Guide to the preparation, use and quality assurance of BLOOD COMPONENTS

European Committee on Blood Transfusion (Partial Agreement) (CD-P-TS)

EDQM

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Guide to the preparation, use and quality assurance of blood components

22nd Edition

European Directorate for the Quality of Medicines & HealthCare

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Foreword

Founded in 1949, the Council of Europe is the oldest and largest of all European organisations and now numbers 46 member states.[1] The aim of the Council of Europe is to achieve a greater unity between its members for the purpose of safeguarding and realising the ideals and principles which are their common heritage and facilitating their economic and social progress.

The Council of Europe has consistently address problems in the field of health. Council of Europe standards for substances of human origin (SoHO) enshrine fundamental ethical principles such as the non-commercialisation of the human body and provide guidance for the quality and safety of human blood, organ, tissues and cells, and their effective use.

With regard to blood transfusion, co-operation among member states started back in the 1950s. The activities were inspired by the following guiding principles: promotion of voluntary, non-remunerated blood

1 Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Republic of Moldova, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Republic of Türkiye, Ukraine, United Kingdom.

donation, mutual assistance, optimal use of blood and blood products and protection of the donor and the recipient.

The Council of Europe has adopted a number of recommendations covering scientific, ethical, social and training aspects of blood transfusion. One of the recommendations include Recommendation No. R (88) 4 on the responsibilities of health authorities in the field of blood transfusion and Recommendation No. R (95) 15, which contains, in a technical appendix, guidelines on the use, preparation and quality assurance of blood components.

Work on Recommendation No. R (95) 15 started in 1986, when the Select Committee of Experts on Quality Assurance in Blood Transfusion Services published proposals on quality assurance in blood transfusion services. Based on these proposals, the Select Committee produced a more comprehensive document entitled *Guide to the preparation, use and quality assurance of blood components* referred to hereafter as the Guide. The immediate success and widespread acceptance of this document was such that the Committee of Ministers adopted it as a technical appendix to the Recommendation No. R (95) 15.

Recommendation No. R (95) 15 states that its technical appendix, the Guide, will be regularly updated to ensure it reflects scientific progress. This task was assigned to the European Committee on Blood Transfusion (CD-P-TS), a steering committee pursuing activities in the field of blood transfusion, directly answerable to the Committee of Ministers of the Council of Europe. In fulfilling this task, the CD-P-TS establishes the 'GTS - an *ad hoc* Working Group' (GTS) tasked to prepare the new edition of the Guide. The European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM) is in charge of the scientific secretariat for these activities.

The *Guide* provides technical guidelines for the preparation, use and quality assurance of blood and blood components, collating the most up-to-date scientific information to provide a comprehensive overview of the most recent advances in the field and to provide technical standards aimed at ensuring the quality, safety and efficacy of blood and blood components. In addition, the *Guide* provides

guiding ethical principles to be considered for the donation of blood and blood components.

Where blood or blood components are the starting material for products covered by other legislative frameworks (e.g. medicinal products, medical devices), the *Guide* standards extend to the donation, collection and testing of blood and blood components. In respect of plasma derived medicinal products, technical matters are addressed by the European Pharmacopoeia, while the European Union has a substantial body of legislation covering medicinal products and medical devices.

Whereas blood establishments in EU member states are required to comply with legislation derived from the European Commission directives, this *Guide* is intended to facilitate ongoing improvements to the preparation, use and quality assurance of blood components through the provision of non-binding recommendations. The *Guide* therefore provides additional information and guidance on best practices consistent with current scientific knowledge and expert opinion.

Further to this, the *Guide* includes the Good Practice Guidelines (GPG) which provide standards for the implementation of quality systems in blood establishments and, where applicable, hospital blood banks. In accordance with European Commission Directive (EU) 2016/1214, the GPG should be taken into account by EU member states in the implementation of quality systems in blood establishments.

The 22nd Edition

The 22nd edition of the *Guide* was elaborated over a two-year period by a GTS working group and introduces a number of updates, including a complete review of all chapters, a complete revision of the chapter on Hemovigilance, and the creation of two new chapters on Blood components for topical use or injection and on Blood supply emergency and contingency planning. The main changes compared to the previous edition relate to donor selection criteria (Creutzfeldt-Jakob disease, malaria, blood pressure and pulse, plasmapheresis,

iron stores, donors age and insulin), along with standardisation of terminology.

Changes included in the 22nd edition of the *Guide* are documented in a change log accompanied by background documents that detail the scientific rationale behind the changes made and decisions taken. Both the change log and background documents are published alongside this 22nd edition of the Guide.

The 22nd edition of the *Guide* refers to Directives 2002/98/EC[1] and 2004/23/EC[2], which remain in force until 7 August 2027, in accordance with the transitional provisions of Regulation (EU) 2024/1938[3] of the European Parliament and Council of 13 June 2024, concerning quality and safety standards for substances of human origin.

Acknowledgments

The elaboration of the 22nd edition of the *Guide* would not have been possible without the outstanding contributions of the members of the GTS working group, composed of internationally recognised experts nominated by the Council of Europe member states and observers to prepare this *Guide*. Special thanks go to all those experts for their valuable contributions and to Betina Sørenson, the Chair of the GTS, for her dedication. This expert group has made an outstanding contribution by sharing their expertise, reviewing the literature and extracting and collating knowledge from numerous international guidelines, collaborative projects and websites, with the aim of ensuring that all of this up-to-date information is made available and accessible to professionals and regulators. A detailed list showing the composition of the GTS is included in the Guide.

1 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

2 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

3 Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

Furthermore, EDQM warmly thank all participants of the stakeholder consultation, who provided many constructive comments.

The drafting and publication of the 22nd edition of the *Guide* was co-ordinated within the EDQM by Rada M. Grubovic Rastvorceva and Richard Forde, assisted by Nevena Kojic and supported by Mirela Busic, Louise Birrell, Sara Chauvin, David Le-Tallec and Alice Eleuterio.

We take this opportunity to honour the blood donors for valuable act of solidarity through blood donation.

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Recommendation No. R (95) 15

of the Committee of Ministers to member states on the preparation, use and quality assurance of blood components

(Adopted by the Committee of Ministers on 12 October 1995 at the 545th meeting of the Ministers' Deputies)

The Committee of Ministers, under the terms of Article 15.*b* of the Statute of the Council of Europe;

Considering that the aim of the Council of Europe is to achieve greater unity between its members and that this aim may be pursued, *inter alia*, by the adoption of common action in the health field;

Recalling its Resolution (78) 29 on harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances;

Recalling also its Recommendations No. R (80) 5 concerning blood products for the treatment of haemophiliacs, No. R (81) 14 on preventing the transmission of infectious diseases in the international transfer of blood, its components and derivatives, No. R (84) 6 on

the prevention of the transmission of malaria by blood transfusion, No. R (85) 12 on the screening of blood donors for the presence of Aids markers, No. (86) 6 on guidelines for the preparation, quality control and use of fresh frozen plasma, No. R (88) 4 on the responsibilities of health authorities in the field of blood transfusion and No. R (93) 4 concerning clinical trials involving the use of components and fractionated products derived from human blood or plasma;

Taking into account the Council Directive 89/381/EEC extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medical products and laying down special provisions for medicinal products derived from human blood or human plasma;

Taking into account Agreement No. 26 on the exchange of therapeutic substances of human origin;

Considering the importance of blood components in modern haemotherapy and the necessity to ensure their safety, efficacy and quality;

Considering that such components are of human origin and that hence specific ethical and technical principles have to be taken into account;

Considering the need for harmonisation of such principles in member states;

Considering that biotechnology does not provide substitutes for most blood products;

Convinced, therefore, of the need to provide health authorities, transfusion services as well as hospital blood banks and clinical users with a set of guidelines for the preparation, use and the quality assurance of blood components;

Aware that the *Guide to the preparation, use and quality assurance of blood components* published by the Council of Europe has already become the generally accepted European standard and that it is therefore appropriate to give a legal basis to this guide;

Considering that this guide will be regularly updated by the committee of experts of the Council of Europe;

Recommends that the governments of member states take all necessary measures and steps to ensure that the preparation, use and quality control of blood components are carried out in accordance with the guidelines set out in the appendix to this recommendation.

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/ Council of Europe) 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 22nd 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 definitions and abbreviations sections 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 good manufacturing practice (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.

In order to facilitate global harmonisation, an alignment of the Good Practice Guidelines with other international organisations is important,

such as the document published by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and World Health Organization (WHO). Despite the fact that the GPG of the different organisations are fully aligned, some very minor differences in wording or structure can be observed. These minor differences are not meant to imply a different meaning of the standards. They are simply the result of the independent drafting processes of the different organisations.

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

1.1.5. Each actor in the supply chain should establish, document and fully implement a comprehensively designed quality

system to deliver quality assurance based on the principles of quality risk management by incorporating good practice and quality control.

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

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

1.2. Quality system

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

1.2.2. The quality system encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, collection, testing and processing, storage, distribution, quality control, blood component recall, and external 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 include 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, including full traceability. This strategy requires the development of clear policies, objectives and responsibilities. It also requires implementation by means of quality planning, quality control, quality assurance and quality improvement to ensure the quality and safety of blood and blood components, and to provide customer satisfaction. The blood establishment should develop appropriate contingency and emergency plans to maintain adequate supplies of blood and blood components.

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

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

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

1.2.8. All blood establishments and hospital blood banks must be supported by a quality assurance function, whether internal or related, in fulfilling quality assurance. That function must be involved in all quality-related matters, and must review

and approve all appropriate quality-related documents *(Directive 2005/62/EC, Annex 1.2.1)*.

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

1.2.11. A general policy regarding qualification of facilities and equipment 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 to monitor the quality system effectiveness and its operations, with the involvement of senior management, and to identify opportunities for continual improvement of blood and blood component processes.

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

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

1.2.17.1. review of starting materials;

1.2.17.2. review of critical in-process controls;

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

1.2.17.4. review of all changes;

1.2.17.5. review of the qualification status of equipment;

1.2.17.6. review of technical agreements and contracts;

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

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

1.2.17.9. review of complaints and recalls;

1.2.17.10. review of donor acceptance criteria;

1.2.17.11. review of donor deferrals;

1.2.17.12. review of look-back cases.

1.3. Good practice

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

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

1.3.1.1.1. 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, and intermediate and finished blood components are taken by approved personnel and methods;

1.3.1.2.3. test methods are validated;

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

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

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

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

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

1.4. Quality risk management

1.4.1. Quality risk management is the part of the quality system that ensures that the process performance and quality

monitoring and review systems are based on risk. Appropriate statistical tools should be used (where appropriate) in the assessment of ongoing process capability.

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

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

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

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, reagents, blood and blood components;

2.3.5. a physician with the responsibility for ensuring the safety of donors (Responsible Physician).

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, 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 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 needs should be identified, planned, delivered and documented appropriately for the 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 3.1)*.

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 testing, 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 the temperature and, if necessary, for 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)*.

3.3.2. 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 which must be used only for the intended purpose *(Directive 2005/62/EC, Annex 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 properly 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 3.5.1)*.

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 3.5.2)*.

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 secure manner.

3.6. Ancillary areas

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

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

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

3.7. Waste disposal area

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

4.2.3. The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance

with an appropriate quality management system. The supplier should be assessed appropriately.

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

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

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.

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

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 minimise 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 for hardware and software should be developed and implemented.

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

4.2.13. 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.

4.2.14. 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.

4.2.15. 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.

4.2.16. 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.

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

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

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

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

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

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

4.2.21.2. be permanently linked to their respective record;

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

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

These arrangements should be adequately documented and tested.

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

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

4.3. Qualification and validation

4.3.1. General principles

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

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

4.3.1.3. A quality risk management approach, consisting of a systematic process for the assessment, control, communication and review of risks to quality across the

life cycle of the blood component, should be applied. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.

4.3.1.4. Data supporting qualification and/or validation studies which were obtained from sources outside of the blood establishment'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, processes and products into consideration.

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

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

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

4.3.2.4.1. qualification and validation policy;

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

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

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

4.3.2.4.5. guidance on developing acceptance criteria;

4.3.2.4.6. references to existing documents;

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

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

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

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

4.3.3. Documentation including VMP

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

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

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

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

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

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

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

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

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

4.3.4. Qualification stages for equipment, facilities and systems

4.3.4.1. Qualification activities should consider all stages from initial development of the user requirements specification

(URS) through to the end of use of the equipment, facility or system. The main stages and some suggested criteria (although these depend on individual project circumstances and may be different) which could be included in each stage are indicated below.

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

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

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

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

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

4.3.4.5.2. verification of the correct installation against predefined criteria;

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

4.3.4.5.4. calibration requirements;

4.3.4.5.5. verification of construction materials.

4.3.4.6. Operational qualification (OQ). The completion of a successful OQ should allow finalisation of calibration, operating and cleaning procedures, operator training and preventive maintenance requirements. OQ normally follows IQ, but depending on the complexity of the equipment, it may be performed as a combined 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. Requalification

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

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

4.4. Process validation

4.4.1. General

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

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

4.4.1.3. Process validation of new blood components should cover all intended processes and sites of preparation. A scientific and risk-based validation approach could be justified for new blood components based on extensive process knowledge

from the development stage in conjunction with an appropriate ongoing statistical process control. The design assumes that the validation performed is representative for all process or product settings.

4.4.1.4. For validation of processes for preparation of blood components that are transferred from one site to another or within the same site, the number of blood components used for process validation could be reduced based on existing process knowledge, including the content of the previous validation that should be available. The same approach may be used for different blood container 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 CQA 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 predefined. The conditions under which they are produced should fully comply with the requirements of good practice, with the validation acceptance criteria and with any continuous process verification criteria (if used).

4.4.2. Concurrent validation

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

4.4.2.2. Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that

any given blood component meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Responsible Person prior to release for clinical use.

4.4.3. Prospective validation

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

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

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

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

4.4.3.4.1. short description of the process;

4.4.3.4.2. functions and responsibilities;

4.4.3.4.3. summary of the CQAs to be investigated;

4.4.3.4.4. summary of CPPs and their associated limits;

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

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

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

4.4.3.4.8. proposed in-process controls with acceptance criteria and the reason(s) for selecting each in-process control;

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

4.4.3.4.10. sampling plan and the rationale behind it;

4.4.3.4.11. methods for recording and evaluating results;

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

4.4.3.4.13. conclusion.

4.4.4. Ongoing process verification and maintenance of the validated state

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

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

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

4.4.4.4. The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product life cycle, it may be appropriate to modify

the requirements taking into account the current level of process understanding and process performance.

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

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

4.4.4.6.1. calibration and monitoring;

4.4.4.6.2. preventive maintenance;

4.4.4.6.3. training and competency;

4.4.4.6.4. supplier requalification;

4.4.4.6.5. periodic review;

4.4.4.6.6. performance monitoring;

4.4.4.6.7. system retirement.

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

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

4.5. Validation of test methods

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

4.6. Change control

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

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

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

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

4.7.2.6. 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 Chapter 5, *Blood component monographs* contained in this *Guide* may be used).

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

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

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

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

5.2.3. Records/reports

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

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

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

5.3. Generation and control of documentation

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

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

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

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

5.3.4. Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. This may also be undertaken electronically. 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. SOPs, work instructions and methods should be written in an imperative mandatory style.

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

5.3.7. All significant changes to documents 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; however, where documents require the entry of data, sufficient space should be provided for such entries.

5.4. Good documentation practices

5.4.1. Records 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 Chapter 5, *Blood component monographs* contained in this *Guide* 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 (e.g. 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. the 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 the testing of materials and blood components at different stages of processing, describing the methods and equipment to be used. The tests performed should be recorded.

5.11. Other

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

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

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

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

5.11.3.2. equipment assembly and calibration;

5.11.3.3. maintenance, cleaning and sanitation;

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

5.11.3.5. environmental monitoring;

5.11.3.6. pest control;

5.11.3.7. complaints;

5.11.3.8. recalls;

5.11.3.9. returns;

5.11.3.10. change control;

5.11.3.11. investigations of deviations and non-conformances;

5.11.3.12. audits of compliance with internal quality/good practice;

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

5.11.3.14. supplier qualification and audits.

5.11.4. Records should be kept for major or critical analytical testing, processing equipment and areas where blood components

have been processed. They should be used to record in chronological order (as appropriate) any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations (including the dates and identity of people who carried out these operations).

6. Blood collection, testing and processing

6.1. Donor eligibility

6.1.1. Procedures for safe identification of donors, suitability interview and eligibility assessment 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 to use accepted guidelines and who works under the responsibility of a physician. This assessment involves an interview, a questionnaire and further direct questions, if necessary.

6.1.6. The questionnaire should be designed to elicit information relevant to the medical history, general health and other known or probable risk factors related to the donor. It should be designed to be understandable by the donor and

given to all donors each time they attend. On completion, it should be signed by the donor.

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

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

6.1.10. Records of suitability and final assessment of donors 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 donations unsuitable for transfusion.

6.1.13. Procedures should be in place to ensure that any abnormal findings arising from the donor selection process are

properly reviewed by a qualified healthcare professional and that appropriate action is taken.

6.2. Collection of blood and blood components

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

6.2.2. Donor identity 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 bag systems 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 blood collection and processing systems 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. SOPs should be in place describing the actions to be taken following an unsuccessful donation. These should specify how to handle already-labelled material and the circumstances under which a repeat venepuncture might be possible.

6.2.9. Laboratory samples 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 and transport temperature appropriate to further processing requirements *(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 for 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 verification of the test system in the laboratory is required prior to its use in routine testing. This validation should demonstrate that:

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

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

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

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

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

6.3.7. There 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 manufacturers of reagents and test kits (unless an alternative method has been validated before their use) before release of the blood component.

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

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

6.3.11. The quality of the laboratory testing 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 infectious 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. SOPs) to deal with initially reactive specimens, and to resolve discrepancies in results after retesting.

6.5. Blood group serological testing of donors and donations

6.5.1. Blood group serology testing 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. This is not required for plasma intended only for fractionation. At least all first-time donors should be tested for clinically significant irregular red cell antibodies.

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

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

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

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

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

6.6. Processing and validation

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

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

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

6.7. Labelling

6.7.1. At all stages, all containers 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)*.

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

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

6.7.4. Labelling systems 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 each single blood sample 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)*.

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

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

6.8.4. Before release, blood and blood components 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 6.5.1 *(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 storage and distribution requirements must comply with Directive 2003/94/EC *(Directive 2005/62/EC, Annex 7.1)*.

7.2. Procedures for storage and distribution must be validated to ensure 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, between 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 and the name and address of the supplier or consignee.

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

7.10. Verification of transportation

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

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

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

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

7.11. Return of blood and blood components into inventories for subsequent reissue must 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)*.

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

8. Outsourced activity management

8.1. General principles

8.1.1. Tasks that are performed externally 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 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 level higher than the blood establishment (e.g. regional or national level) a system should be in place that permits an appropriate evaluation of the suitability (in terms of quality and safety) and the availability of the materials and equipment concerned.

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 action (CAPA) 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 CAPAs 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 (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 resources 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 CAPAs 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 falsification.

9.3. Recall

9.3.1. There must be personnel authorised within the blood establishment to assess the need for blood and blood component recall 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 to the competent authority *(Directive 2005/62/EC, Annex 9.3.2)*.

