

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APPENDIX 2.
TABLES FOR CALCULATION OF BLOOD VOLUMES OR COLLECTION VOLUMES

Appendix 2a

Table 1. Blood volume of women in mL as calculated according to the ICSH formula[1]

The weights and heights corresponding to the minimum acceptable blood volumes of 3 233 mL, 3 400 mL and 3 567 mL are indicated with grey backgrounds.

kg	50	51	52	53	54	55	56	57	58	59
145 cm	3 141	3 167	3 193	3 219	3 244	3 269	3 294	3 319	3 343	3 367
146 cm	3 157	3 183	3 209	3 235	3 260	3 285	3 310	3 335	3 359	3 384
147 cm	3 172	3 199	3 225	3 251	3 276	3 301	3 327	3 351	3 376	3 400
148 cm	3 187	3 214	3 240	3 266	3 292	3 318	3 343	3 368	3 392	3 417
149 cm	3 203	3 230	3 256	3 282	3 308	3 334	3 359	3 384	3 409	3 433
150 cm	3 218	3 245	3 272	3 298	3 324	3 350	3 375	3 400	3 425	3 450
151 cm	3 234	3 261	3 287	3 314	3 340	3 366	3 391	3 416	3 441	3 466
152 cm	3 249	3 276	3 303	3 329	3 356	3 381	3 407	3 433	3 458	3 483
153 cm	3 264	3 291	3 318	3 345	3 371	3 397	3 423	3 449	3 474	3 499
154 cm	3 279	3 307	3 334	3 361	3 387	3 413	3 439	3 465	3 490	3 515
155 cm	3 295	3 322	3 349	3 376	3 403	3 429	3 455	3 481	3 506	3 532
156 cm	3 310	3 337	3 365	3 392	3 418	3 445	3 471	3 497	3 523	3 548
157 cm	3 325	3 353	3 380	3 407	3 434	3 461	3 487	3 513	3 539	3 564
158 cm	3 340	3 368	3 396	3 423	3 450	3 476	3 503	3 529	3 555	3 581
159 cm	3 355	3 383	3 411	3 438	3 465	3 492	3 519	3 545	3 571	3 597
160 cm	3 370	3 399	3 426	3 454	3 481	3 508	3 535	3 561	3 587	3 613
161 cm	3 385	3 414	3 442	3 469	3 497	3 524	3 550	3 577	3 603	3 629
162 cm	3 400	3 429	3 457	3 485	3 512	3 539	3 566	3 593	3 619	3 645
163 cm	3 416	3 444	3 472	3 500	3 528	3 555	3 582	3 609	3 635	3 661
164 cm	3 430	3 459	3 487	3 515	3 543	3 571	3 598	3 625	3 651	3 677
165 cm	3 445	3 474	3 503	3 531	3 559	3 586	3 613	3 640	3 667	3 693
166 cm	3 460	3 489	3 518	3 546	3 574	3 602	3 629	3 656	3 683	3 709
167 cm	3 475	3 504	3 533	3 561	3 589	3 617	3 645	3 672	3 699	3 726
168 cm	3 490	3 519	3 548	3 577	3 605	3 633	3 660	3 688	3 715	3 741
169 cm	3 505	3 534	3 563	3 592	3 620	3 648	3 676	3 703	3 731	3 757

1 Pearson TC, Guthrie DL, Simpson J, Chinn C, Barosi G, Ferrant A, Lewis SM, Najean Y; Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardisation in Haematology. *Br J Haematol*. 1995, 89:748-56.

170 cm	3 520	3 549	3 578	3 607	3 636	3 664	3 692	3 719	3 746	3 773
171 cm	3 535	3 564	3 593	3 622	3 651	3 679	3 707	3 735	3 762	3 789
172 cm	3 550	3 579	3 608	3 637	3 666	3 695	3 723	3 750	3 778	3 805
173 cm	3 564	3 594	3 624	3 653	3 681	3 710	3 738	3 766	3 794	3 821
174 cm	3 579	3 609	3 638	3 668	3 697	3 725	3 754	3 782	3 809	3 837
175 cm	3 594	3 624	3 653	3 683	3 712	3 741	3 769	3 797	3 825	3 853
176 cm	3 608	3 639	3 668	3 698	3 727	3 756	3 784	3 813	3 841	3 868
177 cm	3 623	3 653	3 683	3 713	3 742	3 771	3 800	3 828	3 856	3 884
178 cm	3 638	3 668	3 698	3 728	3 757	3 786	3 815	3 844	3 872	3 900
179 cm	3 652	3 683	3 713	3 743	3 772	3 802	3 831	3 859	3 887	3 916
180 cm	3 667	3 698	3 728	3 758	3 788	3 817	3 846	3 875	3 903	3 931
181 cm	3 682	3 712	3 743	3 773	3 803	3 832	3 861	3 890	3 919	3 947
182 cm	3 696	3 727	3 758	3 788	3 818	3 847	3 877	3 905	3 934	3 962
183 cm	3 711	3 742	3 772	3 803	3 833	3 862	3 892	3 921	3 950	3 978
184 cm	3 725	3 756	3 787	3 818	3 848	3 878	3 907	3 936	3 965	3 994
185 cm	3 740	3 771	3 802	3 832	3 863	3 893	3 922	3 952	3 981	4 009

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kg	**60**	**61**	**62**	**63**	**64**	**65**	**66**	**67**	**68**	**69**
145 cm	3 391	3 414	3 438	3 461	3 484	3 507	3 529	3 552	3 574	3 596
146 cm	3 408	3 431	3 455	3 478	3 501	3 524	3 547	3 569	3 591	3 613
147 cm	3 424	3 448	3 472	3 495	3 518	3 541	3 564	3 587	3 609	3 631
148 cm	3 441	3 465	3 489	3 512	3 535	3 558	3 581	3 604	3 627	3 649
149 cm	3 458	3 482	3 505	3 529	3 552	3 576	3 599	3 622	3 644	3 667
150 cm	3 474	3 498	3 522	3 546	3 570	3 593	3 616	3 639	3 662	3 684
151 cm	3 491	3 515	3 539	3 563	3 587	3 610	3 633	3 656	3 679	3 702
152 cm	3 507	3 532	3 556	3 580	3 604	3 627	3 650	3 674	3 697	3 719
153 cm	3 524	3 548	3 573	3 597	3 621	3 644	3 668	3 691	3 714	3 737
154 cm	3 540	3 565	3 589	3 614	3 638	3 661	3 685	3 708	3 731	3 754
155 cm	3 557	3 581	3 606	3 630	3 654	3 678	3 702	3 725	3 749	3 772
156 cm	3 573	3 598	3 623	3 647	3 671	3 695	3 719	3 743	3 766	3 789
157 cm	3 590	3 615	3 639	3 664	3 688	3 712	3 736	3 760	3 783	3 807
158 cm	3 606	3 631	3 656	3 681	3 705	3 729	3 753	3 777	3 801	3 824