9.3.3. Actions must be taken within predefined 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 CAPAs or any revalidation should be undertaken. The reasons for such corrective actions should be documented. Agreed CAPAs should be completed in a timely and effective manner. There should be procedures for the ongoing management and review of these actions and the effectiveness of these procedures should be verified during self-inspection.

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 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 this *Guide* 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 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 Council of Europe. 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*.

During the revision of the 22nd edition of the *Guide*, the GTS has worked according to the CD-P-TS Terms of Reference for the GTS *ad hoc* Working Group, Elaboration of the *Guide to the preparation, use and quality assurance of blood components* (22nd edition).

The 22nd edition of the *Guide* refers to Directives 2002/98/EC and 2004/23/EC, which remain in force until 7 August 2027, in accordance with the transitional provisions of Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024, concerning quality and safety standards for substances of human origin.

1.1. Tasks and responsibilities of the GTS

To undertake the periodic revision of the *Guide*:

- Based on monitoring and expert evaluation of scientific progress 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 provide valuable input to both the edition under publication and subsequent editions.

1.2. Structure and content of the *Guide*

1.2.1. 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/ Council of Europe) 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 GPG 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 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. Some of the GPG requirements are also replicated in other chapters of the *Guide*. When this occurs the term 'should' is retained for the purposes of consistency.

1.2.2. Standards

The standards are developed to support high-quality transfusion practice in Council of Europe 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 legislation
B. Good Practice Guidelines
C. Scientific evidence

D. International recommendations (organisation 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 legislation or B) GPG, there will be a direct reference in the text to the relevant legislation or GPG standard.

Where new or modified standards are included in the *Guide* based on scientific evidence, international recommendations/practices or expert opinion, there will be a 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*.

1.2.3. 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*.

1.2.4. 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*.

1.2.5. Abbreviations and Definitions of terms

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

1.2.6. Recommendations and Resolutions

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).*

Further guidance is available in the Council of Europe Committee on Bioethics (DH-BIO) Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors, available at: *https://rm.coe.int/guide-financial-gain/16807bfc9a*

Council of Europe Recommendation No. R (95) 14, Article 2 states that '*Donation is considered voluntary and non-remunerated if the person gives blood, plasma or cellular components of his or 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

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. Safety considerations include, for example, donor haemoglobin values, total blood volume estimation and pregnancy-related risks, including risks for HLA/HNA-antibodies*** *(Evidence level C, E).*

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 with 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

based on the biological and physiological differences between male and female individuals.

Accurate use of donor gender by blood establishments in both written records and verbal communications is necessary to allow donors to be appropriately addressed. Accurate knowledge of donor sex is necessary to determine appropriate sex-related biological parameters to ensure donor and recipient safety and to assess donor eligibility.

2.1.3. General requirements

Standards

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

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 blood, the blood donation procedure, the 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)*.

For allogeneic donations: the medical assessment is not a complete assessment of the donor's health and is not a substitute for seeing their own healthcare provider.

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 must be provided.***

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

2.2.1. Donor eligibility

Standards

2.2.1.1. ***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*** *(GPG 6.1.3.)*.

2.2.1.2. ***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)*.

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 an interview, a questionnaire and 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 healthcare professional and that appropriate action is taken*** *(GPG 6.1.13.)***.**

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

2.2.2. 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. ***Where allowed by national legislation, blood donation may be considered from donors aged 17.***

2.2.2.3. ***Donation by first time donors above the age of 60 years is at the discretion of the physician in the blood establishment*** *(Directive 2004/33/EC, Annex III)***.**

2.2.2.4. ***Donation by donors over 65 years is with permission of the physician in the blood establishment, given annually*** *(Directive 2004/33/EC, Annex III)***. This can be given either individually to each donor, or based on a medical risk assessment for a given donor population.**

There is evidence that donation under the age of 18 should not be recommended because of donor safety concerns. There is evidence to support increasing the general upper age limit to 70 years, and for first-time donors to 65 years.

Exceptions to upper age requirements for individual donor permission can be considered if a risk assessment demonstrates that the predicted donor adverse event rate for the given older donor cohort is considered acceptable. Where donation is allowed for healthy individuals over the given upper age of 70 years or for first-time donors after the age 65 years, national donor adverse event data, life expectancy and public health data should be utilised to set a national upper age limit policy. Upper age limits for either first-time or returning donors may be reduced where national data and other public health information indicates a lower age limit is more appropriate.

2.2.3. 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.

Abnormally 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/L (1.24 mmol/L) between two 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 female donors of childbearing years, in frequent whole blood donors, in donors with insufficient absorption of iron (e.g. coeliac disease, bariatric surgery) 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. Monitoring and evaluation of haemoglobin levels or other parameters from previous donations, e.g. mean corpuscular volume (MCV) could indicate the development of iron deficiency.

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 and iron status (Evidence level C, E);
- Use of tests to assess iron status, such as ferritin, soluble transferrin receptor and red blood cell (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 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 staff specifically trained to ask further direct questions to supplement the information in the questionnaire. The person who carries out the assessment should certify that the relevant questions have been asked*** *(GPG 6.1.9.).*

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

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 a medical condition or under medical treatment should be assessed to determine their eligibility. Reasons for donor deferral may 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

Standards

2.3.2.2. ***Donors with local/non-generalised 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 2 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. Some treatments will also require a period of deferral post-cessation (Evidence level C, E).

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

Based on current evidence, the major cause of anaphylaxis in a recipient is their own atopic condition and not transfusion-associated issues. Therefore, excluding donors based on their history of severe allergic/anaphylactic reactions is not an effective risk-reduction strategy and may cause an unacceptable loss of donors.

However, some case studies suggest that blood components with a higher volume of plasma from donors with recurrent severe allergic/anaphylactic reactions may carry a higher risk of anaphylaxis for the recipient. Therefore, consideration may be given to permanently deferring such donors from donating blood components with a high plasma volume, such as fresh frozen plasma (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 and pulse

Measurement of blood pressure or pulse is not required for determination of donor eligibility.

Systematic measurement of blood pressure or pulse is not required for determination of donor eligibility. Subject to national policy and definition of accepted values, specific cases may benefit from these measurements (e.g. donors on antihypertensive treatment, new donors, donors over 60 years of age).

Cancer/malignant diseases

Standard

2.3.2.4. ***Individuals with a malignant disease are permanently deferred, except donors with in situ carcinoma 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 *in situ* carcinoma if the donor has fully recovered with no expectation of recurrence (i.e. cured).

The following conditions apply:

- For cancers with negligible metastatic potential (e.g. basal cell carcinoma), the donor may be accepted following complete recovery.
- For other cancers, at least 5 years should have elapsed since completion of treatment (Evidence level C, D, E).
- No deferral is required for premalignant conditions.

Cardiovascular disease

Standards

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)*.

Provided the donor's diabetes is well controlled and there are no diabetic complications, insulin therapy does not pose a donor safety or product quality risk. The responsible physician may make exceptions if the following conditions apply:

- there is no evidence of infection or of other skin alterations at the injection sites.
- the disease is well controlled, as evidenced by glucose and/or haemoglobin A1c in the target range (according to local guidelines), absence of other complications leading to deferral and absence of hypoglycaemic episodes.

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

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 whole 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, laboratory testing and pathogen inactivation technologies (PIT).

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 to

donor availability or blood component safety. In this situation, donor deferral may not be an option in the newly affected area. Donation testing is an important tool to reduce the risk of transmission. For plasma and platelets, PIT 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 2 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 regions endemic 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.

Standards

2.3.3.7. ***There is no requirement to defer donors because of travel to or residency in geographical areas where cases of BSE or vCJD were identified.***

2.3.3.8. ***There is no requirement to impose any additional restrictions for donors who received transfusions in geographical areas where cases of BSE or vCJD were identified.***

Dengue fever

Standards

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

2.3.3.10. ***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

2.3.3.11. ***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

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

2.3.3.13. ***Persons who have been in close household contact with an individual infected by HBV (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).*

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

2.3.3.15. ***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 nucleic acid amplification***

technique (NAT) and anti HBc tests are performed and both test results are negative.

Hepatitis C (HCV)

Standard

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

HIV 1/2

Standard

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

HTLV 1/2

Standard

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

Jaundice and hepatitis

Standard

2.3.3.19. ***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 provided they have not suffered an inoculation injury or mucous membrane exposure, in which case they must be deferred.

Leishmaniasis (kala-azar), visceral leishmaniasis

Standard

2.3.3.20. ***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

2.3.3.21. ***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

2.3.3.22. ***Blood establishments should have access to a current map or list of endemic areas and seasonal risk periods at the site of blood collection.***

2.3.3.23. ***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;***
- ***individuals who give a history of malaria;***
- ***individuals who report an undiagnosed febrile illness, consistent with malaria, during a visit to or within 6 months following departure from a malarial area.***

Such individuals 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.

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

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

Such individuals 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 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 may be accepted once a period of 6 months has elapsed following departure from the malarial area.

Malaria antibody testing see Chapter 10.

Malaria testing is not required if the donation is used exclusively for plasma for fractionation.

Osteomyelitis

Standard

2.3.3.25. ***Donors suffering from osteomyelitis must be deferred until 2 years after having been declared cured*** *(Directive 2004/33/EC, Annex III)*.

Q fever

Standard

2.3.3.26. ***Donors suffering from Q fever must be deferred until 2 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

2.3.3.27. ***Donors suffering from syphilis must be deferred until 1 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

2.3.3.28. ***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

2.3.3.29. ***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

2.3.3.30. ***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)*.

2.3.3.31. ***Sexual partners of people in 2.3.3.30. 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

2.3.3.32. ***Donors suffering from tuberculosis must be deferred until 2 years after having been confirmed cured*** *(Directive 2004/33/EC, Annex III)*.

West Nile virus (WNV)

Standards

2.3.3.33. ***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)*.

2.3.3.34. ***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

2.3.3.35. ***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.***

2.3.3.36. ***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 using a risk-based approach based on national transfusion-transmissible infection (TTI) disease prevalence and incidence, modifications to standard 2.3.4.1. can be accepted for acupuncture, tattooing, body piercing or skin/mucosa-penetrating aesthetic medical procedures. These may be implemented nationally or by 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.

Tissue or 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 prescribed 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 splash with blood

Standard

2.3.4.5. ***Individuals having an inoculation injury or mucosal splash 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

Standards

2.3.4.7. ***After major surgery, donors must be deferred for 6 months (or 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 to specifically support 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 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 (which may be up to 6 months or longer). A shorter deferral period is possible after clinical evaluation, if the donor has totally recovered from the surgery (i.e. wound healed, no signs of postoperative infection and in a healthy condition) (Evidence level C, E).

- For planned major surgery: allogeneic 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 level pre-donation after major surgery.

Dental care/Oral health care

Standards

2.3.4.9. ***Individuals must be deferred for 1 week after tooth extraction, root filling and similar treatments*** *(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 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 (e.g. gingivitis requiring treatment): defer until cessation and/or 2 weeks after completion of 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. ***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, individuals must be deferred for 4 weeks*** *(Directive 2004/33/EC, Annex III)****.***

2.3.4.13. ***After vaccination for smallpox and monkeypox individuals must be deferred for 8 weeks.***

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

- ***Inactivated viruses, e.g. poliomyelitis (injection), influenza;***
- ***Killed bacteria, e.g. cholera, typhoid, capsular polysaccharide typhoid fever vaccine;***
- ***Polysaccharides, e.g. from pneumococcal polysaccharide;***

- ***Toxoids, e.g. diphtheria, tetanus;***
- ***Hepatitis A or tick borne encephalitis vaccines, if no exposure is reported;***
- ***mRNA vaccines, non-replicating/replication-deficient virus vector-based vaccines and protein subunit vaccines.***

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. ***After xenotransplantation individuals 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 intervals between donations are 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 %. 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 % of the calculated blood volume of the donor.***

The total blood volume (TBV) of the donor can be estimated from their weight, height and sex 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 males 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), while all females 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 females 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 male and up to 4 per year from female donors 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

Donors should be informed of the risks associated with the apheresis procedure and consent should be obtained before each donation.

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.

Published data on long-term effects in apheresis donors are primarily derived from low-frequency apheresis programmes. Data on long-term effects of high-frequency apheresis programmes are very limited.

Therefore, careful monitoring and long-term follow-up studies are needed to demonstrate that programmes with a higher number of annual apheresis procedures are safe. Identified possible risks include:

- Immediate and longer-term harm associated with citrate exposure and white cell depletion in regular plateletpheresis donors;
- Consequences of reduced IgG levels. Regular monitoring of IgG in plasmapheresis donors has been shown to improve donor safety. Donation frequency should be adjusted based on the donor's IgG levels;
- Iron deficiency due to red cell loss (collection of sample tubes and other procedural losses);
- Recurrence of adverse reactions, e.g. vasovagal reactions.

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 least 48 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. post-procedure saline infusion. Loss of iron in donors can also be mitigated by using samples from the 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).

Standards

2.4.2.6. ***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 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.***

2.4.2.7. ***The collection volume for each plasmapheresis (including anticoagulant) should not exceed 880 mL.***

2.4.2.8. ***When the collection volume (including anticoagulant) is determined by the estimation of TBV (Appendix 2a) the donated volume (excluding anticoagulant) should not exceed 16 % 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 % of the estimated TBV.***

2.4.2.9. ***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.

2.4.2.10. ***Total proteins must be measured at least annually and must not be less than 60 g/L*** *(Directive 2004/33/EC, Annex III)****. In addition, total proteins should be measured at the first donation.***

2.4.2.11. ***IgG levels should be measured at least annually, should be within local population reference ranges and should not fall below 6.0 g/L. In addition, IgG levels should be measured at the first donation.***

The time taken for the donor's IgG level to return to the baseline level after plasma donation varies individually. There is evidence to support the safety of plasma donation with a minimum interval of 2 weeks with an annual IgG measurement policy.

2.4.2.12. ***The minimum interval is recommended to be at least 2 weeks.***

2.4.2.13. ***Where the competent authority approves a plasma programme where the donation interval is less than 2 weeks, there are additional requirements.***

2.4.2.14. ***There should be enhanced monitoring of donors to ensure that the programme is safe and sustainable. Where a donation interval between 1 and 2 weeks is allowed, additional monitoring is required to determine the health impact of frequent donation on the individual donor. As a minimum this should include the following:***

- ***Donor adverse events should be captured and regularly monitored to allow for the identification of adverse donor health trends and concerns with donor loss. Concerning health trends should be reported to the national authority and corrective action taken to mitigate the donor health safety concern.***

- ***IgG levels should be measured at least every sixth donation to determine a donation frequency that allows the donor's IgG level to be maintained within the normal range.***

There is evidence showing a significant reduction in IgG levels occurs in a substantial proportion of donors donating with 1 week intervals.

2.4.2.15. ***The donation interval should not be less than one week.***

Additional requirements for donors undergoing plateletpheresis

Standards

2.4.2.16. ***Plateletpheresis must not be carried out on individuals whose platelet count is less than 150 × 10⁹/L*** *(Directive 2004/33/EC, Annex III)****.***

2.4.2.17. ***Haemoglobin values at plateletpheresis 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.

2.4.2.18. ***Donors should not be subjected to a plateletpheresis 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.

Additional requirements for donors undergoing double unit red cell apheresis

Standards

2.4.2.19. ***Minimum limits for haemoglobin values at double unit red cell apheresis donation should not be less than 140 g/L or 8.7 mmol/L for both female and male donors.***

2.4.2.20. ***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 (6.8 mmol/L).***

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

2.4.2.22. ***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 female and 16 weeks for male donors.***

2.4.2.23. ***The maximum volume of red cells collected should not exceed 400 mL (without resuspension solution) per collection procedure.***

2.4.2.24. ***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; G-CSF) to increase circulating granulocyte levels and the use of sedimenting agents (hydroxyethyl starch; HES) during the procedure itself. Both of these have potentially severe side-effects, identified below, that need to be communicated to the donor.

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 USA have not identified any increased risk of AML/MDS in healthy individuals who donated PBSCs and received G-CSF as a pretreatment. 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;

- Requalification 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 transfusions aimed at a graft-versus-leukaemia effect;
- In certain cases of alloimmune neonatal thrombocytopaenia; for instance, if HPA-typed platelets are not available and intravenous 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 RBCs, 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 (TA-GVHD), even in the immunocompetent recipient, and so such components should be irradiated. In the case of platelets, PIT 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

2.5.1. 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 practice.

2.5.2. Donor instruction

Standard

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

2.5.3. 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 or qualified 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 of 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 plasmapheresis or 1 unit RBC and 1 unit plateletpheresis or 1 unit RBC and platelet and plasmapheresis 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 female, 16 weeks male	8 weeks
Plasmapheresis	4 weeks	2 weeks*	48 hours	2 weeks *	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	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 female, 16 weeks male	8 weeks
1 unit RBC and 1 unit plateletpheresis or 1 unit RBC and platelet and plasmapheresis	8 weeks	48 hours	2 weeks	2 weeks	24 weeks female, 16 weeks male	8 weeks
1 unit RBC and plasmapheresis	8 weeks	2 weeks	48 hours	2 weeks	24 weeks female, 16 weeks male	8 weeks
2 units of RBC apheresis	12 weeks	48 hours	48 hours	48 hours	24 weeks female, 16 weeks male	12 weeks
Granulocytapheresis	4 weeks	48 hours	2 weeks	2 weeks	24 weeks female, 16 weeks male	8 weeks**

* High-frequency plasmapheresis: see text.

** The interval should be individually set by a physician, depending 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 system 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. Blood bag systems should be sterile and used in

accordance with the manufacturer's instructions. A check should be made before use to ensure that the blood bag 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 performed by the 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 the 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 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 must be carried out in an area intended for the safe withdrawal of blood from donors, appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation*** *(Directive 2005/62/EC, Annex 3.3)****.***

3.2.1.3. ***The blood collection 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 suitability 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 container must be traceable for each blood component*** *(Directive 2005/62/EC, Annex 6.2.2).*

3.3.1.4. ***Sterile blood bag 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 bag systems should be monitored and reported to the supplier, 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 microorganisms prior to use, particularly if there is a defect such as a pinhole. Abnormal moisture or discolouration on the surface of the container or label after unpacking suggests leakage through a defect. Defects may be hidden behind the label pasted on the container. Recurrent defects should be investigated to ensure the suitability of the blood bag systems for use.

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 blood bag 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 should be inspected for the prescribed content and appearance of the anticoagulant solution. If an individual package which contains a blood bag system is found to be abnormally damp, then that blood bag system 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 container is from the same donor, uniquely labelled and linked to the donor's record to allow for full blood product traceability, while 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 containers 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 bag systems should contain the following eye readable information: the manufacturer's name and address; the name of the blood bag system and/or the name of the blood container 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 blood bag system. 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*** *(GPG 6.2.8.5.)****. 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 blood bag system 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 at the time of each donation and 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 test/assay kit in use. Samples should be taken from the blood bag system tubing or the sample pouch.***

3.6.2.3. ***Where an anticoagulant solution is used in the collection of whole blood, the blood container 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 for the preparation of coagulation factors*** *(Evidence level C)****.***

3.6.2.7. ***If manual mixing is used, the blood container 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 containers 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 bag systems 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 bag systems 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 blood bag system collection tubing should be in place.

3.7.1.4. ***The blood bag system, related paperwork and corresponding samples should not be removed from the donor's bedside until labelling and barcode reconciliation has been checked and is verified as correct.***

3.7.1.5. ***After collection, blood containers 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 blood bag system collection tubing should be completely discharged into the blood container.