159 cm	3 622	3 647	3 672	3 697	3 722	3 746	3 770	3 794	3 818	3 841
160 cm	3 639	3 664	3 689	3 714	3 739	3 763	3 787	3 811	3 835	3 859
161 cm	3 655	3 680	3 705	3 730	3 755	3 780	3 804	3 828	3 852	3 876
162 cm	3 671	3 697	3 722	3 747	3 772	3 797	3 821	3 845	3 869	3 893
163 cm	3 687	3 713	3 738	3 764	3 789	3 813	3 838	3 862	3 886	3 910
164 cm	3 703	3 729	3 755	3 780	3 805	3 830	3 855	3 879	3 903	3 928
165 cm	3 720	3 746	3 771	3 797	3 822	3 847	3 872	3 896	3 921	3 945
166 cm	3 736	3 762	3 788	3 813	3 838	3 864	3 888	3 913	3 938	3 962
167 cm	3 752	3 778	3 804	3 830	3 855	3 880	3 905	3 930	3 955	3 979
168 cm	3 768	3 794	3 820	3 846	3 872	3 897	3 922	3 947	3 972	3 996
169 cm	3 784	3 810	3 837	3 862	3 888	3 914	3 939	3 964	3 988	4 013
170 cm	3 800	3 827	3 853	3 879	3 905	3 930	3 955	3 981	4 005	4 030
171 cm	3 816	3 843	3 869	3 895	3 921	3 947	3 972	3 997	4 022	4 047
172 cm	3 832	3 859	3 885	3 911	3 937	3 963	3 989	4 014	4 039	4 064
173 cm	3 848	3 875	3 901	3 928	3 954	3 980	4 005	4 031	4 056	4 081
174 cm	3 864	3 891	3 918	3 944	3 970	3 996	4 022	4 047	4 073	4 098
175 cm	3 880	3 907	3 934	3 960	3 987	4 013	4 039	4 064	4 090	4 115
176 cm	3 896	3 923	3 950	3 977	4 003	4 029	4 055	4 081	4 106	4 132
177 cm	3 912	3 939	3 966	3 993	4 019	4 046	4 072	4 097	4 123	4 148
178 cm	3 927	3 955	3 982	4 009	4 036	4 062	4 088	4 114	4 140	4 165
179 cm	3 943	3 971	3 998	4 025	4 052	4 078	4 105	4 131	4 156	4 182
180 cm	3 959	3 987	4 014	4 041	4 068	4 095	4 121	4 147	4 173	4 199
181 cm	3 975	4 003	4 030	4 057	4 084	4 111	4 137	4 164	4 190	4 216
182 cm	3 991	4 018	4 046	4 073	4 100	4 127	4 154	4 180	4 206	4 232
183 cm	4 006	4 034	4 062	4 089	4 117	4 143	4 170	4 197	4 223	4 249
184 cm	4 022	4 050	4 078	4 105	4 133	4 160	4 187	4 213	4 239	4 266
185 cm	4 038	4 066	4 094	4 121	4 149	4 176	4 203	4 229	4 256	4 282

9

kg	70	71	72	73	74	75	76	77	78	79
145 cm	3 618	3 639	3 661	3 682	3 703	3 724	3 745	3 765	3 786	3 806
146 cm	3 635	3 657	3 679	3 700	3 721	3 742	3 763	3 784	3 804	3 825
147 cm	3 653	3 675	3 697	3 718	3 739	3 761	3 782	3 802	3 823	3 844

148 cm	3 671	3 693	3 715	3 736	3 758	3 779	3 800	3 821	3 842	3 862
149 cm	3 689	3 711	3 733	3 754	3 776	3 797	3 818	3 839	3 860	3 881
150 cm	3 706	3 729	3 751	3 772	3 794	3 816	3 837	3 858	3 879	3 900
151 cm	3 724	3 746	3 769	3 790	3 812	3 834	3 855	3 876	3 897	3 918
152 cm	3 742	3 764	3 786	3 808	3 830	3 852	3 873	3 895	3 916	3 937
153 cm	3 759	3 782	3 804	3 826	3 848	3 870	3 892	3 913	3 934	3 956
154 cm	3 777	3 800	3 822	3 844	3 866	3 888	3 910	3 931	3 953	3 974
155 cm	3 795	3 817	3 840	3 862	3 884	3 906	3 928	3 950	3 971	3 993
156 cm	3 812	3 835	3 858	3 880	3 902	3 924	3 946	3 968	3 990	4 011
157 cm	3 830	3 853	3 875	3 898	3 920	3 942	3 964	3 986	4 008	4 029
158 cm	3 847	3 870	3 893	3 916	3 938	3 960	3 982	4 004	4 026	4 048
159 cm	3 865	3 888	3 911	3 933	3 956	3 978	4 001	4 023	4 044	4 066
160 cm	3 882	3 905	3 928	3 951	3 974	3 996	4 019	4 041	4 063	4 085
161 cm	3 899	3 923	3 946	3 969	3 992	4 014	4 037	4 059	4 081	4 103
162 cm	3 917	3 940	3 963	3 986	4 009	4 032	4 055	4 077	4 099	4 121
163 cm	3 934	3 958	3 981	4 004	4 027	4 050	4 072	4 095	4 117	4 139
164 cm	3 951	3 975	3 998	4 022	4 045	4 068	4 090	4 113	4 135	4 158
165 cm	3 969	3 992	4 016	4 039	4 062	4 085	4 108	4 131	4 153	4 176
166 cm	3 986	4 010	4 033	4 057	4 080	4 103	4 126	4 149	4 171	4 194
167 cm	4 003	4 027	4 051	4 074	4 098	4 121	4 144	4 167	4 189	4 212
168 cm	4 020	4 044	4 068	4 092	4 115	4 139	4 162	4 185	4 207	4 230
169 cm	4 037	4 062	4 086	4 109	4 133	4 156	4 179	4 203	4 225	4 248
170 cm	4 055	4 079	4 103	4 127	4 150	4 174	4 197	4 220	4 243	4 266
171 cm	4 072	4 096	4 120	4 144	4 168	4 192	4 215	4 238	4 261	4 284
172 cm	4 089	4 113	4 137	4 162	4 185	4 209	4 233	4 256	4 279	4 302
173 cm	4 106	4 130	4 155	4 179	4 203	4 227	4 250	4 274	4 297	4 320
174 cm	4 123	4 147	4 172	4 196	4 220	4 244	4 268	4 291	4 315	4 338
175 cm	4 140	4 165	4 189	4 213	4 238	4 262	4 285	4 309	4 333	4 356
176 cm	4 157	4 182	4 206	4 231	4 255	4 279	4 303	4 327	4 350	4 374
177 cm	4 174	4 199	4 223	4 248	4 272	4 297	4 321	4 344	4 368	4 392
178 cm	4 191	4 216	4 241	4 265	4 290	4 314	4 338	4 362	4 386	4 409
179 cm	4 207	4 233	4 258	4 282	4 307	4 331	4 356	4 380	4 403	4 427

180 cm	4 224	4 250	4 275	4 300	4 324	4 349	4 373	4 397	4 421	4 445
181 cm	4 241	4 266	4 292	4 317	4 341	4 366	4 390	4 415	4 439	4 463
182 cm	4 258	4 283	4 309	4 334	4 359	4 383	4 408	4 432	4 456	4 480
183 cm	4 275	4 300	4 326	4 351	4 376	4 401	4 425	4 450	4 474	4 498
184 cm	4 291	4 317	4 343	4 368	4 393	4 418	4 443	4 467	4 491	4 516
185 cm	4 308	4 334	4 360	4 385	4 410	4 435	4 460	4 485	4 509	4 533