If integral blood bag system collection tubing is used to prepare segments for testing, it should be sealed off at the distal end, filled with anticoagulated 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 pretreatment of donors with corticosteroids and granulocyte colony-stimulating factor.

There is no published evidence that a maximum plasmapheresis procedure time is required from a donor safety or product quality perspective. Blood establishments may choose to set a maximum procedure limit for donor experience and operational reasons, such as to assist with the timing of donor appointments.

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 look-back 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, 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. ***Details of 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. It is acceptable not to move the donor and instead manage the adverse reaction where it occurs; this reduces the potential for additional harm when moving a donor who is experiencing an adverse reaction to a specific space.

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 12 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. In general, patients should receive the component required to correct their specific deficiency, although whole blood may be used in limited clinical settings.

4.1. Processing

4.1.1. General consideration

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 the preparation of high-quality blood components.

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 (blood containers) 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 blood bag system

Blood bag systems and blood containers for blood and blood component collection and processing are medical devices that should comply with the requirements of the relevant regulations (such as the EU Medical Devices Regulation, the 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 bags and tubing, labels and as a result of sterilisation of the system.

4.1.3. Assessing the impact of changes

When changes are planned (e.g. new plastics, plasticiser, filter or additive solution) and there is limited experience or data available, extended testing of relevant parameters should be considered. This should cover the entire blood supply chain from donation to transfusion, including component preparation and storage.

Assessment of the following parameters may be considered:

- Red cells: glucose, pH, haematocrit, haemolysis, ATP, 2,3 DPG, lactate and extracellular potassium ions, haemoglobin, deformability, osmotic fragility;
- Platelets: pH, pO_2, pCO_2, bicarbonate ions, glucose, lactate, ATP, P-selectin, markers of activation (e.g. Annexin V), LDH release, beta-thromboglobulin release, response to hypotonic shock and swirling phenomenon, morphology score and extent of shape change;
- Plasma: factor VIII, fibrinogen and signs of coagulation activation (e.g. thrombin-anti-thrombin complexes).

The suitability of changes 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.

4.1.4. Red cell and platelet preservation

Red cells

The anticoagulant solutions used for whole blood collection have been developed to prevent coagulation and to permit storage of whole blood. 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.

After separation of the red cells, an additive solution is usually added to maintain red cell viability. Commercial additive solutions are typically saline-based and contain glucose, adenine, mannitol and sometimes phosphate and guanosine.

During refrigerated storage, red cells undergo numerous physicochemical changes, which affect the quality, function and *in vivo* survival of the transfused red cells. Glucose is consumed by red cells, hence the availability of glucose helps to maintain red cell viability. When glucose is metabolised to lactic acid, pH decreases 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 partially compensates for this decrease.

Phosphate may be used to enhance glycolysis. Other substances (e.g. mannitol, citrate) may be used to reduce *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 after 3-4 days of storage of whole blood and red

cells. Therefore, standard transfusion filters, in approved transfusion sets for administration, should be used to ensure adequate microaggregate removal. Removal of platelets and/or leucocytes during component preparation reduces microaggregate formation.

Platelets

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 quality and metabolism when compared to platelets stored in plasma. The lower plasma content and reduced cytokine accumulation leads to a reduced risk of allergic transfusion reactions.

The quality of platelets in plasma is impaired when the pH falls below 6.4 and when 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. The decrease in lactic acid production prevents the lowering of the platelet pH. In addition, the production of bicarbonate following acetate oxidation and the addition of buffer further prevents decreases 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 an adequate indicator alone of quality for platelets stored in PAS (Evidence level C).

4.1.5. 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. Other factors are the viscosity of the medium and the 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 and deceleration, 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.

4.1.6. Leucocyte depletion

Leucocytes play no therapeutic role in blood components (except for granulocyte and lymphocyte preparations for specific indications) 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 leucocyte depletion) using filters incorporated in the blood bag system. Pre-storage leucocyte depletion is considered superior to alternative approaches, such as post-storage or bedside filtration, and is the international standard.

The blood establishment should determine the most appropriate blood bag system for the desired component. Blood bag systems for the preparation of leucocyte-depleted blood components should ensure that the final component contains less than 1×10^6 leucocytes.

To enable a comparison of the filters that can be used for leucocyte depletion and to facilitate selection, blood establishments should request relevant data from the manufacturers on the performance of leucocyte depletion filters within each system, under defined conditions, including any effect on storage parameters. Manufacturers are responsible for providing 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 for various reasons, including blood bag system defects, mishandling and 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

4.1.6.1. ***Processes used for leucocyte depletion should be validated. The validation should be carried out by the blood establishment using the manufacturer's instructions and in accordance with the requirements for leucocyte depletion and other quality aspects of the components (including those for plasma for fractionation).***

4.1.6.2. ***For quality control, an appropriately sensitive and validated method should be used for counting leucocytes.***

4.1.6.3. ***Leucocyte-depleted blood components should contain less than 1×10^6 leucocytes.***

4.1.7. Freezing and thawing of plasma for 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 time between collection and freezing should be validated to result in a component meeting the specification.

The rate of cooling during the freezing process 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 as the bags become brittle. The integrity of the blood container should be verified before and after thawing to exclude any defects and leakages. Leaking containers must be discarded. The plasma component should be thawed immediately after removal from storage, using a validated procedure. If warming of the plasma is intended, the plasma temperature should not rise 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 reduction and production of cryoprecipitate, and the freeze-thaw steps should be performed in accordance with the manufacturing requirements.

4.1.8. 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 thawing and centrifuging at low temperature, before 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.

4.1.9. Open and closed systems and sterile connection devices

The use of closed systems is strongly recommended for all steps in component processing (GPG 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 used in an environment specifically designed to minimise the risk of bacterial contamination (GPG 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 minimise the risk of bacterial contamination.

Standards

4.1.9.1. ***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 used in an environment specifically designed to minimise the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures.***

4.1.9.2. ***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.***

4.1.10. 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 donation identification number (preferably consisting of a code for the blood collection organisation, the year of donation and a serial number), relevant blood groups, name of the blood component, essential information about the properties and handling of the blood component and the collection and expiry date (see also labelling requirements in Chapter 5, Blood component monographs).

Standards

4.1.10.1. ***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)****.***

4.1.10.2. ***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)*.

4.1.10.3. ***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)*.

4.1.10.4. ***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.***

4.1.10.5. ***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.***

4.1.11. Release of blood components

Standards

4.1.11.1. ***There must be a safe and secure system to prevent each individual 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 individual 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)*.

4.1.11.2. ***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, Annexes 6.5.1 and 6.6.2)***.**

4.1.11.3. ***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.***

4.1.11.4. ***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.***

4.1.11.5. ***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 donation given by 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.***

4.1.11.6. ***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.***

4.1.11.7. ***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, Annexes 6.6.3, 6.3.2 and 6.3.3)****.***

4.1.11.8. ***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.***

4.1.12. Component recall and traceability (see also Chapter 12)

Standards

4.1.12.1. ***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)****.***

4.1.12.2. ***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.***

4.1.12.3. ***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 they were 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 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 must 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 reissue.***

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

4.2.1.16. ***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)*.

4.2.2. Equipment

The following points should be considered before purchasing 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 storage 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 represents the worst conditions.

The alarm system should have appropriate alarm signals (e.g. acoustic and optical signals, electronic messaging) and should be regularly tested.

Equipment should ideally be connected to a reserve power unit, as well as to the main supply.

4.2.3. Storage of red cell components

The maximum duration of storage (expiry date) must be noted on each container. This duration may vary with the type of preparation (concentration of cells, formula of anticoagulant, use of additive solution, secondary processing) and should ensure a mean 24-hour post-transfusion survival of no less than 75 % 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.

4.2.4. Storage of platelet components

For the preparation of pooled platelets, buffy coats should be stored between + 20 °C and + 24 °C without agitation and for no longer than 24 hours after whole blood separation.

Platelets are normally stored between + 20 °C and + 24 °C. Agitation of platelets during storage should be sufficient to guarantee oxygen availability, but should be as gentle as possible to prevent induction of activation and storage lesions.

The maximum duration of storage (expiry date) must 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.

Frozen platelets should be stored at < – 80 °C in a validated suspension medium in order to produce satisfactory post-transfusion survival figures.

A closed storage 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;
- Keep the bags in place.

4.2.5. Storage of frozen plasma components

The maximum duration of storage (expiry date) must be noted on each container.

Frozen plasma components should be stored in accordance with the following time and temperature specifications;

- 36 months at – 25 °C or below;
- 3 months at between – 18 °C and – 25 °C.

Freezers with automatic defrosting should be avoided, unless it can be guaranteed that the low temperature is maintained during defrosting.

4.2.6. Storage of granulocyte components

For the preparation of granulocyte components, buffy coats should be stored between + 20 °C and + 24 °C without agitation and for no longer than 24 hours after whole blood separation.

Typically, granulocyte components 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 without agitation and for no longer than 24 hours.

4.2.7. Transportation of blood components – general requirements

Blood components should be transported in a temperature-controlled environment, e.g. in an insulated container, to ensure that the recommended transport temperature is maintained for that component.

The transport system used should be validated to maintain the integrity of the component over the proposed maximum time and extremes of ambient temperature of transport.

The impact of transport conditions on the quality of the blood components should be validated by quality control tests at the end of shelf-life, as referenced in the blood component monographs for those specific components.

The integrity of the transport system should be subject to periodic revalidation

On receipt of blood components after transportation, the component should be transferred to storage under the recommended conditions if not intended for immediate transfusion.

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 or exceed + 10 °C over a maximum transit time of 24 hours. Transport times may exceed 24 hours if red cell components are maintained between + 2 °C and + 6 °C. 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.

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. Upon receipt after transportation, it should be verified that the component has remained frozen during transit.

Upon receipt after transportation, frozen plasma components should be transferred at once to storage at the recommended temperature if not intended for immediate use.

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 or pathogen inactivation technologies (PIT). 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 revalidated 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.

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 defects or mishandling.

Bacterial contamination of platelet components is reported more frequently than of other blood components due to their storage at room temperature, which facilitates growth of contaminating bacteria.

In this regard, 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.

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 PIT or a rapid test shortly before transfusion may offer alternative approaches to increase the bacterial safety of platelet components.

When PIT or rapid tests for platelet components are in place, for the purposes of process control, bacterial monitoring of collection and processing should still be performed at a frequency based on risk assessment.

Data on bacterial monitoring should be analysed using statistical process control techniques to ensure that the process remains in control.

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. As 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 PIT can also decrease the risk of CMV transmission.

4.3.4. Pathogen inactivation technologies (PIT)

The aim of PIT is to reduce 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 reduce or 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.

With regard to the efficacy of pathogen-reduced plasma components, loss of some factor VIII and fibrinogen occurs compared to untreated control plasma.

Other 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. Pathogen inactivation of platelets potentially allows the extension of their shelf-life to 7 days. A further advantage of some PIT systems is inactivation of lymphocytes, which obviates the need for irradiation.

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

Part A. Whole Blood components

Part B. Red cell components

Part C. Platelet components

Part D. Plasma components

Part E. White cell components

5.0. Overview

The blood components described in these monographs are those that are currently in use in Europe and for 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 to 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. Conversely, components may also 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 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 provided 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 3).

Quality control may be carried out either as a separate 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.

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	Volume specified excludes anticoagulant
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, Non-Leucodepleted	WB with removal of a major part of the plasma	280 ± 50	≥ 45	0.65–0.75	
B-4.	Red Cells, Non-Leucodepleted, Buffy Coat Removed	WB with removal of a major part of the plasma and the buffy coat	250 ± 50	≥ 43	0.65–0.75	

	Component	Technical information	Volume (mL per unit)	Hb content (g per unit)	Haematocrit	Other
B-5.	Red Cells, Non-Leucodepleted, 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, Non-Leucodepleted, 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 for 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 may be required to comply with national requirements (see also Chapter 10, 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

Parameter to be checked	Requirements	Frequency of control
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 and should be validated.

Validated transport systems should ensure that the temperature does not go below + 1 °C or exceed + 10 °C over a maximum transit time of 24 hours. Transport times may exceed 24 hours if temperature conditions are maintained between + 2 °C and + 6 °C.

Whole Blood for preparation of blood components may be kept between + 2 °C and + 6 °C. Alternatively, it may be kept for up to 24 hours 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 donation (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 childbearing age or younger should not be transfused with *Whole Blood* from RhD-positive donors.

Microaggregates may form on storage.

Whole Blood for transfusion is not recommended in cases of:

- Anaemia without blood volume loss;
- Plasma intolerance;
- Intolerance due to alloimmunisation against leucocyte antigens.

Adverse reactions include:

- Haemolytic transfusion reaction;
- Non-haemolytic transfusion reaction (mainly chills, fever and urticaria);
- Anaphylaxis;

- Alloimmunisation 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 minimal residual content.

Whole Blood, LD contains a minimum haemoglobin content of 43 g.

Whole Blood, LD contains less than 1×10^6 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 10, 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 for transfusion 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 does not go below + 1 °C or exceed + 10 °C over a maximum transit time

of 24 hours. Transport times may exceed 24 hours if temperature conditions are maintained between + 2 °C and + 6 °C.

Whole Blood, LD for preparation of blood components may be kept between + 2 °C and + 6 °C. Alternatively, it may be kept for up to 24 hours between + 20 °C and + 24 °C, which is a prerequisite for the production of platelet preparations from *Whole Blood, LD*.

Labelling

The labelling should comply with relevant legislation and, where in place, international agreements. The following information on *Whole Blood, LD* 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 donation (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 childbearing 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;
- Alloimmunisation against red cell 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.

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 1×10^6 leucocytes.

Preparation

Generally a filtration technique is used to produce *Red Cells, LD*. Processing and leucocyte depletion should be performed within 48 hours after donation.

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 1×10^6 leucocytes.

Preparation

Generally, a filtration technique is used to produce *Red Cells, LD-AS*. Leucocyte depletion should be performed within 48 hours after donation.

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, Non-Leucodepleted

Definition and properties

Red Cells, Non-Leucodepleted is a component obtained by removal of a major part of the plasma from *Whole Blood*.

Red Cells, Non-Leucodepleted also contains the greater part of the *Whole Blood* leucocytes (about 2.5 to 3.0 $\times$ 10^9 cells) and a variable content of platelets, depending on the method of processing.

Preparation

For the preparation of *Red Cells, Non-Leucodepleted* 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*.

Non-leucodepleted components should not be transfused to newborns.

B-4. Red Cells, Non-Leucodepleted, Buffy Coat Removed

Definition and properties

Red Cells, Non-Leucodepleted, 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, Non-Leucodepleted, BCR contains a minimum haemoglobin content of 43 g. The haematocrit is 0.65 to 0.75.

Red Cells, Non-Leucodepleted, 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, Non-Leucodepleted, BCR is derived from *Whole Blood* by centrifugation. The plasma and buffy coat layer are removed from *Whole Blood* after centrifugation, resulting in a small loss 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*.

Non-leucodepleted components should not be transfused to newborns.

B-5. Red Cells, Non-Leucodepleted, in Additive Solution

Definition and properties

Red Cells, Non-Leucodepleted, 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, Non-Leucodepleted, AS contains a minimum haemoglobin content of 45 g. The haematocrit is 0.50 to 0.70.

Red Cells, Non-Leucodepleted, AS also contains the greater part of the *Whole Blood* leucocytes (about 2.5 to 3.0 $\times$ 10^9 cells) and a variable content of platelets, depending on the method of processing.

Preparation

Whole Blood is collected using anticoagulant solution. After centrifugation of *Whole Blood*, plasma is removed and additive solution 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

[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*.

Non-leucodepleted components should not be transfused to newborns.

B-6. Red Cells, Non-Leucodepleted, Buffy Coat Removed, in Additive Solution

Definition and properties

Red Cells, Non-Leucodepleted, 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 additive solution.

Red Cells, Non-Leucodepleted, BCR-AS contains a minimum haemoglobin content of 43 g. The haematocrit is 0.50 to 0.70.

Red Cells, Non-Leucodepleted, 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*.

Non-leucodepleted components should not be transfused to newborns.

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 1×10^6 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 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.

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.

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).

In addition, if two or more units are collected from the donor in one session, each unit should have a unique unit (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 resuspension 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 % 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. 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*, a high-glycerol and 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.

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, as a process control for washing.

Storage and transport

Red Cells, Cryo in frozen state

Red Cells, Cryo in the frozen state should be constantly maintained at:

- Between – 60 °C and – 80 °C if stored in an electric freezer and when a high-glycerol method is used;
- Below – 140 °C if stored in vapour-phase liquid nitrogen and when a low-glycerol method is used.

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 donation (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.

Platelet components

	Component	Technical information	Platelet content	Leucocyte content
C-1.	Platelets, Recovered, Single Unit (SU), in Plasma	Derived from a single Whole Blood donation, suspended in plasma	$> 0.6 \times 10^{11}$	$\leq 0.05 \times 10^{9}$ when prepared from buffy coat $\leq 0.2 \times 10^{9}$ when prepared from PRP or by single centrifugation method
C-2.	Platelets, Recovered, Pooled, in Plasma	Pool of Platelets, Recovered SU, suspended in plasma, the number of which (usually 4-6) is determined by national regulations and the system used	$\geq 2 \times 10^{11}$	$\leq 0.3 \times 10^{9}$ per final unit when prepared from buffy coat $\leq 1 \times 10^{9}$ per final unit when prepared from PRP
C-3.	Platelets, Recovered, Pooled, Leucocyte-Depleted, in Plasma	Pool of Platelets, Recovered, SU, Leucocyte-Depleted, suspended in plasma, the number of which (usually 4-6) is determined by national regulations and the system used	$\geq 2 \times 10^{11}$	$< 1 \times 10^{6}$
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 (usually 4-6) is determined by national regulations and the system used	$\geq 2 \times 10^{11}$	$< 1 \times 10^{9}$

	Component	Technical information	Platelet content	Leucocyte content
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 (usually 4-6) is determined by national regulations and the system used	$\geq 2 \times 10^{11}$	$< 1 \times 10^{6}$
C-6.	Platelets, Recovered, Pooled, Leucocyte-Depleted, Pathogen-Reduced	Pool of Platelets, Recovered, SU, Leucocyte-Depleted, treated with pathogen inactivation technologies, the number of which (usually 4-6) is determined by national regulations and the system used. May be suspended in plasma or a mixture of plasma and additive solution	$\geq 2 \times 10^{11}$	$< 1 \times 10^{6}$
C-7.	Platelets, Apheresis	Obtained by plateletpheresis of a single donor, suspended in plasma	$\geq 2 \times 10^{11}$ standard unit $\geq 0.5 \times 10^{11}$ for neonates and infants	$< 1 \times 10^{9}$
C-8.	Platelets, Apheresis, Leucocyte-Depleted	Obtained by plateletpheresis of a single donor, leucocyte-depleted, suspended in plasma	$\geq 2 \times 10^{11}$ standard unit $\geq 0.5 \times 10^{11}$ for neonates and infants	$< 1 \times 10^{6}$
C-9.	Platelets, Apheresis, in Additive Solution	Obtained by plateletpheresis of a single donor, suspended in 30–40 % plasma and 60–70 % additive solution	$\geq 2 \times 10^{11}$ standard unit $\geq 0.5 \times 10^{11}$ for neonates and infants	$< 1 \times 10^{9}$

	Component	Technical information	Platelet content	Leucocyte content
C-10.	Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution	Obtained by plateletpheresis of a single donor, leucocyte-depleted, suspended in 30–40 % plasma and 60–70 % additive solution	$\geq 2 \times 10^{11}$ standard unit $\geq 0.5 \times 10^{11}$ for neonates and infants	$< 1 \times 10^{6}$
C-11.	Platelets, Apheresis, Leucocyte-Depleted, Pathogen-Reduced	Obtained by plateletpheresis of a single donor, leucocyte-depleted, treated with pathogen inactivation technologies. May be suspended in plasma or mixture of plasma and additive solution	$\geq 2 \times 10^{11}$	$< 1 \times 10^{6}$
C-12.	Platelets, Washed	Secondarily processed by sequential washing of a standard platelet component and resuspension in saline or platelet additive solution	$\geq 2 \times 10^{11}$	$< 1 \times 10^{6}$
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, in Plasma (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 resuspended 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 °C 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 10, Screening for markers of transfusion-transmissible infection).

Demonstration of the swirling phenomenon, which is based on light scattering by platelets of normal morphology in motion, 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

Parameter to be checked	Requirements	Frequency of control
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 donation (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 childbearing 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;
- Alloimmunisation against HLA and red cell antigens;
- Alloimmunisation against HPA 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 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 (TACO).

C-2. Platelets, Recovered, Pooled, in Plasma

Definition and properties

Platelets, Recovered, Pooled, in Plasma (Rec, Pool) is a platelet component derived from fresh *Whole Blood* donations, the number of which (usually 4-6) 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 from PRP or by 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 (usually 4-6) is determined by national regulations and the system used, are pooled in a sterile manner and resuspended 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 Unit (PRP or single centrifugation method)

Units of *Platelets, Rec, SU*, the number of which (usually 4-6) is determined by national regulations and the system used, prepared from PRP or by 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocyte content[a]		as determined by SPC
a. prepared from buffy coat per final unit	a. $\leq 0.3 \times 10^{9}$	
b. prepared from PRP or by single centrifugation method per final unit	b. $\leq 1 \times 10^{9}$	

[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, in Plasma (Rec, Pool, LD) 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 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 1×10^6 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 from PRP or by 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 (usually 4-6) is determined by national regulations and the system used, are pooled in a sterile manner and resuspended 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 Unit (PRP or single centrifugation method)

Units of *Platelets, Rec, SU*, the number of which (usually 4-6) is determined by national regulations and the system used, prepared from PRP or by 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocytes per final unit[a]	$< 1 \times 10^{6}$	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

Definition and properties

Platelets, Recovered, Pooled, in Additive Solution (Rec, Pool, AS) is a platelet component derived from fresh *Whole Blood* donations, the number of which (usually 4-6) 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 %) and an additive solution (60 to 70 %).

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 *Whole Blood*-derived buffy coats or *Platelets, Rec, SU* prepared by the single centrifugation method.

Preparation from 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 (usually 4-6) 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 Unit (single centrifugation method)

Blood group-compatible units of *Platelets, Rec, SU*, the number of which (usually 4-6) 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{9}$	as determined by SPC
Glucose measured at the end of the recommended shelf-life[b], or pH > 6.4	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, Subsection 4.1.4. (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

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 (usually 4-6) 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 %) and an additive solution (60 to 70 %).

Platelets, Rec, Pool, LD-AS contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool, LD-AS contains less than 1×10^{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 (usually 4-6) 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 Unit (single centrifugation method)

Blood group-compatible units of *Platelets, Rec, SU*, the number of which (usually 4-6) 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{6}$	as determined by SPC
Glucose measured at the end of the recommended shelf-life[b], or pH > 6.4	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, Subsection 4.1.4. (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, Leucocyte-Depleted, Pathogen-Reduced

Definition and properties

Platelets, Recovered, Pooled, Pathogen-Reduced (Rec, 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 %) and an additive solution (50 to 70 %). 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 treatment, if validated.

Platelets, Rec, Pool, PR contains a minimum of 2×10^{11} platelets.

Platelets, Rec, Pool, PR contains less than 1×10^{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 graft-versus-host disease (TA-GvHD) is not required.

Preparation

Platelets, Rec, 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 performed according to 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, whenever a removal step is required, 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{6}$	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, Rec, 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 donation (identity) number (the original donations contributing to the pool should be traceable and if multiple units are pooled prior to PIT each final unit should have a unique unit (identity) number).
- The number of donations combined to make the pool.

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, Rec, Pool, 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.

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 plateletpheresis 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 unit should have a unique unit (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 plateletpheresis 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 1×10^{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]	$< 1 \times 10^{6}$	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:

- *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 unit should have a unique unit (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, Aph*eresis*, in Additive Solution (Aph, AS)* is a component obtained by plateletpheresis 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 %) and an additive solution (60 to 70 %).

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: $\geq 2 \times 10^{11}$ 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
Glucose measured at the end of the recommended shelf-life[b], or pH > 6.4	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, Subsection 4.1.4. (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 unit should have a unique unit (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 plateletpheresis 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 %) and an additive solution (60 to 70 %).

Platelets, Aph, LD-AS contains a minimum of 2×10^{11} platelets.

Platelets, Aph, LD-AS contains less than 1×10^{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 additive 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 > 6.4	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, Subsection 4.1.4. (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 unit must have a unique unit (identity) number;
- Leucocyte-depleted;
- The relevant HLA and/or HPA type, if determined.

Warnings

As indicated for *Platelets, Recovered, SU*.

C-11. Platelets, Apheresis, Leucocyte-Depleted, Pathogen-Reduced

Definition and properties

*Platelets, Aph*eresis, *Pathogen-Reduced (Aph, PR)* is a platelet component obtained by plateletpheresis 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 %) and an additive solution (50 to 70 %). 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 1×10^{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 graft-versus-host disease (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 %) and an additive solution (50 to 70 %). Centrifugation, filtration or other in-process steps are included in the process to reduce the number of contaminating leucocytes.

The PIT is performed according to 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, whenever a removal step is required, 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]	$\geq 2 \times 10^{11}$	as determined by SPC
Residual leucocyte content per final unit[a]	$< 1 \times 10^{6}$	as determined by SPC
Glucose measured at the end of the recommended shelf-life[b], or pH > 6.4	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, Subsection 4.1.4. (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 unit should have a unique unit (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 resuspension 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 % 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 % 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 % *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 to 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.

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 technologies	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 technologies	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 defined 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 transfusion should comply with the specifications as given in this section (Chapter 5, Part D).

FFP must contain, on average, 70 % or more of the content of factor VIII of the freshly collected plasma unit *(Directive 2004/33/EC, Annex IV)* and at least similar quantities of the other labile coagulation factors and naturally occurring inhibitors.

FFP 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 system with integral transfer bags using hard-spin centrifugation with freezing commenced within 6 hours of collection, or within a timeframe validated to result in a component meeting the 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 to maintain the temperature between + 20 °C and + 24 °C and may be held at that temperature for a maximum of 24 hours.

Using a validated freezing process, a core temperature of below – 25 °C should be achieved for the plasma within 1 hour.

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 the specification.

Using a validated freezing process, a core temperature of below – 25 °C should be achieved for the plasma within 1 hour.

Quarantine FFP

Quarantine FFP can be released once the donor has been retested, 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 6 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 10, 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 FFP for transfusion	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[a]	Negative by approved screening test	All units
Volume[c]	Stated volume ± 10 %	as determined by SPC
Factor VIII[d]	Average (after freezing and thawing): not less than 70 IU per 100 mL	as determined by SPC on units in the first month of storage

Parameter to be checked	Requirements	Frequency of control
Residual cells[c]	Red cells: $< 6.0 \times 10^9$/L Leucocytes: $< 0.1 \times 10^9$/L Platelets: $< 50 \times 10^9$/L	as determined by SPC
	If leucocyte-depleted: $< 1 \times 10^6$ 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.
[d] A minimum of 90 % of individual units tested should contain at least 50 IU/100 mL.

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 components should be transferred at once to storage at the recommended temperature.

Before use, FFP should be thawed immediately after removal from storage, using a validated procedure in an environment that does not raise FFP temperature above + 37 °C.

Once thawed, the component should not be refrozen 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. 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 for FFP 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 donation (identity) number; if two or more units are collected from the donor in one session, each unit should have a unique unit (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;
- 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 and the integrity of the bag 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 (TACO);
- 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.

Using a validated freezing process, a core temperature of below – 25 °C should be achieved for the plasma within 1 hour.

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 pathogen reduction system.

It contains, on average, about 50 to 70 % 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 performed according to 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, whenever a removal step is required, 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 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 refrozen, unless approved by the manufacturer.

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 between + 2 °C and + 6 °C or by the rapid thaw-siphon 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 and the sedimented cryoprecipitate is 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/refreezing 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, the *Cryoprecipitate* should be thawed immediately after removal from storage, using a validated procedure in an environment that does not raise the *Cryoprecipitate* temperature above + 37 °C. 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 refrozen.

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 pathogen inactivation technology (PIT) and subsequent freezing within a defined 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 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 performed according to 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, whenever a removal step is required, 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 immediately after removal from storage, using a validated procedure in an environment that does not raise the *Cryoprecipitate, PR* temperature above + 37 °C. 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 refrozen.

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*, 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*.

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	Between $1.5–3.0 \times 10^8$ 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 (usually up to 12) is determined by national regulations and the system used, suspended in plasma or a mixture of platelet additive solution and plasma	As defined locally	$> 5 \times 10^9$ 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 pretreatment 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 10, 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 = $0.9–1.8 \times 10^{10}$ 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 donation (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 childbearing age or younger 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 alloimmunised recipients.

Granulocytes, Apheresis should be irradiated.

CMV-seronegative components should be considered for CMV-seronegative recipients.

Administration through a microaggregate 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);
- Alloimmunisation 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 (usually up to 12) 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 bag that allows gas exchange.

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	$> 5 \times 10^9$	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

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 and 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, in some cases, a 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 (PIT) could be an alternative to irradiation for the 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 among 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 limited 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 bags, 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.

Platelet components can be divided into satellite bags by using a closed system.

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.	5	Locally defined	Haematocrit 0.70–0.85
	The component should be irradiated before use.	Within 24 hours of irradiation		

Monograph	Technical information	Storage period	Platelet content	Other
A-2. Platelets, Leucocyte-Depleted for Intrauterine Transfusion	Platelets obtained from a single donor, either by apheresis or from whole blood, for intrauterine use. The platelets may be hyperconcentrated.	As for source component	$45–85 \times 10^9$ per unit	Volume 50–60 mL
	The component should be irradiated before use	Following secondary concentration, depends on concentration factor		

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.	5	40	Haematocrit as for WB
	The component should be irradiated unless delay would compromise the clinical outcome.	Within 24 hours of irradiation		
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.	5	40	Haematocrit as clinically prescribed or locally defined
	The component should be irradiated unless delay would compromise the clinical outcome.	Within 24 hours of irradiation		
B-3. Red Cells, Leucocyte-Depleted, Suspended in Fresh Frozen Plasma, for Exchange Transfusion	Prepared from Red Cells, Leucocyte-Depleted with additive solution/plasma removed and thawed FFP added to reach the clinically required haematocrit.	5 from day of collection of red cells	40	Haematocrit as clinically prescribed or locally defined
	The component should be irradiated unless delay would compromise the clinical outcome.	Within 24 hours of irradiation		

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 bags using a closed system.	Up to that of original component	40 (pre-split)	Volume 25–100 mL per unit
	May be irradiated when clinically indicated.	Storage period after irradiation as specified		

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 of 0.70–0.85.

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 alloantibodies.

The component should not contain irregular antibodies of clinical significance.

Requirements and quality control

As indicated for the source component with the additional requirements specified 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.

Red Cells, IUT should be used within 5 days of donation.

Red Cells, IUT should be irradiated and used within 24 hours of irradiation.

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 (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 transfusion-associated graft-versus-host disease (TA-GvHD), 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 (TACO).

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 hyperconcentrated.

Platelets, IUT contains $45–85 \times 10^9$ platelets (on average, 70×10^9) in 50 to 60 mL of suspension medium.

Preparation

Platelets, IUT is prepared either from P*latelets, Apheresis, LD* or by leucocyte depletion of P*latelets, 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 resuspended in an additive solution.

Platelets, IUT should be irradiated.

Requirements and quality control

As indicated for the source component, with the additional requirements specified 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	$45–85 \times 10^9$ 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 the storage time following secondary concentration of *Platelets, IUT* depends on the concentration factor and should be validated.

Labelling

The additional and/or amended labelling requirements to those of the source component for *Platelets, IUT* are:

- If components are split for use in neonates and infants, each satellite bag 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 (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 transfusion-associated graft-versus-host disease (TA-GvHD), 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 (TACO).

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 alloantibodies.

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 (as appropriate).

Warnings

Blood group compatibility with any maternal alloantibodies 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;
- Transfusion-associated graft-versus-host disease (TA-GvHD), unless irradiated;
- Transfusion-associated circulatory overload (TACO);
- 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 alloantibodies.

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 additional requirements specified 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 (as appropriate).

Warnings

Blood group compatibility with any maternal alloantibodies 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;
- Transfusion-associated graft-versus-host disease (TA-GvHD), unless irradiated;
- Transfusion-associated circulatory overload (TACO);
- 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 or Plasma, Fresh Frozen, PR* 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 (FFP) 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 alloantibodies. 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 (R*ed Cells, LD; Red Cells, LD-AS and FFP*), with the additional requirements specified 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 (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;
- Transfusion-associated graft-versus-host disease (TA-GvHD), unless irradiated;
- Transfusion-associated circulatory overload (TACO);
- 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 bags 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 additional requirements specified 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 bag should have a unique unit identity number that 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 (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 (TACO);

- Cytomegalovirus infection;
- Transfusion-associated graft-versus-host disease (TA-GvHD), unless the component is irradiated.

Chapter 7

Blood components for topical use or injection

7.0. Overview

The components described in this chapter are those for topical use or injection.

In recent years, novel preparations originating from blood components (autologous or allogeneic) have been used in various clinical situations. Examples include serum or plasma eye drops and several platelet preparations. Serum eye drops have become a commonly used therapy for dry eye treatment as they offer potential advantages over traditional therapies.

Platelet preparations, including platelet-rich plasma (PRP), platelet gel, platelet-rich fibrin (PRF) and platelet lysate eye drops, are emerging products but their clinical efficacy remains uncertain. In addition, several techniques for the manufacture of platelet preparations are available, with each method yielding a different product with different composition of biologically active substances and potential uses.

As a result, specific monographs for platelet preparations have not been included in this edition of the *Guide*.

The component monograph for S*erum Eye Drops* has a standardised structure consistent with other components in the *Guide*, which encompasses the headings 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.

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 3).

Quality control may be carried out either as a separate 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.

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.

Topical components

	Component	Technical information	Volume (mL per unit)	Other
A-1.	Serum Eye Drops	Derived from serum prepared from WB without anticoagulant	Depends on process	Sterile filtration is recommended May be diluted in saline

A-1. Serum eye drops

Definition and properties

Serum Eye Drops, both autologous and allogeneic, is a component prepared from the serum after coagulation of whole blood collected without anticoagulant. The serum, either undiluted or diluted in saline, is dispensed in small aliquots into eye dropper bottles or suitable dispensers. S*erum Eye Drops* have a potential advantage over traditional therapies for dry eye syndrome and persistent epithelial defects because human serum not only replicates the mechanical functions of tears (lubricating the eyelid, and rinsing particles from the ocular surface), but also serves as a lacrimal substitute, containing many of the same growth factors and other biochemical components that are present in natural tears.

Preparation

Whole blood that has been collected using a blood bag system without anticoagulant is allowed to clot for 6–24 hours at room temperature (depending on national requirements). The fluid part is separated after employing hard-spin centrifugation, if necessary followed by a second hard-spin centrifugation to result in a clear serum component. The serum is frozen within a timeframe validated

to meet the component specification. Using a validated freezing process, a core temperature of below – 25 °C should be achieved for the serum within 1 hour. Aliquoting can be performed before freezing, or later in time by rapidly thawing serum, immediate aliquoting and rapid freezing of the aliquots.

For allogeneic *Serum Eye Drops*, to ensure ABO compatibility and minimise anti-HLA antibody titres, male donors with AB blood type and without blood transfusion history should preferably be selected.

To reduce the natural variability in serum composition, pooling can be considered. Pooling of donations increases donor exposure; therefore, the rationale for pooling, including the number of donations in the pool, must be justified with a risk assessment that must include consideration of further measures to mitigate the risk of infection transmission from donor to recipients.

Quarantining for 4 months, followed by retesting for the relevant infectious disease markers on the donor's subsequent donation, is recommended to enhance product safety. If the outcome of this further screening is negative, the serum can be released for clinical application. If the initial screening includes NAT, and if appropriate donor-referral criteria and donor-compliance monitoring are in place to cover the risk of window-period infections, this quarantine period may not be necessary.

Eye-drop preparation must be carried out using aseptic technique. If the process involves open dispensing, clean rooms must be used for eye-drop manufacture. It is strongly recommended that a closed system is used for aliquoting. Microbiological control for each batch is mandatory (GPG 6.6).

Requirements and quality control

Table 7A-1 lists the requirements for *Serum Eye Drops* for topical use. Additional testing may be required to comply with national requirements (see also Chapter 10, Screening for markers of transfusion-transmissible infection).

Table 7A-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	Stated volume ± 10 %	As determined by SPC
Leakage	No leakage in any part of container	All units
Microbial control[a]	No growth or sterile filtration	Per batch, number of containers determined by SPC

[a] Microbial control to be performed where sterile filtration is not performed.

Storage and transport

Serum Eye Drops should be stored frozen at – 15 °C or below and transported under appropriate conditions to maintain the required temperature.

The shelf-life of *Serum Eye Drops* should be specified for a defined temperature(s) based on internal validation data and/or literature data. The shelf-life could be based on studies of the presumptive active components of *Serum Eye Drops* at the designated storage temperature.

Once thawed and opened, the product should be stored at 2 - 6 °C for a maximum of 24 hours or at room temperature for a maximum of 8 hours.

Labelling

The labelling should comply with relevant legislation and, where in place, international agreements. The following information must

be shown on the package label, dispenser 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 donation (identity) number; if *Serum Eye Drops* are derived from pooled sera the original donations must be traceable;
- The producer's identification;
- The ABO and RhD groups;
- The date of expiry;
- The storage temperature;
- The name of the anticoagulant solution (if any).

The following additional information should be shown on the package label, dispenser label or contained in the component information leaflet, as appropriate:

- If the component is intended for autologous use;
- The date of donation;
- Additional component information: irradiated, etc. (if appropriate).

Warnings

As storage and use after distribution is performed by the patient in a non-controlled environment, *Serum Eye Drops* require a strict protocol with special patient guidance for proper use and storage. The patient must be provided with written instructions for storage and handling of the eye drops at home, as well as information about the risk of, and signs of, potential bacterial contamination of the product and whom to contact if they have any concerns.

Before use, the component should be thawed and the integrity of the blood container should be verified to exclude any defects or leakages. No insoluble precipitate should be visible on completion of the thaw procedure.

Viral transmission (hepatitis, HIV, etc.) is possible, despite careful donor selection and screening procedures.