10

kg	80	81	82	83	84	85	86	87	88	89	90
145 cm	3 826	3 846	3 866	3 886	3 906	3 925	3 944	3 964	3 983	4 002	4 021
146 cm	3 845	3 865	3 885	3 905	3 925	3 944	3 964	3 983	4 002	4 021	4 040
147 cm	3 864	3 884	3 904	3 924	3 944	3 964	3 983	4 003	4 022	4 041	4 060
148 cm	3 883	3 903	3 923	3 943	3 963	3 983	4 003	4 022	4 042	4 061	4 080
149 cm	3 902	3 922	3 942	3 963	3 983	4 002	4 022	4 042	4 061	4 081	4 100
150 cm	3 920	3 941	3 961	3 982	4 002	4 022	4 041	4 061	4 081	4 100	4 119
151 cm	3 939	3 960	3 980	4 001	4 021	4 041	4 061	4 081	4 100	4 120	4 139
152 cm	3 958	3 979	3 999	4 020	4 040	4 060	4 080	4 100	4 120	4 139	4 159
153 cm	3 977	3 997	4 018	4 039	4 059	4 079	4 099	4 119	4 139	4 159	4 178
154 cm	3 995	4 016	4 037	4 057	4 078	4 098	4 119	4 139	4 159	4 178	4 198
155 cm	4 014	4 035	4 056	4 076	4 097	4 117	4 138	4 158	4 178	4 198	4 218
156 cm	4 032	4 053	4 074	4 095	4 116	4 136	4 157	4 177	4 197	4 217	4 237
157 cm	4 051	4 072	4 093	4 114	4 135	4 155	4 176	4 196	4 217	4 237	4 257
158 cm	4 069	4 091	4 112	4 133	4 154	4 174	4 195	4 215	4 236	4 256	4 276
159 cm	4 088	4 109	4 130	4 152	4 173	4 193	4 214	4 235	4 255	4 275	4 295
160 cm	4 106	4 128	4 149	4 170	4 191	4 212	4 233	4 254	4 274	4 295	4 315
161 cm	4 125	4 146	4 168	4 189	4 210	4 231	4 252	4 273	4 293	4 314	4 334
162 cm	4 143	4 165	4 186	4 208	4 229	4 250	4 271	4 292	4 312	4 333	4 353
163 cm	4 161	4 183	4 205	4 226	4 248	4 269	4 290	4 311	4 332	4 352	4 373
164 cm	4 180	4 202	4 223	4 245	4 266	4 288	4 309	4 330	4 351	4 371	4 392
165 cm	4 198	4 220	4 242	4 263	4 285	4 306	4 328	4 349	4 370	4 390	4 411
166 cm	4 216	4 238	4 260	4 282	4 304	4 325	4 346	4 368	4 389	4 410	4 430
167 cm	4 234	4 257	4 279	4 300	4 322	4 344	4 365	4 386	4 408	4 429	4 450
168 cm	4 253	4 275	4 297	4 319	4 341	4 362	4 384	4 405	4 427	4 448	4 469

169 cm	4 271	4 293	4 315	4 337	4 359	4 381	4 403	4 424	4 445	4 467	4 488
170 cm	4 289	4 311	4 334	4 356	4 378	4 400	4 421	4 443	4 464	4 486	4 507
171 cm	4 307	4 329	4 352	4 374	4 396	4 418	4 440	4 462	4 483	4 505	4 526
172 cm	4 325	4 348	4 370	4 392	4 415	4 437	4 459	4 480	4 502	4 523	4 545
173 cm	4 343	4 366	4 388	4 411	4 433	4 455	4 477	4 499	4 521	4 542	4 564
174 cm	4 361	4 384	4 407	4 429	4 451	4 474	4 496	4 518	4 540	4 561	4 583
175 cm	4 379	4 402	4 425	4 447	4 470	4 492	4 514	4 536	4 558	4 580	4 602
176 cm	4 397	4 420	4 443	4 466	4 488	4 511	4 533	4 555	4 577	4 599	4 620
177 cm	4 415	4 438	4 461	4 484	4 506	4 529	4 551	4 574	4 596	4 618	4 639
178 cm	4 433	4 456	4 479	4 502	4 525	4 547	4 570	4 592	4 614	4 636	4 658
179 cm	4 451	4 474	4 497	4 520	4 543	4 566	4 588	4 611	4 633	4 655	4 677
180 cm	4 468	4 492	4 515	4 538	4 561	4 584	4 607	4 629	4 651	4 674	4 696
181 cm	4 486	4 510	4 533	4 556	4 579	4 602	4 625	4 648	4 670	4 692	4 714
182 cm	4 504	4 528	4 551	4 574	4 598	4 621	4 643	4 666	4 689	4 711	4 733
183 cm	4 522	4 546	4 569	4 592	4 616	4 639	4 662	4 684	4 707	4 729	4 752
184 cm	4 540	4 563	4 587	4 610	4 634	4 657	4 680	4 703	4 725	4 748	4 770
185 cm	4 557	4 581	4 605	4 628	4 652	4 675	4 698	4 721	4 744	4 767	4 789

Table 2. Blood volume of men in mL as calculated according to the ICSH formula

kg	50	51	52	53	54	55	56	57	58	59
160 cm	3 774	3 813	3 852	3 890	3 927	3 965	4 001	4 038	4 074	4 110
161 cm	3 795	3 834	3 873	3 911	3 949	3 986	4 023	4 060	4 096	4 132
162 cm	3 816	3 855	3 894	3 932	3 970	4 008	4 045	4 082	4 118	4 154
163 cm	3 837	3 876	3 915	3 954	3 992	4 030	4 067	4 104	4 140	4 177
164 cm	3 858	3 897	3 936	3 975	4 013	4 051	4 089	4 126	4 162	4 199
165 cm	3 878	3 918	3 957	3 996	4 035	4 073	4 110	4 148	4 184	4 221
166 cm	3 899	3 939	3 978	4 017	4 056	4 094	4 132	4 169	4 206	4 243
167 cm	3 919	3 960	3 999	4 038	4 077	4 116	4 154	4 191	4 228	4 265
168 cm	3 940	3 980	4 020	4 060	4 098	4 137	4 175	4 213	4 250	4 287
169 cm	3 961	4 001	4 041	4 081	4 120	4 158	4 197	4 235	4 272	4 309
170 cm	3 981	4 022	4 062	4 102	4 141	4 180	4 218	4 256	4 294	4 331
171 cm	4 002	4 042	4 083	4 123	4 162	4 201	4 240	4 278	4 316	4 353

172 cm	4 022	4 063	4 103	4 144	4 183	4 222	4 261	4 300	4 338	4 375
173 cm	4 042	4 084	4 124	4 164	4 204	4 244	4 283	4 321	4 359	4 397
174 cm	4 063	4 104	4 145	4 185	4 225	4 265	4 304	4 343	4 381	4 419
175 cm	4 083	4 125	4 166	4 206	4 246	4 286	4 325	4 364	4 403	4 441
176 cm	4 103	4 145	4 186	4 227	4 267	4 307	4 347	4 386	4 424	4 463
177 cm	4 124	4 166	4 207	4 248	4 288	4 328	4 368	4 407	4 446	4 484
178 cm	4 144	4 186	4 228	4 269	4 309	4 349	4 389	4 429	4 468	4 506
179 cm	4 164	4 206	4 248	4 289	4 330	4 371	4 410	4 450	4 489	4 528
180 cm	4 184	4 227	4 269	4 310	4 351	4 392	4 432	4 471	4 511	4 550
181 cm	4 205	4 247	4 289	4 331	4 372	4 413	4 453	4 493	4 532	4 571
182 cm	4 225	4 267	4 310	4 351	4 393	4 433	4 474	4 514	4 554	4 593
183 cm	4 245	4 288	4 330	4 372	4 413	4 454	4 495	4 535	4 575	4 614
184 cm	4 265	4 308	4 350	4 393	4 434	4 475	4 516	4 556	4 596	4 636
185 cm	4 285	4 328	4 371	4 413	4 455	4 496	4 537	4 578	4 618	4 657
186 cm	4 305	4 348	4 391	4 434	4 476	4 517	4 558	4 599	4 639	4 679
187 cm	4 325	4 368	4 412	4 454	4 496	4 538	4 579	4 620	4 660	4 700
188 cm	4 345	4 389	4 432	4 475	4 517	4 559	4 600	4 641	4 682	4 722
189 cm	4 365	4 409	4 452	4 495	4 537	4 579	4 621	4 662	4 703	4 743
190 cm	4 385	4 429	4 472	4 515	4 558	4 600	4 642	4 683	4 724	4 764
191 cm	4 405	4 449	4 492	4 536	4 578	4 621	4 663	4 704	4 745	4 786
192 cm	4 424	4 469	4 513	4 556	4 599	4 641	4 683	4 725	4 766	4 807
193 cm	4 444	4 489	4 533	4 576	4 619	4 662	4 704	4 746	4 787	4 828
194 cm	4 464	4 509	4 553	4 597	4 640	4 683	4 725	4 767	4 808	4 849
195 cm	4 484	4 529	4 573	4 617	4 660	4 703	4 746	4 788	4 829	4 871
196 cm	4 503	4 549	4 593	4 637	4 681	4 724	4 766	4 809	4 850	4 892
197 cm	4 523	4 568	4 613	4 657	4 701	4 744	4 787	4 829	4 871	4 913
198 cm	4 543	4 588	4 633	4 677	4 721	4 765	4 808	4 850	4 892	4 934
199 cm	4 562	4 608	4 653	4 698	4 742	4 785	4 828	4 871	4 913	4 955
200 cm	4 582	4 628	4 673	4 718	4 762	4 806	4 849	4 892	4 934	4 976

13

kg	60	61	62	63	64	65	66	67	68	69
160 cm	4 145	4 180	4 215	4 249	4 283	4 317	4 350	4 384	4 417	4 449

161 cm	4 168	4 203	4 238	4 272	4 306	4 340	4 374	4 407	4 440	4 473
162 cm	4 190	4 225	4 260	4 295	4 329	4 363	4 397	4 431	4 464	4 497
163 cm	4 212	4 248	4 283	4 318	4 352	4 387	4 421	4 454	4 488	4 521
164 cm	4 235	4 270	4 306	4 341	4 375	4 410	4 444	4 478	4 511	4 544
165 cm	4 257	4 293	4 328	4 364	4 398	4 433	4 467	4 501	4 535	4 568
166 cm	4 279	4 315	4 351	4 386	4 421	4 456	4 490	4 525	4 558	4 592
167 cm	4 302	4 338	4 374	4 409	4 444	4 479	4 514	4 548	4 582	4 615
168 cm	4 324	4 360	4 396	4 432	4 467	4 502	4 537	4 571	4 605	4 639
169 cm	4 346	4 383	4 419	4 454	4 490	4 525	4 560	4 594	4 629	4 663
170 cm	4 368	4 405	4 441	4 477	4 513	4 548	4 583	4 618	4 652	4 686
171 cm	4 390	4 427	4 464	4 500	4 535	4 571	4 606	4 641	4 675	4 710
172 cm	4 413	4 449	4 486	4 522	4 558	4 594	4 629	4 664	4 699	4 733
173 cm	4 435	4 472	4 508	4 545	4 581	4 617	4 652	4 687	4 722	4 756
174 cm	4 457	4 494	4 531	4 567	4 603	4 639	4 675	4 710	4 745	4 780
175 cm	4 479	4 516	4 553	4 590	4 626	4 662	4 698	4 733	4 768	4 803
176 cm	4 501	4 538	4 575	4 612	4 649	4 685	4 721	4 756	4 792	4 826
177 cm	4 522	4 560	4 598	4 635	4 671	4 708	4 744	4 779	4 815	4 850
178 cm	4 544	4 582	4 620	4 657	4 694	4 730	4 766	4 802	4 838	4 873
179 cm	4 566	4 604	4 642	4 679	4 716	4 753	4 789	4 825	4 861	4 896
180 cm	4 588	4 626	4 664	4 701	4 739	4 775	4 812	4 848	4 884	4 919
181 cm	4 610	4 648	4 686	4 724	4 761	4 798	4 835	4 871	4 907	4 942
182 cm	4 632	4 670	4 708	4 746	4 783	4 820	4 857	4 894	4 930	4 966
183 cm	4 653	4 692	4 730	4 768	4 806	4 843	4 880	4 916	4 953	4 989
184 cm	4 675	4 714	4 752	4 790	4 828	4 865	4 902	4 939	4 975	5 012
185 cm	4 697	4 736	4 774	4 812	4 850	4 888	4 925	4 962	4 998	5 035
186 cm	4 718	4 757	4 796	4 834	4 872	4 910	4 947	4 984	5 021	5 058
187 cm	4 740	4 779	4 818	4 856	4 895	4 932	4 970	5 007	5 044	5 080
188 cm	4 761	4 801	4 840	4 878	4 917	4 955	4 992	5 030	5 067	5 103
189 cm	4 783	4 822	4 862	4 900	4 939	4 977	5 015	5 052	5 089	5 126
190 cm	4 804	4 844	4 883	4 922	4 961	4 999	5 037	5 075	5 112	5 149
191 cm	4 826	4 866	4 905	4 944	4 983	5 021	5 060	5 097	5 135	5 172
192 cm	4 847	4 887	4 927	4 966	5 005	5 044	5 082	5 120	5 157	5 194

193 cm	4 869	4 909	4 949	4 988	5 027	5 066	5 104	5 142	5 180	5 217
194 cm	4 890	4 930	4 970	5 010	5 049	5 088	5 126	5 165	5 202	5 240
195 cm	4 911	4 952	4 992	5 032	5 071	5 110	5 149	5 187	5 225	5 263
196 cm	4 933	4 973	5 014	5 053	5 093	5 132	5 171	5 209	5 247	5 285
197 cm	4 954	4 995	5 035	5 075	5 115	5 154	5 193	5 232	5 270	5 308
198 cm	4 975	5 016	5 057	5 097	5 137	5 176	5 215	5 254	5 292	5 330
199 cm	4 997	5 038	5 078	5 119	5 158	5 198	5 237	5 276	5 315	5 353
200 cm	5 018	5 059	5 100	5 140	5 180	5 220	5 259	5 298	5 337	5 375

14

kg	70	71	72	73	74	75	76	77	78	79
160 cm	4 482	4 514	4 545	4 577	4 608	4 639	4 670	4 701	4 731	4 761
161 cm	4 506	4 538	4 570	4 601	4 633	4 664	4 695	4 726	4 756	4 787
162 cm	4 530	4 562	4 594	4 626	4 657	4 689	4 720	4 751	4 782	4 812
163 cm	4 553	4 586	4 618	4 650	4 682	4 713	4 745	4 776	4 807	4 837
164 cm	4 577	4 610	4 642	4 675	4 706	4 738	4 770	4 801	4 832	4 862
165 cm	4 601	4 634	4 667	4 699	4 731	4 763	4 794	4 826	4 857	4 887
166 cm	4 625	4 658	4 691	4 723	4 755	4 787	4 819	4 850	4 882	4 913
167 cm	4 649	4 682	4 715	4 747	4 780	4 812	4 844	4 875	4 906	4 938
168 cm	4 673	4 706	4 739	4 772	4 804	4 836	4 868	4 900	4 931	4 963
169 cm	4 696	4 730	4 763	4 796	4 828	4 861	4 893	4 925	4 956	4 988
170 cm	4 720	4 753	4 787	4 820	4 852	4 885	4 917	4 949	4 981	5 012
171 cm	4 744	4 777	4 811	4 844	4 877	4 909	4 942	4 974	5 006	5 037
172 cm	4 767	4 801	4 835	4 868	4 901	4 934	4 966	4 998	5 030	5 062
173 cm	4 791	4 825	4 858	4 892	4 925	4 958	4 990	5 023	5 055	5 087
174 cm	4 814	4 848	4 882	4 916	4 949	4 982	5 015	5 047	5 080	5 112
175 cm	4 838	4 872	4 906	4 940	4 973	5 006	5 039	5 072	5 104	5 136
176 cm	4 861	4 896	4 930	4 963	4 997	5 030	5 063	5 096	5 129	5 161
177 cm	4 885	4 919	4 953	4 987	5 021	5 054	5 088	5 121	5 153	5 186
178 cm	4 908	4 943	4 977	5 011	5 045	5 079	5 112	5 145	5 178	5 210
179 cm	4 931	4 966	5 001	5 035	5 069	5 103	5 136	5 169	5 202	5 235
180 cm	4 955	4 990	5 024	5 059	5 093	5 127	5 160	5 193	5 227	5 259
181 cm	4 978	5 013	5 048	5 082	5 116	5 150	5 184	5 218	5 251	5 284