Certain systemic side-effects and reactions that can be caused by blood components for transfusion, such as allergic reactions, may also occur after use of *Serum Eye Drops*. Given the small droplet volume, of which only a small part will enter the blood stream, the likelihood of such a reaction is extremely low.

The occurrence of a local hypersensitivity reaction resulting in eye irritation cannot be excluded. In rare cases, a protein deposit (e.g. immune complex deposition) may form on the surface of the eye. This can be corrected by temporary interruption of treatment.

Chapter 8

Pre-deposit autologous donation

8.0. 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 alloimmune 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 perioperative 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 compared with allogeneic blood donors.

8.1. Selection of patients for PAD and blood collection

8.1.1. 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 preoperative 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 autologous transfusion, and that allogeneic transfusion may still be required.

Standards

8.1.1.1. ***PAD should be performed in or under the control of a blood establishment.***

8.1.1.2. ***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.***

8.1.2. 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. A risk/benefit approach should be taken for donors with underlying conditions. Particular consideration should be given to the risk of bacterial contamination of the autologous component and the handling of autologous components from donors with blood-borne pathogens.

Standards

8.1.2.1. ***The physician in charge of blood collection has ultimate responsibility for ensuring that the patient's clinical condition allows PAD.***

8.1.2.2. ***When autologous donation is contraindicated, the physician in charge of blood collection should inform the patient and the physician in charge of the patient.***

8.1.2.3. ***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 parent(s) or legal guardian(s) who should give written informed consent.***

8.1.3. 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 collection, 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 g/L (6.21 mmol/L) and 110 g/L (6.83 mmol/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 (6.21 mmol/L).

Standards

8.1.3.1. ***PAD should not be performed in a patient with an active bacterial infection.***

8.1.3.2. ***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.***

8.1.3.3. ***Haemoglobin levels should be measured before each collection.***

8.1.4. 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.

8.1.5. 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 where 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 % 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.

8.2. Testing, processing, storage and distribution of PAD blood components

8.2.1. Blood group testing and screening for infectious disease

Standard

8.2.1.1. ***Blood group testing and screening for infectious disease should be carried out according to the minimum requirements for the equivalent allogeneic components.***

8.2.2. Processing

Standard

8.2.2.1. ***Autologous blood should be processed as for the equivalent allogeneic components.***

8.2.3. Labelling

Standards

8.2.3.1. ***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).*

8.2.3.2. ***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.***

8.2.4. Storage and handling

Transfusion of allogeneic blood components should normally only proceed after the relevant available autologous components have been issued and transfused.

Standards

8.2.4.1. ***Pre deposit autologous blood components should be stored, transported and distributed under the same conditions as, but clearly separated from, the equivalent allogeneic components.***

8.2.4.2. ***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).*

8.2.4.3. ***Untransfused autologous blood components should not be used for allogeneic transfusion or for plasma for fractionation.***

8.3. 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 postoperatively;
- The actual use of the prepared preoperative autologous blood components;
- The concurrent use of perioperative autologous transfusion techniques;
- The use of allogeneic blood components;
- The occurrence of any adverse reactions.

8.4. Audit

Blood establishments should audit the use of PAD, where it is provided on a regular basis.

Chapter 9

Immunohaematology

9.0. 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 for 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.

9.1. Requirements for samples

9.1.1. Identity of donors and donations

Standard

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

9.1.2. Identity of patients

Standard

9.1.2.1. ***Documented criteria for safe patient identification and labelling should be in place. These should comply with national requirements, where available.***

9.1.3. Sample handling, retention and storage

Samples for immunohaematology testing of patients should be drawn in accordance with national requirements. Gross haemolysis and other factors such as lipemia that may affect test performance should be noted in the patient's records.

Standards

9.1.3.1. ***Blood samples for immunohaematology testing should be used, handled and stored according to the reagent and/or device manufacturer's instructions.***

9.1.3.2. ***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.***

9.2. Selection of reagents and validation of methods

9.2.1. General requirements

Standards

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

9.2.1.2. ***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)****.***

9.2.1.3. ***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*** *(GPG 6.5.6.)****. In house manufactured reagents may be used for rare occasions (e.g. blood group phenotyping and genotyping of high or low frequency antigens where commercial CE marked reagents are not available).***

9.2.1.4. ***The qualification of reagents should detect deviations from the established minimal quality requirements (specifications)*** *(see GPG 6.3.3.)****.***

9.2.1.5. ***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.).*

9.2.1.6. ***All techniques and modifications to techniques in use should be validated.***

9.3. Quality control and quality assurance

9.3.1. Quality control

Quality control procedures for immunohaematology can 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. However, even where such procedures are in use, there is always a possibility that incorrect results may be generated. This may be due to inadequacy of the method or, more often, to operational errors such as inaccurate performance of the test or incorrect interpretation of the results.

Standard

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

The frequency of control should be informed by a risk-based assessment, taking into consideration all relevant factors, including the manufacturer's recommendations.

9.3.2. Internal quality control

Quality control of reagents and techniques

Recommended quality control procedures 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 lot numbers of 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 the manufacturers' instructions.

Equipment for automated blood grouping should also have system controls in accordance with the manufacturer's instructions.

9.3.3. External quality assurance (proficiency testing)

Standard

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)***.**

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.

9.4. Blood group testing

9.4.1. General requirements

Standards in this section apply to testing of donors, donations and patients, whether performed by serological or molecular methods.

Extended phenotyping is the determination of the red blood cell antigen profile by serology or predicted antigen profile by molecular-based testing for red blood cell antigens other than ABO and RhD. 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. Current indications for molecular typing include (but are not limited to) the following situations:

- Where serological testing renders unclear results;
- Where there is a suspicion of weak antigens or variants (within ABO, RH, 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) and to guide the use of anti-D prophylaxis.

It can also be useful in chronically transfused patients to predict their red cell phenotype and aid the selection of phenotyped or genotyped red cell components.

Testing can be undertaken on genomic DNA isolated from validated samples such as blood, amniocentesis, biopsy of chorionic villi, buccal swabs 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

9.4.1.1. ***Blood group testing should be undertaken in accordance with the instructions provided by the manufacturers of the reagents and kits.***

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

9.4.2. Blood group testing of blood donors and donations

Standards

9.4.2.1. ***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)****.***

9.4.2.2. ***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

9.4.2.3. ***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.***

9.4.2.4. ***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 relevant weak D and D variants.***

9.4.2.5. ***ABO and RhD testing should be performed on all donations except for plasma intended only for fractionation.***

Additional Phenotyping or Genotyping

9.4.2.6. ***If additional typing for non-ABO and RhD antigens is performed, before the result of the confirmed phenotype is printed on the label, a test should be done using 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 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

9.4.2.7. ***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.***

9.4.2.8. ***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

9.4.2.9. ***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 to determine the

management of the donation and the donor. The policy should be based on a risk assessment of the antibody specificity and strength.

Positive direct antiglobulin test (DAT)

A positive DAT result in donors 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.

9.4.3. Blood group testing of patients

ABO and RhD typing

Standard

9.4.3.1. ***The ABO and RhD blood group and, when needed, other blood types should be determined on the patient's blood sample before selecting and 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.***

The ABO and RhD blood group of patients tested for the first time should be based upon the results of two independent ABO and RhD tests. At least one of the ABO tests should include reverse grouping in patients ≥ 6 months old.

Antibody screening and identification

Standards

9.4.3.2. ***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.***

9.4.3.3. ***Sufficiently sensitive techniques for the detection of clinically significant red cell alloantibodies should be used, including reagent red cells that cover all appropriate antigens with the strongest expression (dosage) for the most clinically significant alloantibodies.***

It may not be possible to include reagent red cells with the strongest expression where the phenotype is considered rare. Inclusion of a more common phenotype with a lower expression may be used, but should be noted as a limitation for detection of weaker antibodies.

9.5. Pre-transfusion testing

9.5.1. 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 can 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 crossmatching 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 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

9.5.1.1. ***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 alloantibodies should be used.***

9.5.1.2. ***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.***

9.5.1.3. ***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 undergoing 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.

9.5.1.4. ***An antiglobulin crossmatch should be performed if clinically significant red cell alloantibodies are suspected or have been identified by current or previous testing.***

9.5.1.5. ***Laboratories should maintain records of the tests performed and of the destination of all units handled (including the identity of the patient).***

9.5.2. 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 may 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. However, if the patient has clinically significant antibodies, antiglobulin crossmatch testing should be completed before issuing red cell components.

9.5.3. 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 prerequisite is that the system should not allow the issue of ABO-incompatible red cells.

Standards

9.5.3.1. ***A type and screen procedure may be used as a replacement for antiglobulin crossmatch testing if the patient has no known history of clinically significant antibodies and antibody screening has not detected clinically significant red cell antibodies.***

9.5.3.2. ***The antibody screening procedure should include the use of reagent red cells that cover all appropriate, clinically significant antigens, with the strongest expression (dosage).***

It may not be possible to include reagent red cells with the strongest expression where the phenotype is considered rare. Inclusion of a more common phenotype with a lower expression may be used, but should be noted as a limitation for detection of weaker antibodies.

9.5.3.3. ***Electronic release systems should utilise a reliable, computerised and validated procedure that ensures compatibility between the donor red blood cells and recipient plasma.***

9.5.4. Selection of red cells

Transfusion support for patients with clinically significant red cell alloantibodies

Standard

9.5.4.1. ***Whenever possible, red cell components that lack the corresponding antigens should be selected for transfusion, and an antiglobulin crossmatch between donor red cells and recipient plasma/serum should be undertaken before issuing red cell components for transfusion.***

9.5.5. Additional considerations

Use of extended red cell antigen matching to avoid alloimmunisation

Chronically transfused patients are at increased risk of developing red cell alloantibodies. Consideration may be given to providing red cell components matched for additional antigens to avoid this occurring. This may also apply to females of childbearing potential when selection of red cell components lacking clinically important antigens could be considered to avoid the future risk of HDFN.

Infants less than 4 months of age and intrauterine transfusion (IUT)

Red cell alloantibodies in the mother should be considered when selecting red cell components for the infant (< 4 months) or IUT. Postpartum, where the mother's red cell antibody status is not known

and/or a maternal sample is not available, pre-transfusion testing should be performed on a sample from the infant.

Emergencies and requirement for matching

RhD matching in emergencies

In emergencies when blood is transfused before the recipient's blood group is known, males, and females who no longer have childbearing potential, may be transfused with O RhD-positive red cells for resuscitation pending full compatibility testing. In all but exceptional circumstances, females of childbearing potential should receive O RhD-negative red cells pending full compatibility testing. Clinical departments and blood banks should have policies in place to guide when this may occur, including a requirement to take samples for compatibility testing prior to transfusion even if proceeding before the result is available.

Massive transfusion in immunised patients

In cases 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. The decision to transfuse should be based on consultation between the patient's clinician and a transfusion medicine specialist/laboratory director, taking into account the clinical significance of the antibody.

9.6. Investigation of suspected haemolytic transfusion reactions

If there are clinical symptoms of a haemolytic transfusion reaction, a blood sample should be drawn from the patient and sent together with the blood bag in question to the laboratory for testing. Where possible, the pre-transfusion sample should be tested in parallel. Minimum testing should include ABO/RhD typing, DAT and antibody screening on the pre- and post-transfusion samples, ABO/RhD typing and DAT on the blood unit. The crossmatch should be repeated with

both the pre- and post-transfusion samples. The results should be reported to the treating physician without delay.

Chapter 10

Screening for markers of transfusion-transmissible infection

10.0. Overview

In combination with donor education, judicious donor selection and pathogen inactivation technologies (PIT), 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 the pre-test probability of an accurate result and the test performance.

Current tests for markers of TTI are based on the detection of relevant antigens and/or antibodies, usually in a combined assay, and pathogen nucleic acids.

- 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 they often use different detection targets in order to maximise the 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 concordant screening and supplementary tests may be sufficient to exclude the majority of false reactive 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 confirm the result and 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, or has had, the infectious disease.

It is recommended that algorithms be developed nationally to enable the appropriate and consistent investigation and resolution of reactivity in 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 involves 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.

10.1. Selection of infectious marker tests and validation of methods

10.1.1. 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, serological tests are intended/validated to be applied as either screening or confirmatory assays, but not suitable for use in both settings. Molecular tests may initially be performed as a pooled test and subsequently confirmed on individual testing.

Standards

10.1.1.1. ***Only tests that have been licensed or evaluated and considered suitable by the responsible health authorities can be used. In the EU, these reagents and test kits are considered as in vitro diagnostic devices and must comply with Regulation (EU) 2017/746.***

10.1.1.2. ***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)****.***

10.1.1.3. ***TTI screening tests should be performed in accordance with the instructions provided by the manufacturers of the reagents and test kits.***

10.1.1.4. ***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, where a sample is taken from the primary tube and is then aliquoted, may be used for NAT testing of mini pools of individual samples*** *(GPG 6.4.4.)****.***

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

10.1.1.6. ***All laboratory assays and test systems for TTI marker screening, including any upgrades from the manufacturer (including software upgrades), used by blood establishments should be validated before introduction to ensure compliance with the intended use of the test.***

10.1.1.7. ***Correct determination of negative and positive controls, as provided by and in accordance with the manufacturer's instructions, is a minimum requirement.***

10.1.1.8. ***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)****.***

10.1.1.9. ***Initially reactive samples should be retested in duplicate. If any of the repeat tests are reactive, then the sample is deemed repeatedly reactive. Blood and blood components linked to the reactive sample should not be used for transfusion or the manufacture of medicinal products unless allowed by national regulations.***

10.1.1.10. ***Algorithms to enable consistent resolution of repeatedly reactive samples and linked donations should be in place.***

10.1.1.11. ***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.***

10.1.1.12. ***Appropriate confirmatory testing must take place. In 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)*.

It is recommended that initial and repeat reactivity rates and confirmed positive results of screening for TTIs, as well as epidemiological data, be collected and monitored at least on a national level. This will allow international comparisons to be made.

10.2. Requirements for samples

10.2.1. Identity of donors and donations

Standard

10.2.1.1. ***The procedure for blood collection 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)*.

10.2.2. Sample handling and storage

Standards

10.2.2.1. ***The handling and storage of samples should follow the reagent and/or device manufacturer's instructions.***

10.2.2.2. ***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 look-back 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.

10.3. Quality control and quality assurance

The specific approach to ensuring 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 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 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 performance.

10.3.1. 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. However, even where such procedures are in use, there is always a possibility that incorrect results may be generated. This may be due to inadequacy of the method or, more often, to operational errors such as inaccurate performance of the test or incorrect interpretation of the results.

10.3.2. Internal quality control

Quality control of reagents and techniques

Recommended quality control procedures are applied to TTI marker screening tests. Those performed on automated instruments 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 control.

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.

Standard

10.3.2.1. ***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 the requirements set by the 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.

10.3.3. External quality assurance (proficiency testing)

Standard

10.3.3.1. ***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).*

10.4. Confirmatory testing, donor notification and look-back

10.4.1. General requirements

Standards

10.4.1.1. ***Repeat reactive samples in TTI screening tests require confirmatory testing performed by an authorised laboratory.***

10.4.1.2. ***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.***

10.4.1.3. ***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 as soon as possible;***
- ***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.***

A risk assessment may be performed to determine which previous donations are at risk and thereby guide the extent of the look-back. For example, the availability of external negative test results, whether

pathogen inactivation was in place, what type of testing was used (e.g. ID NAT versus serology) and whether the donor had a documented seroconversion illness.

10.5. Classification of TTI testing

Some infectious disease screening tests are always performed on all donations. Others are performed only when a risk is identified or on a subset of donations to meet the requirements for particular patient groups.

TTI testing is classified as follows:

- *Mandatory blood donor screening* tests include HIV, hepatitis B and hepatitis C. These tests are always performed on all donations.
- *Additional blood donor screening* refers to testing in addition to HIV, hepatitis B and hepatitis C, that is performed on all donations. The decision to perform additional testing takes into account the epidemiological situation in any given region or country and other factors such as the effectiveness of any PIT that may be in place. Additional blood donor screening may always be performed on all donations (such as HEV NAT) or the introduction of such testing may be triggered by a change in epidemiological risk and only take place on all donations during a higher risk period (such as West Nile virus (WNV) NAT).
- *Selective blood donor screening* of donations involves the application of a test on a subset of the overall donor population. Such testing may be in place routinely, such as the screening of donations for anti-CMV antibodies to establish a panel of anti-CMV negative components for dedicated use in highly susceptible patients. Other selective screening may be performed in response to the medical history provided by the donor, such as travel history (e.g. malaria enzyme immunoassay (EIA)).

10.5.1. Mandatory testing requirements

Standards

10.5.1.1. ***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)****.***

10.5.1.2. ***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).***

10.5.1.3. ***Appropriate quality control measures should be in place for the mandatory serological blood donor screening tests*** *(see* ***10.3.2.1.****)****.***

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 NAT 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; alternatively the donor can be referred to an external clinician for confirmation.

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.

10.5.2. Nucleic acid amplification techniques (NAT)

The application of NAT techniques shortens the window period compared with serological testing and therefore has a positive impact on blood safety.

Standards

10.5.2.1. ***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.***

10.5.2.2. ***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 reassign pool results to individual donations should be in place.***

10.5.2.3. ***Appropriate quality control measures should be in place for NAT testing*** *(see* ***10.3.2.1.****).*

10.5.3. Additional screening

Additional testing of all donors for other agents or markers may be required, taking into account the epidemiological situation in any given region or country and other factors such as the effectiveness of any PIT that may be in place. Such tests may include:

- Antibody to 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
- Antibody to malaria
- West Nile virus RNA
- Antibody to *Trypanosoma cruzi*

Standard

10.5.3.1. ***Appropriate quality control measures should be in place when screening for additional TTI markers*** *(see* ***10.3.2.1.****).*

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.

Leucodepletion reduces the risk of HTLV 1/2 transfusion transmission, as does PIT.

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 their 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 10.1.1.10. do not necessarily apply to all donations found repeatedly reactive for anti-HBc. Additional testing, e.g. for anti-HBs and/or HBV DNA, may enable some repeatedly reactive donations to be used clinically.

This test is not required for plasma for fractionation.

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. Reactive syphilis screening results should be confirmed. This test is not required for plasma for fractionation.

10.5.4. Selective screening

Selective screening of donations involves the application of a test to reduce the risk of TTIs from a subset of the overall donor population considered at higher risk for the infection (e.g. malaria, *T. cruzi*, WNV RNA, Zika RNA, dengue RNA and chikungunya RNA), or screening of selected donations with the aim of 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.

The decision to implement selective screening should take into account the epidemiological situation and other factors such as the effectiveness of any PIT that may be in place.

Standard

10.5.4.1. ***Appropriate quality control measures must be in place when screening for selective TTI markers*** *(see* ***10.3.2.1.****)*.

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.

Leucodepletion reduces the risk of CMV transfusion transmission.

HEV screening

NAT testing for HEV RNA may be performed to remove donations with active HEV infection. This test is not required for plasma for fractionation.

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 as a unique strategy 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.

However, high-sensitivity molecular tests may represent a valuable complementary screening option for specific donor groups or in specific contexts, such as residents of non-endemic areas where autochthonous malaria cases are reported.

Standard

10.5.4.2. ***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*. In addition, if the donor's mother is from a country endemic for *T. cruzi*, selective screening may be considered in view of the risk of congenital transmission of *T. cruzi*. This test is not required for plasma for fractionation.