182 cm	5 001	5 036	5 071	5 106	5 140	5 174	5 208	5 242	5 275	5 308
183 cm	5 024	5 060	5 095	5 129	5 164	5 198	5 232	5 266	5 300	5 333
184 cm	5 047	5 083	5 118	5 153	5 188	5 222	5 256	5 290	5 324	5 357
185 cm	5 071	5 106	5 142	5 177	5 211	5 246	5 280	5 314	5 348	5 381
186 cm	5 094	5 129	5 165	5 200	5 235	5 270	5 304	5 338	5 372	5 406
187 cm	5 117	5 153	5 188	5 224	5 259	5 293	5 328	5 362	5 396	5 430
188 cm	5 140	5 176	5 212	5 247	5 282	5 317	5 352	5 386	5 420	5 454
189 cm	5 163	5 199	5 235	5 270	5 306	5 341	5 376	5 410	5 444	5 478
190 cm	5 186	5 222	5 258	5 294	5 329	5 364	5 399	5 434	5 468	5 503
191 cm	5 209	5 245	5 281	5 317	5 353	5 388	5 423	5 458	5 492	5 527
192 cm	5 231	5 268	5 304	5 340	5 376	5 412	5 447	5 482	5 516	5 551
193 cm	5 254	5 291	5 327	5 364	5 400	5 435	5 470	5 506	5 540	5 575
194 cm	5 277	5 314	5 351	5 387	5 423	5 459	5 494	5 529	5 564	5 599
195 cm	5 300	5 337	5 374	5 410	5 446	5 482	5 518	5 553	5 588	5 623
196 cm	5 323	5 360	5 397	5 433	5 470	5 506	5 541	5 577	5 612	5 647
197 cm	5 345	5 383	5 420	5 456	5 493	5 529	5 565	5 600	5 636	5 671
198 cm	5 368	5 405	5 443	5 479	5 516	5 552	5 588	5 624	5 660	5 695
199 cm	5 391	5 428	5 466	5 503	5 539	5 576	5 612	5 648	5 683	5 719
200 cm	5 413	5 451	5 488	5 526	5 562	5 599	5 635	5 671	5 707	5 742

15

kg	80	81	82	83	84	85	86	87	88	89
160 cm	4 791	4 821	4 851	4 880	4 909	4 938	4 967	4 995	5 024	5 052
161 cm	4 817	4 847	4 876	4 906	4 935	4 964	4 993	5 022	5 050	5 078
162 cm	4 842	4 872	4 902	4 932	4 961	4 990	5 019	5 048	5 076	5 105

APPENDIX 3.
STATISTICAL PROCESS CONTROL

Introduction

Statistical process control (SPC) is a tool that enables an organisation to detect changes in the processes and procedures it carries out by monitoring data collected over a period of time in a standardised fashion. SPC became mandatory in 2005 for blood establishments in the EU (Directive 2004/33/EC). Methods and standards for the application of SPC to quality assurance of blood components need to be continuously studied and further developed. The technique can be applied to all activities in a blood facility, including administrative/clerical, scientific and technical processes. It is important that the processes to which SPC are to be applied are prioritised due to the amount of work involved. Currently, SPC is proving most beneficial in monitoring the performance of infectious markers and leucocyte-depletion testing. SPC is one of the few methods that can show how an improvement to a process has achieved the desired result, and enables decision-making to be placed on a much more rational and scientific basis.

Implementation of SPC

As for all other aspects of quality, implementation of SPC demands understanding and commitment on the part of the management of the blood facility. It must be included in the quality system of the facility, and a training programme should be introduced for senior management as well as operational staff. Plans must be made for data collection, including of control charts, and all matters dealing with changes detected in processes, especially sudden situations. Regular reviews of processes against SPC data should take place, with the specific objective of continuous improvement.

Strategy for statistical sampling

As much as possible, the number and frequency of components sampled for quality control and the number of test failures per sample that trigger an appropriate response (e.g. investigation or re-validation of materials and procedures) should be based on the considerations detailed below.

Tolerance of failure

A ‘target failure rate’ should be established as the failure rate that should not be exceeded. This ensures that monitoring of aspects of quality is continuous and that a failure rate exceeding target values triggers appropriate corrective action.

Confidence level

A confidence level should be set for the detection of an actual failure rate that lies above the ‘target failure rate’.

A valid method of statistical analysis should be used to determine either actual failure rate lies above the ‘target failure rate’.

Frequency of control sampling

A number of challenges arise in framing statistically based quality control testing programs for labile blood components. Due to the complexity of the transfusion system, blood facilities should consult statistical experts when designing process control systems. Issues include the: very large variation in volumes of blood components at different blood establishments; need to minimise losses in blood components through testing at small centres; very low expected rate of non-conformance for some processes, and the number of discrete conditions that arise in the manufacture of otherwise similar components. These may include:

- Number of sites, operators and work shifts;
- Different collection and processing systems and equipment;
- Use of multiple reagent lots;
- Alternative preparation times and temperatures;

- Donor-related variables may affect the final quality of the blood component, even in a fully controlled process (e.g. for HbS donor blood with poor leucofiltration properties);
- The fact that blood components may be used for more than one clinical indication and require different levels of control (e.g. leucocyte-depleted RBCs for neonates vs for general transfusion).

Additionally, in many cases, the medical basis for currently accepted quality standards has not been rigorously established, making it difficult to determine the level of deviation from the expected level of conformance that can be tolerated. Nevertheless, to implement SPC, blood establishments need to establish the 'target failure rate' that should not be exceeded for each control test.

It is also desirable that the criterion for non-conformance should have at least a power of 80 per cent to detect the target failure rate, while giving a false-positive result in fewer than 5 per cent of determinations.

Consideration must also be given to the strategy for representative sampling of units for control testing. Because similar components are prepared under a variety of conditions, it is important that the sample set should include representative units prepared in all possible ways. Sampling may need to be stratified accordingly (i.e. to include a minimum number of samples from each condition).

The sample numbers specified for statistically valid process controls are minimum samples. In circumstances in which there are multiple processing conditions, and in blood establishments with large volumes of blood components, quality-control testing should be increased above the statistically determined minimum. This should be done in a controlled manner through the application of more rigorous statistical parameters, such as an increase in the expected proportion of samples that conform to a defined standard.

Additional considerations that may apply to the design of a quality control strategy include:

- The public-health importance of the standard being controlled (i.e. the period of time during which a process deviation could be tolerated before detection and correction);
- The overall blood component volume;
- The capacity for sampling and quality-control testing of the facility, including whether the quality-control testing is ablative (i.e. destructive of the processed blood component);
- The target failure rate of a process that is in control;
- A pre-defined strategy for managing non-process failures, e.g. a failed leucocyte-depletion procedure where further evaluation determined that the donor was HbS positive.