West Nile virus screening

NAT testing for WNV RNA may be performed as an alternative to donor deferral for potential donors returning from areas with ongoing transmission of WNV and should be able to detect all currently known WNV genotypes. The need for and timing of WNV screening in areas with seasonal (autochthonous) WNV cases should be based on a risk assessment. This test is not required for plasma for fractionation.

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 interrelated 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 professionals. 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, the need for special requirements (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 intravascular coagulation;
- Hospital out-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 may 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.

11.2.2. 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 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.

11.2.3. Alternatives to the transfusion of allogeneic 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 their 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 reinfusion 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 postoperative 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 processing 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 %) 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 microaggregate 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 % 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 where 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.

Sickle cell carrier status of the patient: each red blood cell will contain a variable proportion – typically 20–30 % – of sickle haemoglobin

(HbS) with the remainder being normal HbA. Thus, there will be a risk for cells to sickle. Processing this blood by CS may be deleterious. A decision to use CS in the presence of sickle cell carrier status should be carefully made on an individual patient basis with appropriate informed consent.

11.3. Completion of the transfusion request form, identification of the 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 undertake 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 their name and date of birth, if conscious, and/or these or other identifiers should be checked on a wristband securely attached to the patient.

If possible, all relevant data (patient´s wristband, sample collection number and number of blood components to be transfused) should be monitored by an electronic system (complete transfusion chain).

The information on the request form, patient's wristband (where 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 immunohaematology testing is provided in Chapter 9 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 blood component unit should 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 inventory for subsequent reissue must 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).*

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 so, 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.***

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 their name and date of birth and/or checking the identification details on the patient's wristband 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 remove 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.

Transfusion should be completed within 4 hours of removal of blood components from controlled storage.

To ensure traceability, all blood components administered should be recorded in the patient clinical 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 contents 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. alloimmunisation 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-transmissible 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, are also necessary when significant alloimmunisation 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 (HTCs)

Establishment of HTCs is strongly advised. The hospital chief executive and senior hospital management are responsible for providing support and resources to 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.

Chapter 12

Haemovigilance

12.0. 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)*.

The goal of haemovigilance is continuous quality improvement of the transfusion chain from donation of blood to transfusion of components, through corrective and preventive actions to ensure donor and patient safety, improve transfusion appropriateness and reduce wastage.

12.1. Introduction

A haemovigilance system should be an integral part of the comprehensive quality system for every organisation that has responsibility for any part of that chain. The system should cover all aspects of the transfusion chain from donor to recipient, including blood collection, testing, processing, storage, distribution and availability of blood and blood components, administration and monitoring the results of blood transfusions. The information provided by the haemovigilance system provides guidance on

potential strategies and other measures to prevent recurrence of incidents and improve safety. The results of data analyses should be fed back periodically to the providers of the haemovigilance data and communicated to the competent authorities.

Standard

12.1.0.1. ***Haemovigilance procedures should be in place to ensure the organised surveillance of serious or unexpected adverse events or reactions in donors and in recipients of blood and blood components which may be attributable to the quality and safety of blood and blood components and for the epidemiological assessment of infections in donors.***

12.1.1. Setting up an effective haemovigilance system

Each country should have an effective haemovigilance system, which should be well organised and structured. WHO recommends that haemovigilance should be incorporated into national health and blood policies, strategies and systems.

Haemovigilance is the shared responsibility of the professionals in the field and the competent authorities. It requires operational links between clinical departments, hospital blood banks (HBBs), blood establishments (BEs) and national authorities.

An effective haemovigilance system requires co-ordination of blood transfusion activities at national level. Ideally the following should be in place:

- national blood policy and plan;
- legislative and regulatory national blood commission or authority;
- well organised, nationally co-ordinated blood transfusion service;
- quality systems in blood transfusion services and hospitals (particularly their blood banks);
- hospital-based transfusion committees with oversight of all aspects of clinical transfusion practice.

The establishment of a haemovigilance system involves all relevant stakeholders and should be co-ordinated between the national blood programme under the ministry of health or national competent authority, blood services, hospital clinical units and transfusion laboratories, hospital transfusion committees, professional bodies, public health institutions, regulatory agencies, donors, patients and other stakeholders.

It should include the identification, reporting, investigation and analysis of adverse events (AEs) and adverse reactions (ARs) in recipients and blood donors, as well as incidents in manufacturing processes, errors and 'near-misses'. Haemovigilance should be strongly linked to quality management, triggering corrective and preventive actions when required.

Co-ordination and communication between various systems of vigilance (e.g. haemovigilance, medical device vigilance, pharmacovigilance) should also be in place, both at local and national level.

12.1.2. Guiding principles of haemovigilance

The effectiveness and efficiency of a haemovigilance system rests on the following pillars:

- *Traceability* - The ability to reliably follow the information trail from donor to recipient, and vice versa, in a timely manner. Traceability is described further in Section 12.2 in this chapter.
- *Trusting and blame-free culture* - Staff should be comfortable and empowered to report incidents and be assured that they will not be blamed for their occurrence. Leadership commitment, policies and practical steps should be in place to foster a supportive environment and ensure a positive reporting culture.
- *Confidentiality and independence* - Haemovigilance activities should be independent, driven by data and not adversely influenced by any health care organisation. Data protection and confidentiality measures must be in place, in accordance

with the local and national data protection laws, ensuring that donor, patient and staff confidentiality is maintained.

- *Clear, accessible reporting and acknowledgement* - Competent authorities should provide guidance and templates for the submission of serious adverse reaction (SAR) or serious adverse event (SAE) notification and investigation reports, based on the Good Practice Guidelines (GPG). The report forms (paper-based or digital) should be as easy as possible for the reporter to submit; the submission should be acknowledged. Electronic storage of data, preferably in well-protected databases for easy and quick access by authorised personnel, is preferred to paper-based information collections.
- *Feedback loops, preventive actions and promotion* - Whenever possible, direct feedback should be provided, to the reporting individual, on the actions taken in response to a notification, in addition to collective feedback to the community and competent authorities.
- *Team approach* - All key individuals (staff, donor, patient, family) who were directly involved or associated with the incident should contribute to the process. Typically, a facilitator with expertise in incident analysis and a clinician leader with operational responsibility and a good understanding of the analysis process, will share primary accountability for co-ordinating and conducting the analysis according to established organisational procedures.
- *Education and training* - Staff involved in the transfusion process should be trained, including in reporting and investigation of incidents, and receive retraining on a periodic basis to maintain and revalidate their skills and knowledge. The training should be tailored as required to meet the needs of different health professionals.

Haemovigilance cycle

The haemovigilance cycle can be summarised as follows:

- ***Detection/Identification*** - All health professionals involved in the transfusion chain should be trained and be able to

promptly recognise adverse reactions and events and initiate their optimal management.

- ***Initial reporting/Notification*** - Accurate, timely documentation is vital for haemovigilance. Clear instructions should be available on how to report adverse reactions and events, preferably using standardised documentation, to ensure that all relevant details are available as part of the report submitted to the haemovigilance system.
- ***Investigation*** - Every case should be investigated by appropriately qualified professionals. This may involve reporting to blood establishments, the national haemovigilance system and health authority.
- ***Final report/Final notification*** - The outcome of the incident investigation should be provided as a final report.

The last step of the incident management process is communication/ dissemination to share lessons learnt.

12.1.3. Haemovigilance co-operation and communication

An effective national haemovigilance system requires active participation by all institutions and facilities that are involved in the blood transfusion chain. Co-operation is essential to ensure complete investigation of any adverse event or reaction.

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). Where required, the process may be described in the contract(s) between the blood establishment and the hospital(s).

All stakeholders, blood establishments and clinicians should promote a culture that encourages reporting in a non-punitive context for the benefit of patients and donors. It should be accepted that mistakes happen and that no blood transfusion is risk-free. The reporting process should maintain patient confidentiality and be simple and

quick to facilitate prompt reporting such that timely actions can be taken as required, including preventing the transfusion of blood components from implicated donor(s), donations or processes. Complex or time-consuming procedures will be burdensome and will result in poor participation.

An individual should be identified in each organisation as the 'haemovigilance co-ordinator' with responsibility for internally co-ordinating haemovigilance activity. Responsibilities with respect to haemovigilance should be documented in the relevant job descriptions. All relevant staff should be trained and documentation of training should be kept. National co-ordination of training and standardisation of forms, procedures and educational materials is encouraged; this approach is cost-effective and drives consistency at the national level. Standardised definitions, procedures, forms and reports should be used.

Within a given organisation, adverse incidents (including ARs in donors and patients, accidents, errors, deviations, near misses) should be handled in accordance with the requirements of the established quality management system, including the execution of appropriate corrective and preventive actions. All organisations involved in the transfusion chain should submit an annual report of haemovigilance activity, including relevant denominator data, to the national haemovigilance co-ordinator.

Results of haemovigilance programmes should be published without identifying individual centres, hospitals or people, and should promote and encourage haemovigilance awareness in all professionals involved in the blood transfusion field, from donation to transfusion. To achieve this awareness, it is necessary to educate and train professionals about the benefits of implementing a haemovigilance system. This can be done with a high-quality educational programme and well organised workshops, by disseminating messages in meetings, publishing reports with anonymised data, etc.

12.2. Traceability of blood components

Traceability is defined as the ability to trace, in all directions, every individual unit of blood and any blood component 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, and vice versa.

A system of haemovigilance is dependent on the traceability of blood and blood components (both allogeneic and autologous) from donors to recipients and vice versa (bi-directional tracking). Key steps include identification of the donor, the blood establishment collecting, processing or storing the blood or blood component, the transfusing facility, the recipient and the physician responsible for the recipient. Traceability also covers the ability to locate and identify all relevant data relating to products and materials that may impact the quality or safety of blood or blood components.

Blood establishments should implement a traceability system. 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.

A procedure should be in place to verify that each unit has been transfused to the intended recipient; this may be a laboratory record or verification from the recipient's medical record. 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 is disposed of.

Importing blood establishments should ensure an equivalent level of traceability with regard to imported blood components or products.

All materials or equipment coming into contact with the blood/blood components that may pose a risk to their quality or safety should be recorded.

The use of unique identifiers for donations and components as well as for recipients provides an approximate denominator that can be used to calculate 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 blood units or components.

This information enables calculation of the rate of adverse events and reactions and supports the estimation of risks.

Standards

12.2.3.1. ***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*** *(from Directive 2005/61/EC)***.**

12.2.3.2. ***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 subsequent disposition.***

12.2.3.3. ***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.***

12.3. Definitions and categorisation

Incidents can happen at any step from donation to transfusion or directly to a donor or a recipient. Incidents can be preventable and arise from errors or deviations from standard operating procedures or unpreventable (e.g. adverse reactions from blood transfusion). Incidents can be harmful, cause no harm or be discovered before they involve the donor or patient.

Incidents can be categorised into 'adverse events' and 'adverse reactions'.

- Adverse events are unintended and sometimes harmful occurrences that may expose a recipient or donor to risk; they

are due to a process failure, such as an incident involving an error or procedural deviation.
- Adverse reactions are untoward responses or effects in donors or recipients associated with the donation or transfusion process.

An adverse event may or may not cause an adverse reaction. Similarly, an adverse reaction may or may not be related to an adverse event. Adverse events and adverse reactions can be further categorised according to the probability of occurrence, severity and imputability (see 12.3.1, 12.3.5 and 12.3.6). Categorisation is essential in haemovigilance and necessary for data collection, corrective actions and benchmarking. Those that are classified as 'serious' should be notified to competent authorities, in accordance with national or regional requirements.

12.3.1. Definitions

The definitions in Directive 2002/98/EC are very narrow; non-serious adverse reactions and events, near misses and events happening in the clinical setting are also important for identifying weaknesses in the transfusion chain and thereby contributing to reducing risk. While there are a range of definitions and classifications in use, the following definitions can be considered more appropriate. EU member states should be aware of requirements and definitions for mandatory reporting and non-mandatory definitions and requirements.

Incident: any deviation from usual medical care that either causes an injury to the recipient or donor or poses a risk of harm, including errors, preventable adverse events and hazards.

Adverse reaction (AR): any incident that could be reasonably associated with the quality or safety of blood or blood components, or its collection or application to a recipient, that caused harm to a blood donor or to a blood recipient.

Adverse event (AE): any incident or error associated with activities that may affect the quality or safety of blood or blood components in such a way that involves a risk of harm to a blood donor or to a blood recipient.

Serious adverse reaction (SAR): an adverse reaction that results in any of the following: death, life-threatening, disabling or incapacitating condition, including transmission of a pathogen or a toxic substance that might cause such a condition, hospitalisation or prolongation of hospitalisation, the need for a major clinical intervention to prevent or reduce the effects of any of the above, prolonged sub-optimal health of a donor following single or multiple donations.

Serious adverse event (SAE): an adverse event that involves a risk of any of the following: inappropriate distribution of blood or blood components, a defect posing a potential risk to recipients or donors detected in a blood establishment, hospital blood bank that could have implications for other recipients or donors because of shared practices, services, supplies or critical equipment, loss of a quantity of blood or blood components that causes human applications to be postponed or cancelled, loss of highly matched or autologous blood or blood components, event resulting in loss of the traceability of blood or blood components.

Near-miss event: an error or deviation from standard procedures or policies that is recognised before transfusion. These can be considered a subgroup of adverse events.

Seriousness: the degree of severity of an adverse reaction, involving harm to a blood donor, a blood recipient or for public health in general, or an adverse event involving a risk of such harm.

Imputability: the likelihood that an adverse reaction in a blood donor is associated with the collection process or, in a blood recipient with the application of the blood and blood components.

12.3.2. Adverse reactions

Adverse reactions must be detected, reported, investigated and evaluated in terms of severity, imputability, probability of recurrence or frequency and consequences.

Donors

A commonly used classification '*Standards for the Surveillance of Complications Related to Blood Donation*' is published by the

International Society of Blood Transfusion Working Party on Haemovigilance (ISBT WP HV) in partnership with the Association for the Advancement of Blood and Biotherapies (AABB) and the International Haemovigilance Network (IHN).

'*Severity Grading Tool for Blood Donor Adverse Events*', published by the AABB Donor Hemovigilance Working Group in 2018 is an example of a classification for assessing the severity of adverse reactions in donors.

Reporting of adverse reaction in donors is highly recommended, and analysis of the reports of adverse reactions in donors can assist in the continual improvement of safety in blood collection and is considered good practice.

Information on the management of adverse reactions in donors is provided in Chapter 3 of this *Guide*.

Recipients

Several classifications for adverse reactions in recipients have been developed. A commonly used classification for non-infectious transfusion reactions is published by the International Society of Blood Transfusion Working Party on Haemovigilance in partnership with other professional associations (AABB, IHN) '*Proposed Standard Definitions for Surveillance of Non-Infectious Adverse Transfusion Reactions | The International Society of Blood Transfusion*'.

12.3.3. Adverse events

Adverse events are preventable process failures and can occur at any stage from donor selection to transfusion (donor selection, whole blood or apheresis collection, testing, processing, storage, distribution, component selection, compatibility testing/crossmatching, issue, transfusion). An adverse event may not lead to a reaction in the donor or recipient, but has the potential to do so. 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 adverse events.

Errors in clinical or blood bank laboratory practice may lead to adverse events in patients. Significant errors may include incorrect results of compatibility testing due to misidentification of the recipient's blood sample (e.g. wrong blood in tube from a clinical area and detected in the hospital blood bank) or correctly cross-matched, labelled and issued blood components that are transfused to the wrong patient. Reporting of these errors to a local or national hemovigilance system may allow weaknesses in the transfusion chain to be identified and enable risk-reduction measures.

The term 'near-miss event' is not defined in the EU Blood Directive but is a commonly used term. Near-miss events are adverse events which, if they meet the definitions listed below, are reportable as SAE. Non-compliances with operational policies and procedures should be documented and investigated as part of the internal quality management system of the blood establishment/hospital blood bank. The following are examples of significant non-compliances that should be considered as a serious adverse event and reported through a haemovigilance system.

- Inappropriate blood/blood components have been issued/distributed for use, even if not used. For instance:
  - blood components distributed for use with incorrect blood group labels;
  - blood components distributed for use without the mandatory donor testing results;
  - blood components issued with incorrect crossmatching information;
  - blood components distributed for use despite a post-donation notification from the donor implying a disease transmission risk;
  - blood components distributed/issued for use despite having been stored at temperatures outside the required range;

  - blood components issued by a hospital blood bank without specific characteristics requested by the treating physician (e.g. irradiation).

- The adverse event resulted in loss of an irreplaceable, highly matched (i.e. recipient specific) blood/blood component, For instance:
  - blood components prepared for a patient with highly specific and urgent needs lost due to a storage or processing error;
  - blood components of a very rare group collected for a specific recipient and lost due to a storage or processing error.
- The adverse event resulted in the loss of a significant quantity of unmatched blood or blood components, such that patient care is compromised (e.g. though delay or cancellation of surgery):
  - an undetected cold-room breakdown with the consequent discard of a number of red cell concentrates, creating a delay in supply to hospitals;
  - a failure of the virology testing equipment that results in the expiry of platelet stock that cannot be cleared for issue.
- The adverse event could have implications for other patients or donors because of shared practices, services, supplies or donors:
  - a defect is detected in a haemoglobin testing device known to be used by other blood establishments. (This should also be reported via the medical devices reporting system).
- The adverse event could significantly impact the blood transfusion system (e.g. by jeopardising the confidence of blood donors or recipients). For instance:
  - confidential donor information is accidentally made publicly accessible;
  - donations are collected, in error, from underage donors.

12.3.4. Near misses

Near misses are often overlooked as they do not result in actual harm. The recognition, reporting and investigation of near-miss errors is vital in identifying processes and factors which increase the risk of resulting in actual transfusion errors. It is important to have clear definitions of and processes for the investigation of near-miss errors. These processes should also lead to the identification of causal factors and the implementation of corrective actions. Without these, in-depth investigations are futile. 'Near-miss' is a subgroup of adverse events and can in some cases fulfil requirements for serious adverse events and should be reported as such (see Subsection 12.3.3).

12.3.5. Severity information

Standard

12.3.5.1. ***The severity of adverse reactions and events should be determined.***

Commonly used grading scales for the assessment of severity of adverse reactions for both donors and recipients have been developed by the ISBT WP HV in partnership with IHN and other stakeholders and are accessible via the ISBT web page (Standard for Surveillance of Complications Related to Blood Donation and Proposed Standard Definition for Surveillance of Non-infectious Adverse Transfusion Reactions). A validation performed in 2017 showed that the definitions in this guideline may be difficult to directly apply to donor reactions. A grading tool specific for donor reactions has been developed and published by AABB in partnership with other professional associations and is more appropriate for use (*Severity Grading Tool for Blood Donor Adverse Events*).

The following seriousness assessment table (Table 12-1) should be applied when reporting to the competent authority. Table 12-1 is applicable both to recipient SAR and to SAR in donors.