Three methods of statistical process control are provided below as examples.[1]

Example 1. Use of control charts

By plotting historical and prospective data on specially constructed charts, signs of process change can often be detected at an early stage, enabling remedial action to be taken. Steps for the construction of SPC charts are the same for all applications:

- Collection of historical data;
- Calculation of 'location and variation statistics' (see below);
- Calculation of statistical control limits for the location and variation statistics;
- Construction of the chart;
- Plotting of prospective data.

Two types of data are conventionally collected:

1 Beckman N, Nightingale MJ, Pamphilon D. Practical guidelines for applying statistical process control to blood component blood component. *Transfus Med* 2009; 19: 329-39.

- Variable data, appropriate to anything that is measured directly such as cell count, pH, time taken for a process, etc.;
- Attribute data, appropriate to anything that is counted on a 'yes or no' basis.

The type of SPC chart used depends on the type of data collected.

Control charts for variable data

Major applications in a blood establishment are likely to be Individual/Moving Range charts and Average/Range charts.

Individual/Moving Range charts are used where a process is monitored by a single measurement on the sample, of the parameter in question e.g. residual leucocyte count on a platelet preparation. The steps for constructing an SPC chart are as follows:

- Historical data are collected by measuring a random sample each day, and the moving range established by taking the difference between each sample and its predecessor;
- The location statistic is the average of the individual counts, whereas the variation statistic is the average moving range;
- The natural variation in a process is defined as the process average, plus or minus 3 standard deviations. Hence, the upper control limit (UCL) and the lower control limit (LCL) for the location and variation statistics are determined as the appropriate average, plus and minus 3 standard deviations;
- SPC charts conventionally have two distinct parts: one for the location statistic, which appears above the other for the variation statistic. For each part, the average is drawn as a solid line between two dotted lines that signify the UCL and LCL.

Prospective data are plotted on SPC charts in a similar way.

Average/Range charts are used in a situation where an early statistical response to a small process change is required, and where multiple control samples (up to 10) are subjected to the process. A typical example might be repeated use of a control sample during the daily use of a cytometer. In this situation, the average daily count on the control sample is calculated, the location statistic being the average of the averages. Each day shows a range in the control counts; the variation statistic is the average of these ranges. The Average/Range chart is then constructed in a similar manner to the Individual/Moving Range chart, except that the LCL for the Range part of the chart is, by definition, zero.

Control charts for attribute data

Attribute data, in general, fall into one of two categories: those counting the number of units sampled which are defective, and those counting the incidence of non-conformance to a requirement (each non-conformance in this case being classified as a defect). For example, a completed form is classified as 'defective' even if it contains only one non-conformance (though it may, in fact, contain multiple defects).

Attribute charts for the proportion of defective units (sometimes known as p-charts) are based on the calculation of the proportion of units found to be defective, i.e. having one or more defects per unit sampled, in sets of units sampled at intervals. The location statistic for the attribute is calculated by dividing the total number of defective units by the total number of units sampled, unless the sets of samples are always the same size, in which case the average of the proportion of defective units in each set may be taken. Since the data stem from yes/ no criteria, attribute charts do not have a variation statistic.

UCL and LCL are determined as described above. In this system, it is possible to arrive at a negative value for the LCL, in which case it defaults to zero.

It should be noted that the calculation of standard deviation in a yes/no system such as this depends on the sample size. Hence, an increase or decrease in the set of units sampled necessitates re-establishing the UCL and LCL. An increase in sampling size generally results in convergence of UCL and LCL, making the system more sensitive to changes in the process.

Construction of the chart is carried out as described above.

Attribute charts for defects (sometimes known as u-charts) are generally useful when the object under investigation often has more than one non-conformance with requirements. They are well-suited to the control of clerical procedures. Collection of historical data involves counting the number of defects in each unit of a set of samples, repeated at intervals.

The location statistic is the average number of defects per unit, calculated by dividing the total number of defects in the total number of historical samples. As before, there is no variation statistic for attribute data.

Once again, UCL and LCL are calculated on the basis of the location statistic, plus and minus 3 standard deviations. Standard deviation in this system again depends on sample size, and any prospective increase requires re-establishment of the UCL and LCL.

The likely result is a convergence on the average, facilitating the detection of smaller changes in the process.

Construction of the u-chart follows the convention set for all SPC charts.

Interpretation of control charts

In general, if prospective data are plotted on the control chart and they follow the pattern established using historical data, the process may be assumed to be 'in control'. Changes in the pattern area reliable and sensitive means of detecting that a change has taken place in the process, warranting investigations into the cause. Rules have been established to give guidance to users as to when a change has occurred:

- Rule 1: any point outside one of the control limits;
- Rule 2: seven consecutive points all above or all below the average line;
- Rule 3: seven consecutive points all increasing or all decreasing (a particular indicator of drift in the process average or range).

In addition, any unusual pattern or trend within the control lines may be an indicator of change.

Should information from the charts indicate that unplanned change is taking place within the process, action should be taken to identify any specific or common cause of the change. Application of SPC is the most reliable way of confirming that measures taken to improve the efficiency of a process are giving the desired results, by showing reduction in variation around the mean (for measured data) or a trend toward zero defects (for counted data).

Example 2. Method of scan statistics

The method of scan statistics provides a suitable model for determining the frequency of control testing.[2] In this method, the number of non-conforming test results in a fixed sample size is determined. However, the sample set is regarded as a 'window' of observations that 'moves' progressively as test results are accumulated. For example, if the 'window size' is set at 60 observations, the first test set includes observations 1 through to 60; the second test set includes observations 2 through to 61; the third test set includes observations 3 through to 62. Progression of the 'window' can also be done a few samples at a time, such as by addition of daily test results as a group. To apply this method, the blood facility must identify a reasonably large 'universe' of ultimate test samples, typically representing a year or more of testing, or a period after which routine re-validation might be expected to occur because of process modifications (e.g. equipment replacement, software upgrades). The size of the moving window can then

2 Glaz J, Naus J, Wallenstein S, Scan Statistics. 2001; Springer, New York.

be determined based on the expected rate of failed tests for a conforming process (as defined in the Quality Control tables of each component described in Chapter 5), the size of the test universe, and the target failure rate to be detected as indicating a non-conforming process. The table below shows the minimum failure rate that can be detected at 80 per cent or greater power in any single window of control tests for test criteria with false-positive rates below 5 per cent.

Requiring that the number of control tests in the 'window' should take place in the desired time interval yields the frequency of control testing.

The following example illustrates how the method of scan statistics can be used.

A blood facility seeks to monitor the failure rate of Leucocyte-Depleted. The expected failure rate (rate of non-conforming tests for a conforming process) is taken to be 0.1 per cent. The facility sets an action trigger at 5 per cent as a means to detect a defective lot of filters. The quality-control standard is established to ensure, with at least 80 per cent confidence, that a true failure rate of 5 per cent would be detected, but at a false-positive rate below 5 per cent for a declaration of non-conformance.

For a blood facility with 400 quality-control tests per year (approximately 34 per month), a non-conforming process can be declared if, in any 'moving window' of 60 consecutive such tests, two or more non-conforming test results are found (i.e. the trigger is greater than one non-conforming test in any window of 60 tests). This model has a power of 80.8 per cent to detect a true rate of non-conformance of 5 per cent in any window of 60 tests, and near certainty to detect this rate over 1 year. Based on scan statistics, the false-positive rate of such declarations is only 2.0 per cent.