Table 12-1. **Seriousness assessment**

Insignificant	No harm to the recipient or donor
Non-serious	Mild clinical consequences. No hospitalisation[1]. No anticipated long-term consequence/disability
Serious	Adverse reaction resulted in: • hospitalisation or prolongation of hospitalisation and/or • persistent or significant disability or incapacity[2] and/or • intervention to preclude permanent damage or impairment of a body function and/or • evidence of transmission of a serious communicable disease
Life-threatening[3]	Major intervention including vasopressor, intubation and transfer to intensive care to prevent death and/or Evidence of a life-threatening communicable disease
Fatal	Death in a recipient (transfused patient) or a donor: • report if you suspect that the death was an outcome of the adverse reaction. *Recipient SAR*: Deaths that are possibly, likely/probable, or certain to be attributable to the transfusion should be reported. Deaths associated with a patient's underlying conditions, or any other cause should not be included in this category. *Donor SAR*: this applies to all fatalities where a link cannot be excluded, i.e. imputability possible, probable or certain.

1 Hospitalisation: overnight admission to the hospital or prolongation of hospitalisation as a result of the adverse reaction (AR), even if the admission was precautionary. The criterion of hospitalisation also applies in the case of a donor. Emergency room visits that do not result in admission to the hospital should be evaluated for other serious outcomes (e.g. life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

2 Disability, incapacity, or prolongation of morbidity: a substantial disruption of a person's ability to conduct normal life functions, i.e. the reaction resulted in persistent or significant disability or incapacity or significant disruption in the patient or donor's physical activities or quality of life.

3 Life-threatening: report if suspected that the patient or donor was at substantial risk of dying as a result of the AR or medical intervention was necessary to prevent death. Report major interventions including vasopressor, intubation and transfer to intensive care.

12.3.6. Imputability information

Standard

12.3.6.1. ***The possible relationship between the observed adverse reaction and the transfusion of blood components (imputability) should be determined.***

Imputability levels to assess serious adverse reactions, as defined in Directive 2005/61/EC, are provided in the Table 12-2, below. For donor reactions the imputability level is linked to the donation process, and only included if phlebotomy was started. Other guidelines also include imputability levels, e.g. '*Standard for Surveillance of Complications Related to Blood Donation*' and '*Proposed Standard Definition for Surveillance of Non-infectious Adverse Transfusion Reactions*' published by ISBT HV WP.

Table 12-2. **Imputability scale**

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 components.
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.

12.4. Management of haemovigilance

Haemovigilance can be managed at three organisational levels: national, blood establishment and in the clinical setting, including hospital blood banks.

Blood establishments and hospital blood banks should implement and maintain, as part of their quality management system, an efficient process for the management of all incidents/deviations.

Standards

12.4.0.1. ***Facilities where transfusion occurs 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.***

12.4.0.2. ***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, Article 5.1).*

12.4.0.3. ***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 reactions 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, Article 15.1).*

12.4.0.4. ***The clinical outcome of serious adverse reactions, if known, in the recipients of blood components should be notified to the competent authority.***

12.4.0.5. ***Deviations from established procedures should be avoided as much as possible and should be documented and explained. Any errors, accidents or significant deviations that may affect***

the quality or safety of blood 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.

12.4.0.6. ***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.***

The process for the management of the haemovigilance cycle begins with detection of a reaction or event and the quality loop ends with dissemination of findings for learning purposes.

12.4.1. Detection/identification

All health professionals involved in the transfusion chain should be trained and able to promptly recognise adverse reactions and events. They should be able to respond appropriately to recognised adverse reactions/events and initiate optimal management.

The first stage is to identify cases that could be described as adverse reactions and events.

12.4.2. Initial reporting/notification

When an incident has been identified, an Initial Impact Assessment should be completed, which provisionally determines severity, probability of occurrence and imputability. This assessment should be included in the initial notification report.

All incidents (i.e. accidents or errors) that are associated with a reported adverse reaction and/or event must be reported using a detailed incident form. If multiple incidents occur in association with an adverse reaction, all should be reported. Incidents may occur

before (e.g. wrong product released) or after (e.g. failure to report adverse reaction to blood bank) an adverse reaction. A standardised reporting process, implemented at national/regional level, is desirable.

Each incident should be identified, evaluated and reported promptly. This enables the blood establishment to take action, as required, including action to prevent the transfusion of blood components from implicated donor(s), donations or processes.

Any incident suspected as being serious should be reported or notified to the competent authority, even if the investigation is not concluded. If there is a suspicion that other centres, blood establishments, donors or recipients could be affected or involved, they should be alerted promptly by the blood establishment or competent authority to prevent further complications. The haemovigilance system should operate in a non-punitive environment and the reporting should be confidential and anonymous.

Although reactions in donors are not reportable under the EU legal framework, reporting of adverse events in donors may promote donor safety, leading to measures that may reduce the frequency and severity of donor complications and instil greater confidence in the blood donation process.

Standardisation of reporting

There should be standardisation of reporting throughout the haemovigilance network and reporting should be well structured. This involves the use of defined data sets and agreed definitions of the different types of adverse events and adverse reactions. A training programme that ensures consistency in the notification and interpretation of an incident is highly recommended. Reporting should enable both adverse reactions in recipients and donors, and adverse events to be assessed. Reports should include a brief summary that describes the event, as well as the corrective actions taken.

Post-transfusion infection reported to the blood establishment

Where a transfusion-associated infection is suspected, the following trace-back actions should be taken:

- Blood establishments should be informed, without delay, whenever a recipient of blood components develops disease symptoms or has laboratory confirmation indicating that a blood component may have been infectious.
- The blood establishment should request relevant information from the hospital about the infection and the course of disease in the recipient.
- 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.
- The blood establishment should establish a plan of investigation, the results of which should be recorded.
- Investigation 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.
- The relevant organisation that carried out plasma fractionation (if relevant) is notified.
- Confirmed transfusion-transmitted infections should be reported to the competent authorities and the national haemovigilance system.

Blood establishments should initiate a look-back procedure to identify other recipients of blood components from a potentially infectious blood donation. The look back procedures should ensure that:

- The blood establishment informs the transfusing entity in writing about the incident, to trace the recipient(s) of the implicated blood component(s) and to inform the treating physician about the potentially infectious transfusion as soon as possible;

- If the recipient is confirmed to be positive for the given infection, the incident is reported to the national haemovigilance system and the competent authorities.

Information on post-donation information is provided in Chapter 2 of this *Guide*.

Standards

12.4.2.1. ***Blood establishments should be informed, without delay, whenever a recipient of blood components develops disease symptoms or has laboratory confirmation indicating that a blood component may have been infectious.***

12.4.2.2. ***The blood establishment should request relevant information from the hospital about the infection and the course of disease in the recipient.***

12.4.2.3. ***The blood establishment should establish a plan of investigation, the results of which should be recorded.***

12.4.2.4. ***Confirmed transfusion-transmitted infections should be reported to the competent authorities and the national haemovigilance system.***

12.4.3. Investigation

Every case should be investigated by appropriately qualified professionals. This may involve reporting to blood establishments, the national haemovigilance system and the health authority.

An investigation is a team based, structured approach involving data collection and analysis directed at identification of the cause(s) of an incident. The main purposes of an investigation are to determine what happened, the contributing causes and, if possible, root causes or at least most probable causes, and, based on the above, to recommend actions for each identified cause. Effective incident investigation processes can reduce errors, improve practices and lead to safer systems. Experience and learning from all incidents can prevent harmful incidents from recurring and enhance safety.

The reactions need to be investigated to determine the type and severity, in collaboration with the hospital blood bank that issued the transfused blood component. Policies, strategies, processes and procedures should be in place for documentation, evaluation, investigation and follow-up of all adverse reactions. The severity of the suspected adverse reactions should be evaluated according to the seriousness assessment table (severity levels) set out in this chapter of the Guide (12.3.5. Severity information) and the possible relationship (imputability) between the observed adverse reaction and the donation or the transfusion of blood components should be determined according to the assessment table (imputability levels) set out in this chapter of the Guide (12.3.6. Imputability information).

Root-cause analysis

Finding the main cause(s) is essential for determining appropriate corrective and/or preventive actions. Suitable analytical methodology should be used to facilitate determination of root cause(s). Root-cause analysis is a methodology that allows the questions 'when, what, how, why' to be asked in a structured way. Conclusions should be based upon evidence.

12.4.4. Corrective and preventive actions

The corrective and preventive action (CAPA) plan should outline the results of the investigation and any recommended actions or resolutions. The role of the CAPA owner is to identify and initiate feasible and targeted actions from the investigation report recommendations.

Corrective and preventive action is a cornerstone of the quality procedures required to eliminate the causes of an existing nonconformity, and to prevent recurrence of non-conforming products, processes and other quality problems. To determine the most important (critical) contributing factors, the factors are evaluated for impact and likelihood of occurrence. This allows targeted solutions to be selected from among the potential actions recommended in the investigation report.

It is important to determine effective corrective and preventive action to reduce future risks. Corrective action seeks to remove the cause of the identified nonconformity, so as to prevent a recurrence. Preventive actions seek to prevent future incidents through an assessment of risks, followed by appropriate risk-reduction activities. The effectiveness of such preventive and corrective actions should be monitored and assessed in accordance with quality risk management principles (GPG 1.2.13).

12.4.5. Final report/Final notification to competent authorities

A risk assessment of the seriousness and likelihood of recurrence should be included in the communication. If the incident meets the criteria for SAR/E, it must be reported to the national competent authority in a timely manner. The final report should include key facts and findings, conclusions, actions and recommendations laid down in a clearly understandable language and format. This final report should detail how to act on similar occasions in the future in order to prevent the recurrence of incidents.

The last step of the incident management process is communication/dissemination of the outcomes to share lessons learnt.

12.4.6. Rapid alert system for blood and blood components

The haemovigilance system can include a rapid alert or early warning mechanism for the rapid dissemination of information on important events, emerging hazards or trends. Such a system should not replace urgent notification to the blood centre of adverse events requiring immediate action, e.g. post-transfusion sepsis or blood bag system defects.

In some circumstances, a particular event or reaction requires rapid communication nationally or internationally to facilitate urgent actions, such as a recall of product or critical materials, or the quarantine of affected blood components. In such cases, a communication system must be available at all times. Rapid alerts should only be issued in

exceptional circumstances. A rapid alert system for blood and blood components can be initiated by national authorities.

12.5. Data management

Effective and precise documentation in the transfusion chain is very important. It serves several purposes:

- Correct, complete, clear, accurate, coherent and concise records should enable identification of all the actions undertaken from donor selection through donation, testing and preparation of blood components to administration to the recipient. Ensuring traceability of all these activities, through good record keeping, enables the effective investigation of all quality incidents, adverse events or reactions.
- To provide relevant information about each critical procedure or process that took place from blood donor selection and blood donation to the administration of blood components. Adequate records ensure correct understanding, thus eliminating the risk of misinterpretation and errors throughout the transfusion chain.
- To document the occurrence of adverse reactions in donors and in recipients. This fulfils the regulatory requirement for control/management of incidents in donors and recipients.
- To obtain data on the occurrence and causes of adverse events and reactions, to evaluate them and enable implementation of corrective actions.
- To enable benchmarking.

Documentation as a source of data should be managed in accordance with Section 5 of the Good Practice Guidelines for blood establishments and hospital blood banks (GPG).

Retention of documents/data takes place in accordance with local, national and EU legislation. Specific retention requirements for certain data are mentioned in articles 5.5.2.2. and 5.5.2.3. of the GPG (*Directive 2002/98, Article14.3*, *Directive 2005/61, Article4*)

12.5.1. Data collection

Data collection and analysis can be performed electronically, through clinical information systems, laboratory information systems, other electronic data collection systems or manually. All data should be held securely and protected against unintended loss and unauthorised access. Only authorised persons may have access to the data.

Standard

12.5.1.1. ***Confidentiality of haemovigilance data - 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.***

Relevant data related to haemovigilance should be collected and retained at several levels:

- by the clinical facilities where the transfusion of blood components takes place;
- by hospital blood banks;
- by blood establishments.

Clinical facilities, hospital blood banks and blood establishments are also defined as reporting establishments, which report haemovigilance data to the national authority through the national haemovigilance system. The national authority then provides data for survey at the level of the European Commission and the Council of Europe. (*Directive 2002/98, Directive 2005/61*).

Data to be collected by the clinical facility, hospital blood bank or blood establishment responsible for issuing the blood components for administration to patients, include but are not limited to:

- number of units issued according to blood component type;
- number of units transfused according to blood component type;
- number of patients transfused;

- number of adverse transfusion reactions according to the type of reaction, its severity and imputability with regard to the type of administered component;
- number of adverse events according to type, with regard to the impact on the quality of the blood component or the safety of the recipient;
- number of near-miss events according to type, with regard to the possible impact on the quality of the blood component or the safety of the recipient.

Data to be collected by the blood establishment include, but are not limited to:

- number of blood and blood component collections;
- number of units produced according to type of blood component;
- number of units distributed to clinical facilities and their blood banks according to type of blood component;
- number of adverse reactions in donors according to type of reaction, its severity and imputability with regard to the type of donation;
- number of adverse events according to type, with regard to the impact on the quality of the blood component or the safety of the recipient;
- number of near-miss events according to type, with regard to the possible impact on the quality of the blood component or the safety of the recipient;
- number of recalls of the blood components according to reason;
- number of post-donation information (PDI) according to reason;
- number of look-back procedures according to reason;'
- epidemiological situations affecting donor selection and testing.

Data collection, monitoring, analysis and evaluation are important for further improvement and for risk assessment and early detection of

negative trends that may affect the quality of blood components and the safety of the recipient and donor.

12.6. Epidemiology and surveillance

Globalisation has resulted in migration and worldwide trade, factors which favour the faster spread of infectious agents and changes their distribution. Rapid changes in global epidemiology may threaten the provision of a safe blood inventory. The science of epidemiology plays a central role in ensuring the safety of transfusion through continuous surveillance and timely identification of risks.

The European Centre for Disease Prevention and Control (ECDC) monitors trends on communicable diseases in the EU/EEA countries, as well as any multinational communicable disease outbreaks relevant to the EU/EEA. The relevant information is published in the weekly *Communicable Disease Threat Report (CDTR)* and may provide useful data to support the development of donor selection policy and surveillance.

The provision of a safe blood supply is supported by surveillance of transfusion-transmissible infections, donor behaviour posing a risk to blood safety, and also the serious adverse reactions and events associated with blood donation and blood transfusion.

The prevalence, incidence and risk factors of infectious diseases observed in the general population directly influence transfusion medicine practice, especially blood donor selection, to ensure blood safety. The mode of transmission of the infection may influence donor selection: the risk factors of the most significant blood-borne infections have led to the development of the pre-donation questionnaire so that at-risk donors are likely to be excluded. The prevalence of infections also has an impact on blood screening strategy.

Surveillance of serious adverse reactions and events in recipients and donors can help to provide indicators and information on stratification of risks. Routine monitoring of clinical outcomes should be part of the surveillance system, in order to monitor the quality

of transfusion therapy. When a surveillance system is implemented, periodic analyses can follow the trends of serious adverse events and reactions to identify whether risks are increasing Where adverse trends are identified, these should be reported to the competent authority, a root-cause analysis should be initiated and corrective measures should be implemented. Surveillance programmes should also include active scanning for new risks (horizon scanning) that have not been recognised previously or have not yet occurred. Newly emerging infectious diseases represent an example of one type of new risk.

Horizon scanning requires a systematic examination of a range of evidence and should provide early warning of new risks (risk identification and monitoring), management of the evolving epidemiological situation (risk management) and communication processes to relevant stakeholders (risk communication). Newly emerging or re-emerging infectious diseases, for example, can be identified through monitoring of trends (risk identification); management of such risk may include targeted testing or individual risk-based assessment of donors and recipients.

Reporting and further analysis are very useful tools for learning how to avoid mistakes and other errors, and the resulting analysis is beneficial for the safety of donors and patients.

Chapter 13

Blood supply contingency and emergency planning

13.0. Overview

Contingency planning and emergency preparedness are key elements in safeguarding the supply of blood and blood components (hereafter referred to as blood supply) during disaster or emergency situations. It is essential to ensure that when faced with such situations, a safe and adequate blood supply can be maintained and made available for all essential transfusions.

Contingency planning ensures that, when faced with disruptions, the capability to continue the delivery of blood, blood components and associated services is maintained.

Emergency preparedness is the development, implementation and maintenance of plans through which the impact of an unexpected event is managed, which enables the required blood, blood components and associated services to be provided to the healthcare community throughout the ongoing emergency/disruption. A cornerstone of emergency preparedness is training and exercising of such plans.

Contingency planning and emergency preparedness are fundamental in order to be able to react at each level of the blood supply chain in an efficient and adequate way to a sudden emerging issue or emergency situation that may result in a disruption of the blood supply. Having defined plans in place can ensure a shortened response time and enable fast and accurate mitigation strategies that lay the foundation for blood supply continuity in such situations.

13.1. Blood supply contingency and emergency plans

13.1.1. General requirements

Blood supply contingency and emergency plans should be established, implemented, tested and maintained. Key stakeholders within the blood supply chain should be identified and their expected responsibilities and actions should be defined according to different key risk scenarios.

Depending on the scope of these blood supply contingency and emergency plans (B-SCEP), the following aspects should be defined:

- Organisational and operational structure of the relevant blood supply chain;
- Key stakeholders and operators including their functions and interactions;
- Regulatory requirements in place that apply;
- A detailed overview of the blood supply chain including associated critical activities, equipment/material resources and contingency arrangements, blood supply levels and monitoring system;
- Key risk scenarios that may impact the blood supply and corresponding actions, mitigation and communication strategies;
- Strategies for recovery and assessment of the effectiveness of the response;
- Strategies for management of the plan, including establishment, implementation and maintenance, testing, training and continuous improvement.

13.1.2. Key stakeholders

The key stakeholders within the blood supply chain should be identified.

Key stakeholders should include blood establishments, hospital blood banks and others, where relevant, for example: regulatory oversight bodies, the ministry of health, local/civil authorities, public health surveillance agencies, material suppliers, donor testing laboratories, transport providers, donor or patient associations, hospitals/hospital transfusion committees (HTCs), rescue services and the armed forces.

The roles and actions of each key stakeholder for each key risk scenario should be defined, based on the role of the stakeholder within the blood supply chain and on the severity of risk to the blood supply.

13.1.3. Key risk scenarios

Key risk scenarios and their consequences for the safety and sufficiency of the blood supply should be defined. Identified key risk scenarios should be assessed and classified based on their severity and duration, their likelihood of occurrence and estimated impact on the blood supply.

Risks to blood supply continuity could include: disruption to critical activities, interruption of the supply chain of critical material, breakdown of computerised systems, disruption or damage to premises, equipment or facilities, disruption of transport (e.g. due to adverse weather conditions), etc., and should be considered in the corresponding contingency plans.

Risks due to disaster or emergency situations, such as infectious risks due to epidemics, pandemics or as a result of mass casualties, terrorist attacks, natural disasters, cyberattacks, etc. should be considered in emergency preparedness plans.

According to the nature and level of risk to the blood supply, different key risk scenarios require the co-ordination and collaboration of different key stakeholders.

13.1.4. Establishing, implementing and maintaining plans

There should be a defined process, with roles and responsibilities assigned for each key stakeholder, for the establishment, implementation, maintenance and revision of blood supply contingency and emergency plans.

Consideration should be given to the wider national healthcare system, ensuring integration with existing health sector arrangements, in particular, those related to contingency and emergency planning. National legislation, guidelines and standards, local contingency or business continuity plans and any additional relevant structure or body involved with the blood supply should be taken into account when establishing contingency and emergency plans.

A clear strategy for the implementation and communication between all key stakeholders should be defined for emergency preparedness plans. It should include who, what, when, with whom and how to communicate prior to, during and after a response to an emergency situation.