If the number of quality control tests is 1 200 per year (100 per month), a non-conforming process can be declared if in any 'moving window' of 120 sequential quality control tests, three or more non-conforming test results are found. The false-positive rate of such declarations is only 0.7 per cent. The power is 80.7 per cent to detect a non-conformance rate of 4.6 per cent (the power is 85.6 per cent to detect a 5 per cent failure rate) for any window of 120 tests, and near certainty over 1 year.

Table 1. Sample size ('window') and maximum number of failed tests allowed for a conforming process based on scan statistics

Allowed failure rate for a conforming process	Number of tests in 'universe' (e.g. the number of tests per year)	Sample size (i.e. the fixed number of tests in a moving 'window')	Maximum allowed number of failed tests in window	False positive rate of test criterion	Minimum failure rate of a non-conforming process detectable at > 80 % power in any single 'window'	
					Minimum 'target failure rate' for a non-conforming process	Power to detect non-conforming process in any window of quality control tests
25 %	400	30	16	2.5 %	63 %	81.9 %
		60	26	2.9 %	50 %	81.7 %
	1 200	30	17	2.0 %	66 %	81.3 %

		60	27	3.8 %	52 %	83.0 %
10 %	400	30	9	3.5 %	40 %	82.4 %
		60	14	2.7 %	30 %	83.8 %
	1 200	30	10	2.8 %	43 %	81.1 %
5 %	400	30	6	3.7 %	29 %	81.0 %
		60	9	2.3 %	21 %	83.7 %
	1 200	30	7	2.2 %	33 %	82.3 %
1 %	400	30	3	1.0 %	18 %	81.4 %
		60	4	0.9 %	11 %	80.3 %
	1 200	60	4	2.7 %	11 %	80.3 %
0.1 %	400	30	1	1.1 %	10 %	81.6 %
		60	1	2.0 %	5 %	80.8 %
	1 200	30	1	3.2 %	10 %	81.6 %
		120	2	0.7 %	4.6 %	80.7 %

Example 3. Statistical process control for dichotomous outcomes: an approach based upon hypergeometric/binomial distributions

A hypergeometric distribution is based upon random sampling (without replacement) of a factor that has a dichotomous outcome. This distribution is applicable for the assessment of quality control measures related to blood components for which the outcome is pass/fail. A binomial distribution is very similar to a hypergeometric distribution, but it is based upon sampling with replacement. At sampling levels of $n \geq 59$ to meet the 95 per cent criterion, these two distributions are essentially identical.

For statistical quality control using the hypergeometric/binomial approach, a cycle is defined as the blood-component volume that is being subject to quality assessment within a defined time period. The appropriate size for a quality-control cycle is determined based upon the desired frequency of control sampling as described above and the selected proportion of conforming samples.[3]

3 For example, 95 % conformance (and the resulting high level of quality-control testing) would be appropriate for a safety-related blood component standard such as residual leucocytes in a Leucocyte-Depleted component. However, 75 % conformance may be acceptable for a standard such as components content, where standardisation is desirable, but is not directly related to recipient safety.

Statistical quality control based upon a hypergeometric distribution is applicable for cycle sizes between n = 30 and n = 4 500.[4] Successful control requires that predetermined random sample sizes be assessed with an outcome of 0, 1 or 2 failures, depending on the cycle size.

For cycle sizes above n = 4 500, the hypergeometric distribution approaches the binomial distribution and the traditional binomial approach can be applied, i.e. assessing n = 60 random samples per cycle with an outcome of zero failures; n = 93 with one failure or n = 124 with 2 failures.

The table below provides random sample sizes across a range of cycle sizes. With a larger cycle size, 1 or 2 occurrences of non-conformance are allowed in conjunction with a larger pre-specified sample size.

For example, if the cycle size is 65 (95 per cent/95 per cent), there are three options that need to be pre-determined: a sample size of 34 without any failure, a sample size of 49 with 1 failure, or a sample size of 59 with 2 failures. If (i) a sample size of 34 and observation of one failure, or (ii) a sample size of 49 and observation of two failures is chosen, 100 per cent quality control can still be done to make the final determination, whether or not greater than 95 per cent of the components meet the standard.

After the cycle size reaches 7 000 for 95 per cent/95 per cent and 13 000 for 95 per cent/75 per cent, the results based on the hypergeometric distribution are same as those based on a binomial distribution.

4 For a cycle size of 30, greater than 95 % conformance is reflected by, at most, one non-conforming unit because 29/30 = 96.7 % and 28/30 = 93.3 %. To define this conformance statistically, it is necessary to be able to conclude with 95 % confidence that greater than 95 % of the units are conforming (i.e. ≤ n = 1 non-conforming unit for a cycle size of n = 30). Using a null hypothesis that there are at least two non-conforming units among the 30 units, the alternative hypothesis is that there are fewer than two non-conforming units among the 30 units. Under this null hypothesis, the probability that the first 22 units are all good is 6.4 %, which is calculated as:

$$\frac{28}{30}\times\frac{27}{29}\times\frac{26}{28}\cdots\frac{9}{11}\times\frac{8}{10}\times\frac{7}{9}=\frac{8\times7}{30\times29}=0.064$$

So the null hypothesis cannot be rejected at the 5 % significance level, which corresponds to ‘with 95 % confidence’.

Under the null hypothesis stated above, the probability that the first 23 units are all good is 4.8 %:

$$\frac{28}{30}\times\frac{27}{29}\times\frac{26}{28}\cdots\frac{8}{10}\times\frac{7}{9}\times\frac{6}{8}=\frac{7\times6}{30\times29}=0.048$$

So the null hypothesis can be rejected at the 5 % significance level which corresponds to ‘with 95 % confidence’. Thus, 23 samples without a non-conformance are needed to conclude with 95 % confidence that greater than 95 % of the units are conforming.

225 **Table 2. Sizes of random samples needed at various quality control cycle sizes to assess 95 %, 90 %**
226 **or 75 % conformance to a standard with 95 % confidence**

	95 %/95 %				**95 %/90 %**				**95 %/75 %**			
	95 % confidence that > 95 % of the components meet the standard				*95 % confidence that > 90 % of the components meet the standard*				*95 % confidence that > 75 % of the components meet the standard*			
Lot size	**Failures allowed in lot**	**Sample size**			**Failures allowed in lot**	**Sample size**			**Failures allowed in lot**	**Sample size**		
		No failure	*1 failure allowed*	*2 failures allowed*		*No failure*	*1 failure allowed*	*2 failures allowed*		*No failure*	*1 failure allowed*	*2 failures allowed*
30	1	23	30	N/A	2	19	26	30	7	9	13	17
31	1	24	31	N/A	3	16	23	28	7	9	14	18
32	1	25	32	N/A	3	17	24	29	7	9	14	18
33	1	26	33	N/A	3	17	25	30	8	9	13	17
34	1	26	34	N/A	3	18	25	31	8	9	14	18
35	1	27	35	N/A	3	18	26	32	8	9	14	18
36	1	28	36	N/A	3	19	27	33	8	9	15	19
37	1	29	37	N/A	3	19	28	33	9	9	14	18
38	1	30	38	N/A	3	20	28	34	9	9	14	18
39	1	30	39	N/A	3	20	29	35	9	9	15	19
40	1	31	39	N/A	3	21	30	36	9	10	15	19
45	2	28	39	45	4	20	29	36	11	9	14	19
50	2	31	43	50	4	22	33	40	12	9	15	19
55	2	35	48	55	5	21	32	40	13	10	15	20
60	2	38	52	60	5	23	34	43	14	10	16	21

65	3	34	49	59	6	22	33	42	16	10	15	20
70	3	37	52	63	6	24	36	46	17	10	16	20
75	3	39	56	68	7	23	35	44	18	10	16	21
80	3	42	60	72	7	24	37	47	19	10	16	21
85	4	38	56	69	8	23	36	46	21	10	16	21
90	4	40	59	73	8	25	38	49	22	10	16	21
95	4	42	62	77	9	24	37	47	23	10	16	21
100	4	45	65	81	9	25	39	50	24	10	16	22
120	5	47	69	87	11	26	40	52	29	10	17	22
140	6	48	72	92	13	26	41	53	34	11	17	22
160	7	49	75	95	15	27	41	54	39	11	17	22
180	8	50	77	98	17	27	42	55	44	11	17	22
200	9	51	78	101	19	27	42	55	49	11	17	23
220	10	52	79	103	21	27	42	56	54	11	17	23
240	11	52	80	104	23	27	43	56	59	11	17	23
260	12	53	81	106	25	27	43	57	64	11	17	23
280	13	53	82	107	27	28	43	57	69	11	17	23
300	14	54	83	108	29	28	43	57	74	11	17	23
320	15	54	83	109	31	28	44	57	79	11	17	23
340	16	54	84	110	33	28	44	58	84	11	17	23
360	17	54	85	111	35	28	44	58	89	11	17	23
380	18	55	85	111	37	28	44	58	94	11	17	23

400	19	55	85	112	39	28	44	58	99	11	17	23
450	22	54	84	111	44	28	44	59	112	11	17	23
500	24	56	87	114	49	28	44	59	124	11	17	23
550	27	55	86	113	54	28	45	59	137	11	17	23
600	29	56	88	116	59	28	45	59	149	11	17	23
650	32	56	87	115	64	28	45	59	162	11	17	23
700	34	57	89	117	69	28	45	60	174	11	17	23
750	37	56	88	116	74	28	45	60	187	11	17	23
800	39	57	89	118	79	28	45	60	199	11	17	23
850	42	56	89	117	84	28	45	60	212	11	17	23
900	44	57	90	119	89	28	45	60	224	11	17	23
950	47	57	89	118	94	29	45	60	237	11	17	23
1000	49	57	90	119	99	29	45	60	249	11	17	23
1500	74	58	91	121	149	29	45	60	374	11	17	23
2000	99	58	92	122	199	29	46	61	499	11	17	23
2500	124	58	92	122	249	29	46	61	624	11	17	23
3000	149	58	92	123	299	29	46	61	749	11	17	23
3500	174	58	93	123	349	29	46	61	874	11	17	23
4000	199	58	93	123	399	29	46	61	999	11	17	23
4500	224	59	93	123	449	29	46	61	1124	11	17	23
5000	249	59	93	123	499	29	46	61	1249	11	17	23
6000	299	59	93	123	599	29	46	61	1499	11	17	23

7000	349	59	93	124	699	29	46	61	1749	11	17	23
8000	399	59	93	124	799	29	46	61	1999	11	17	23
9000	449	59	93	124	899	29	46	61	2249	11	17	23
10000	499	59	93	124	999	29	46	61	2499	11	17	23
11000	549	59	93	124	1099	29	46	61	2749	11	17	23
12000	599	59	93	124	1199	29	46	61	2999	11	17	23
13000	649	59	93	124	1299	29	46	61	3249	11	18	23
14000	699	59	93	124	1399	29	46	61	3499	11	18	23
15000	749	59	93	124	1499	29	46	61	3749	11	18	23

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APPENDIX 4.
HEALTH ECONOMICS IN BLOOD TRANSFUSION

Overview

Providing blood is expensive and the heavy burden that it places on national health budgets may continue to grow as it becomes necessary to implement further safety measures, including extra screening tests, new pathogen inactivation technologies and additional quality requirements. Under these circumstances, costs throughout the blood transfusion chain from donor to recipient are bound to come under intense scrutiny as funders seek to economise and increasingly demand value for money.

The objective for blood establishments responsible for preparing, controlling and issuing blood components should be to use appropriate means in order to economise and reduce capital and recurrent costs in the blood transfusion service, but without compromising the quality, effectiveness and safety of their therapeutic blood components for the benefit of patients in need of transfusion.

Therefore, healthcare managers and professionals in blood transfusion and quality management should be aware of cost structures in the blood transfusion chain, in conjunction with efforts to optimise the use of blood components and minimise relative costs.

Investing in quality

Evidence-based data and research on the economics of blood are limited. Standard methods for costing and financial planning should be established to enable the calculation of total economic costs associated with blood services, bench-marking, budget planning, financial accountability, purchasing and logistics.

Competent authorities for blood transfusion should define priorities and decide on the data and indicators that must be collected. The blood supply chain from donor to patient should be analysed to identify opportunities for cost reductions. Best practices should be implemented using effective bench-marking procedures. The contribution of management tools towards controlling costs and improving the efficiency of blood transfusion should be evaluated.

Costing analysis

The criteria used for cost analysis and realistic cost-effectiveness projections at national, regional and local level should comply with WHO guidelines for costing blood transfusion services.

An important step towards a cost-effectiveness analysis is to define the regulatory framework in order to allow the estimation of costs and outputs of specific activities. An activity-based cost procedure should identify major groups of activities in the blood service, with cost-output measurable indicators defined for each area (e.g. blood collection, blood processing, blood storage and distribution, haemovigilance). The total costs for each activity include both capital (building, equipment, training, furniture, vehicles, etc.) and recurrent costs (personnel, supplies, transportation, utilities, administration, insurance, etc.).

Managers of blood transfusion services (BTS) should define the objectives of cost analyses for the purposes of budget planning, financial accountability and evaluation, and cost effectiveness analysis. In this way, cost information can be used to monitor the efficiency of the components of BTS, and for resource mobilisation and other tasks.

Modelling cost-effectiveness analysis in transfusion

BTS managers need to collect data to support analyses of cost-effectiveness based on the following rules:

- The central element is the activity, defined as a set of interlinked tasks resulting in the production of goods and services;
- Activities are not isolated, but are part of a process;
- Each activity has a supplier and a client (internal and external) and contributes to the creation of value.

The BTS manager should perform for each activity:

- Calculation of blood component costs;

- Calculation of selling prices;
- Calculation of margins between selling prices and costs;
- Cost accounting with a view to benchmarking;
- Decision-making regarding the possible introduction of an innovation and the choice between alternative methods.

Economic aspects of the clinical use of blood

The economic aspects of the clinical use of blood should also be evaluated in relation to outcomes and effectiveness, taking into account parameters such as the amount of blood component administered, duration of treatment, length of hospital stay and quality adjusted life years (QALYs). Inappropriate use of blood (i.e. in terms of having unexpected adverse reactions and a direct bearing on healthcare budgets) should be investigated in order to substantiate the cost-benefit and the cost-effectiveness of transfusion.

Carrying out an economic evaluation of expenditures related to the use of blood and blood components involves the identification of the therapeutic use of blood components and the costs from the initiation of treatment to its completion.

Assessing the economic implications and effectiveness of therapeutic interventions would be facilitated by measuring outcomes and effectiveness. Therefore, it is necessary to record data both before and after the use of blood components, in order to substantiate the benefits that accrue.

Alternative treatment strategies using blood components need to be examined with respect to therapeutic outcomes and in relation to cost-benefit, cost-effectiveness and cost utility.

Methods for evaluating a more expensive therapy (e.g. leucocyte-depleted cells) against a cheaper one should be considered, given that the former may result in a shorter hospital stay and as a consequence reduced hospital charges.

Inappropriate use of blood has a direct bearing on healthcare budgets. Over and under-use of blood components may harm the patient. Misuse of blood may also result in an unexpected adverse outcome.