A strategy for the recovery process after a response to an emergency situation should be defined. The strategy should include an assessment of the effectiveness of the actions executed and, if needed, suggestions for improvements. All key stakeholders should be involved in the recovery process.

There should be a defined process for testing and training on contingency and emergency plans at regular intervals, at least upon implementation and in the event of a significant change. Testing and training may involve desk-based reviews or practical exercises.

The contingency and emergency plans should be subject to regular review, continuous improvement and updating at least after a significant change or evaluated as part of a recovery strategy.

13.2. Blood supply continuity management

13.2.1. National level

The blood supply chain is a critical element of the national healthcare system and, as such, ensuring the continuity and safety of the blood supply should be considered a national healthcare priority. The blood system should be sufficiently resourced (financial, technical and human) and supported by appropriate governance, policies, systems and structures to ensure that a safe and adequate supply of blood and blood components is maintained and made available for all essential transfusions.

The needs and functioning of the blood supply chain should be estimated, monitored and regularly evaluated on a national level. Mechanisms should be established for the collection of data and reporting on the blood supply, in routine and emergency situations.

Arrangements, including elements of patient blood management (PBM), should be in place to support the clinical management of blood and blood components in emergency situations, and to support the determination of strategies for the optimal and selective use of blood *in situ*ations of increased demand or decreased availability of any or several kinds of blood components.

Consideration should be given to establishing specific working groups or taskforces on a national level, with assigned responsibility for emergency preparedness to ensure the continuity of the national blood supply. This should include regulatory mechanisms to assess the need for and implementation of derogations from existing regulatory requirements, if this is necessary to maintain the blood supply.

There should be structural frameworks in place to support the blood system in developing collaborative contingency arrangements between blood establishments (local, interregional, intercountry) to allow mitigation of possible disruptions of the blood supply.

13.2.2. Blood establishments

Blood establishments should have a defined system in place for effective monitoring of their blood supply, identification of acceptable supply levels and detection of early indicators of disruption in accordance with the defined needs.

Blood establishments should have defined communication strategies on when to promote/discourage donation in accordance with different key risk scenarios.

Blood establishments should have defined strategies for back-up donation, processing, storage, distribution and testing of blood and blood components in accordance with different key risk scenarios. Where needed, blood establishments should establish alternate blood supply back-up, for instance by collaborative contingency arrangements with other blood establishments (interregional and/or intercountry). These arrangements could include: back-up supply of blood components and back-up provision of critical activities, facilities, equipment, material and staff.

Blood establishments should establish contingency measures in their contracts with suppliers of critical equipment and materials, in order to strengthen back-up provision of disposables, kits and similar items needed for the collection, processing, storage, distribution and testing of blood and blood components. Such measures could include: agreed ranges of routinely held stock, reserved spare consumable batches/equipment and/or the concurrent use of multiple different consumable batches, and involvement in production forecasting and supply chains.

Blood establishments should establish contingency arrangements with associated testing laboratories in blood quality and safety, including immunohematology, donor screening and component quality control and assurance.

13.2.3. Hospital blood banks

Hospital blood banks should have defined strategies in place to control and manage their local stock of blood components and

communication policies with the blood establishments responsible for providing them with blood components.

Hospital blood banks, where required, should collaborate and communicate with the clinical transfusion service and/or HTC to support the optimal and selective use of blood and blood components in response to an emergency situation.

Hospital blood banks should have preparedness for scaling up the capacity of their routine immunohaematological laboratory testing, such as blood group typing, antibody screening, identification and compatibility testing, as required.

Hospital blood banks should establish contingency measures in their contracts with suppliers of critical equipment and material, in order to strengthen back-up provision of disposables, kits and similar items needed for immunohaematological laboratory testing. Such measures could include: agreed stock levels, reserved spare batches/equipment and/or concurrent use of multiple different consumable batches, and involvement in production forecasting and supply chains.

13.3. Model preparedness plan

The EDQM B-SCEP model preparedness plan[1] aims to assist national bodies, blood establishments and hospital blood banks in the development of appropriate blood supply contingency and emergency plans through:

- providing a template which aids in the structuring of key elements of the blood supply chain;
- assisting in defining the organisational structure and critical activities of the blood supply chain;
- providing a guided risk assessment tool to help:
  - define relevant key risk scenarios (what),
  - identify key stakeholders (who) for each key risk scenario,

1 https://www.edqm.eu/en/blood-supply-contingency-and-emergency-plan-b-scep-

– decide how and when the key stakeholders should operate and interact with each other.

Using this model, action and mitigation plans based on the overall impact on the blood supply can be tailored accordingly, to accommodate individual blood systems.

The B-SCEP model preparedness plan can be applied to any blood system, irrespective of its organisational setting, and it can include all main stakeholders.

The standardised format provided by the model preparedness plan can also facilitate intercountry, interregional and local contingency collaboration.

APPENDIX 1.
KEY CRITERIA FOR DONOR ELIGIBILITY

The Standards require medical assessment of all prospective donors to be undertaken using a combination of interview, questionnaire and, if necessary, further direct questions. The questionnaire must be designed to elicit information on aspects of 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 and that aligns with national requirements. Therefore, it is not possible to provide a generic questionnaire in this *Guide*. This questionnaire acts as an example. It consists of examples of the wording for 'core' questions (critical for the safety of donors and recipients) and examples of the wording for optional questions (adding value to the selection process, but which may be used instead as information provided to the donors before each donation). There are some questions which are required only once during the donor's career and are usually asked at the first donation. For operational ease, such questions may also be asked when lapsed donors return to donate. In addition, some questions are not required if the donation is to be used exclusively for plasma for fractionation.

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only 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	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 one 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	Y (1. time)
General – previous deferral	To identify people who have previously been permanently deferred from donating blood.		Have you previously been told not to give blood?	Y	N	Y (1. time)
General – weight	Total blood volume is proportional to donor weight. Donors must weigh at least 50 kg to safely donate blood. NOTE: If not included as an optional question, blood establishments should have a formal process to obtain, consider and record this information.		Is your weight over 50 kg?	Y	Y	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
General – donor comprehension	For the donor interview process to be effective, the donor must first understand the questions being asked of them and then truthfully and accurately complete the questionnaire to the best of their knowledge. NOTE: If not included as an optional question, blood establishments should include it in the donor declaration used to obtain 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	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? • epilepsy or diseases of the nervous system? • chronic diseases such as diabetes or malignancies?		Y	Y	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
Serious illness – physician and hospital visits	Illness that is serious enough to require medical consultation may be relevant to donor selection.		In the last 6 months or since your last donation, have you been to see a doctor or to hospital?	Y	Y	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. NOTE: If not included as an optional question, blood establishments should have a formal process to obtain, consider and record this information.		Do you have a hazardous occupation or hobby such as driving public transport, operating heavy machinery, underwater diving, piloting a plane or other activities?	Y	Y	Y
Pregnancy	To protect donors from iron depletion and/or 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: Are you or have you been pregnant in the last 6 months or since your last donation?		Y	Y	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
	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/ given birth?	Y	N	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/ in the last four weeks?		Y	Y	Y
Medications – teratogenic	Medications with known teratogenic potential require donor deferral to cover the maximum 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.	Have you ever taken medication containing: • 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)?		Y	Y	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
Medications – vaccinations	Recent vaccination may harm immunocompromised 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	Y
Blood-borne risks – intravenous use of drugs	Intravenous 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	Y
Sexual activity	To identify donors who are considered (based on national guidelines or legislation) to have increased risk for blood-borne and sexually transmitted infections.	Questions will vary based on local infectious marker epidemiology and will be influenced by the assessment approach, such as gender neutral versus specific questions for different donor cohorts.		Y	Y	Y
Travel – entry question	Several infectious diseases relevant to blood safety are restricted to certain geographical regions and pose a higher risk for individuals born in or have lived in the area. These include malaria, Chagas disease.	Were you born or have you lived abroad?		Y	Y	N

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
Travel - general	Several infectious diseases relevant to blood safety are restricted to certain geographical regions and pose a travel risk. These include malaria and other vector-borne diseases such as West Nile fever, dengue fever and chikungunya.	Have you travelled abroad in the last 6 months or since your last donation?		Y	Y	N
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	N
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 6 months)? If so, check whether the donor visited any malaria-endemic areas.		Y	Y	N

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
Travel – unexplained fever	A donor who visits a malaria risk area could harbour asymptomatic infection after returning to their country of residence.		If you have you been abroad since your last donation (or, for new donors, in the last 6 months), did you have an unexplained fever while or after travelling abroad?	Y	Y	N
Travel – Chagas exposure	To identify donors who were born in a Chagas-endemic country or who are at risk for vertical transmission of Chagas disease.	What was your country of birth? Was your mother born in south or central America?		Y	N	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	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
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 6 months? If so, was a flexible instrument used and was any biopsy performed?	Y	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	N

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
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 or tattoo? • acupuncture treatment by anyone other than a registered practitioner? • an accidental injury involving a needle or mucous membrane exposure to human blood?		Y	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	Y
Other blood-borne risks – pituitary extracts	Most reported cases of iatrogenic CJD have been associated with human-derived pituitary hormone treatment.	Have you ever had treatment with human pituitary extracts?		Y	N	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
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	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, rashes or sores?	Y	Y	N
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	Y
Other blood-borne risks – transfusion	Blood transfusion may cause transmission of blood-borne infections, including geographically restricted infections such and Chagas disease.	Have you ever (new donors) or since your last donation (returning donors) received a blood transfusion or injection of blood products? If so, where and when?		Y	Y	Y

Key evaluative topic for donor eligibility	Intent of question	Core sample question	Optional sample question	First-time & lapsed donors	Regular donors	Plasma for fractionation only donors
Other blood-borne risks – positive infectious disease testing	HIV, hepatitis B, hepatitis C, syphilis and HTLV are transfusion-transmissible infectious agents, and all may be transmitted between partners by sexual or blood contact.	Have you or your partner ever had a test which showed you had HIV, hepatitis B, hepatitis C, syphilis or HTLV?		Y	Y	Y

APPENDIX 2.
TABLES FOR CALCULATION OF BLOOD VOLUMES OR COLLECTIONS VOLUMES

Appendix 2a

Table 1. Blood volume of females 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

1 Pearson TC, Guthrie DL, Simpson J *et al.* 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.

kg	50	51	52	53	54	55	56	57	58	59
167 cm	3475	3504	3533	3561	3589	3617	3645	3672	3699	3726
168 cm	3490	3519	3548	3577	3605	3633	3660	3688	3715	3741
169 cm	3505	3534	3563	3592	3620	3648	3676	3703	3731	3757
170 cm	3520	3549	3578	3607	3636	3664	3692	3719	3746	3773
171 cm	3535	3564	3593	3622	3651	3679	3707	3735	3762	3789
172 cm	3550	3579	3608	3637	3666	3695	3723	3750	3778	3805
173 cm	3564	3594	3624	3653	3681	3710	3738	3766	3794	3821
174 cm	3579	3609	3638	3668	3697	3725	3754	3782	3809	3837
175 cm	3594	3624	3653	3683	3712	3741	3769	3797	3825	3853
176 cm	3608	3639	3668	3698	3727	3756	3784	3813	3841	3868
177 cm	3623	3653	3683	3713	3742	3771	3800	3828	3856	3884
178 cm	3638	3668	3698	3728	3757	3786	3815	3844	3872	3900
179 cm	3652	3683	3713	3743	3772	3802	3831	3859	3887	3916
180 cm	3667	3698	3728	3758	3788	3817	3846	3875	3903	3931
181 cm	3682	3712	3743	3773	3803	3832	3861	3890	3919	3947
182 cm	3696	3727	3758	3788	3818	3847	3877	3905	3934	3962
183 cm	3711	3742	3772	3803	3833	3862	3892	3921	3950	3978
184 cm	3725	3756	3787	3818	3848	3878	3907	3936	3965	3994
185 cm	3740	3771	3802	3832	3863	3893	3922	3952	3981	4009

kg	60	61	62	63	64	65	66	67	68	69
145 cm	3391	3414	3438	3461	3484	3507	3529	3552	3574	3596
146 cm	3408	3431	3455	3478	3501	3524	3547	3569	3591	3613
147 cm	3424	3448	3472	3495	3518	3541	3564	3587	3609	3631
148 cm	3441	3465	3489	3512	3535	3558	3581	3604	3627	3649
149 cm	3458	3482	3505	3529	3552	3576	3599	3622	3644	3667
150 cm	3474	3498	3522	3546	3570	3593	3616	3639	3662	3684
151 cm	3491	3515	3539	3563	3587	3610	3633	3656	3679	3702
152 cm	3507	3532	3556	3580	3604	3627	3650	3674	3697	3719
153 cm	3524	3548	3573	3597	3621	3644	3668	3691	3714	3737
154 cm	3540	3565	3589	3614	3638	3661	3685	3708	3731	3754
155 cm	3557	3581	3606	3630	3654	3678	3702	3725	3749	3772

kg	60	61	62	63	64	65	66	67	68	69
156 cm	3573	3598	3623	3647	3671	3695	3719	3743	3766	3789
157 cm	3590	3615	3639	3664	3688	3712	3736	3760	3783	3807
158 cm	3606	3631	3656	3681	3705	3729	3753	3777	3801	3824
159 cm	3622	3647	3672	3697	3722	3746	3770	3794	3818	3841
160 cm	3639	3664	3689	3714	3739	3763	3787	3811	3835	3859
161 cm	3655	3680	3705	3730	3755	3780	3804	3828	3852	3876
162 cm	3671	3697	3722	3747	3772	3797	3821	3845	3869	3893
163 cm	3687	3713	3738	3764	3789	3813	3838	3862	3886	3910
164 cm	3703	3729	3755	3780	3805	3830	3855	3879	3903	3928
165 cm	3720	3746	3771	3797	3822	3847	3872	3896	3921	3945
166 cm	3736	3762	3788	3813	3838	3864	3888	3913	3938	3962
167 cm	3752	3778	3804	3830	3855	3880	3905	3930	3955	3979
168 cm	3768	3794	3820	3846	3872	3897	3922	3947	3972	3996
169 cm	3784	3810	3837	3862	3888	3914	3939	3964	3988	4013
170 cm	3800	3827	3853	3879	3905	3930	3955	3981	4005	4030
171 cm	3816	3843	3869	3895	3921	3947	3972	3997	4022	4047
172 cm	3832	3859	3885	3911	3937	3963	3989	4014	4039	4064
173 cm	3848	3875	3901	3928	3954	3980	4005	4031	4056	4081
174 cm	3864	3891	3918	3944	3970	3996	4022	4047	4073	4098
175 cm	3880	3907	3934	3960	3987	4013	4039	4064	4090	4115
176 cm	3896	3923	3950	3977	4003	4029	4055	4081	4106	4132
177 cm	3912	3939	3966	3993	4019	4046	4072	4097	4123	4148
178 cm	3927	3955	3982	4009	4036	4062	4088	4114	4140	4165
179 cm	3943	3971	3998	4025	4052	4078	4105	4131	4156	4182
180 cm	3959	3987	4014	4041	4068	4095	4121	4147	4173	4199
181 cm	3975	4003	4030	4057	4084	4111	4137	4164	4190	4216
182 cm	3991	4018	4046	4073	4100	4127	4154	4180	4206	4232
183 cm	4006	4034	4062	4089	4117	4143	4170	4197	4223	4249
184 cm	4022	4050	4078	4105	4133	4160	4187	4213	4239	4266
185 cm	4038	4066	4094	4121	4149	4176	4203	4229	4256	4282

kg	70	71	72	73	74	75	76	77	78	79
145 cm	3618	3639	3661	3682	3703	3724	3745	3765	3786	3806
146 cm	3635	3657	3679	3700	3721	3742	3763	3784	3804	3825
147 cm	3653	3675	3697	3718	3739	3761	3782	3802	3823	3844
148 cm	3671	3693	3715	3736	3758	3779	3800	3821	3842	3862
149 cm	3689	3711	3733	3754	3776	3797	3818	3839	3860	3881
150 cm	3706	3729	3751	3772	3794	3816	3837	3858	3879	3900
151 cm	3724	3746	3769	3790	3812	3834	3855	3876	3897	3918
152 cm	3742	3764	3786	3808	3830	3852	3873	3895	3916	3937
153 cm	3759	3782	3804	3826	3848	3870	3892	3913	3934	3956
154 cm	3777	3800	3822	3844	3866	3888	3910	3931	3953	3974
155 cm	3795	3817	3840	3862	3884	3906	3928	3950	3971	3993
156 cm	3812	3835	3858	3880	3902	3924	3946	3968	3990	4011
157 cm	3830	3853	3875	3898	3920	3942	3964	3986	4008	4029
158 cm	3847	3870	3893	3916	3938	3960	3982	4004	4026	4048
159 cm	3865	3888	3911	3933	3956	3978	4001	4023	4044	4066
160 cm	3882	3905	3928	3951	3974	3996	4019	4041	4063	4085
161 cm	3899	3923	3946	3969	3992	4014	4037	4059	4081	4103
162 cm	3917	3940	3963	3986	4009	4032	4055	4077	4099	4121
163 cm	3934	3958	3981	4004	4027	4050	4072	4095	4117	4139
164 cm	3951	3975	3998	4022	4045	4068	4090	4113	4135	4158
165 cm	3969	3992	4016	4039	4062	4085	4108	4131	4153	4176
166 cm	3986	4010	4033	4057	4080	4103	4126	4149	4171	4194
167 cm	4003	4027	4051	4074	4098	4121	4144	4167	4189	4212
168 cm	4020	4044	4068	4092	4115	4139	4162	4185	4207	4230
169 cm	4037	4062	4086	4109	4133	4156	4179	4203	4225	4248
170 cm	4055	4079	4103	4127	4150	4174	4197	4220	4243	4266
171 cm	4072	4096	4120	4144	4168	4192	4215	4238	4261	4284
172 cm	4089	4113	4137	4162	4185	4209	4233	4256	4279	4302
173 cm	4106	4130	4155	4179	4203	4227	4250	4274	4297	4320
174 cm	4123	4147	4172	4196	4220	4244	4268	4291	4315	4338
175 cm	4140	4165	4189	4213	4238	4262	4285	4309	4333	4356
176 cm	4157	4182	4206	4231	4255	4279	4303	4327	4350	4374

kg	70	71	72	73	74	75	76	77	78	79
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

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

kg	80	81	82	83	84	85	86	87	88	89	90
166 cm	4216	4238	4260	4282	4304	4325	4346	4368	4389	4410	4430
167 cm	4234	4257	4279	4300	4322	4344	4365	4386	4408	4429	4450
168 cm	4253	4275	4297	4319	4341	4362	4384	4405	4427	4448	4469
169 cm	4271	4293	4315	4337	4359	4381	4403	4424	4445	4467	4488
170 cm	4289	4311	4334	4356	4378	4400	4421	4443	4464	4486	4507
171 cm	4307	4329	4352	4374	4396	4418	4440	4462	4483	4505	4526
172 cm	4325	4348	4370	4392	4415	4437	4459	4480	4502	4523	4545
173 cm	4343	4366	4388	4411	4433	4455	4477	4499	4521	4542	4564
174 cm	4361	4384	4407	4429	4451	4474	4496	4518	4540	4561	4583
175 cm	4379	4402	4425	4447	4470	4492	4514	4536	4558	4580	4602
176 cm	4397	4420	4443	4466	4488	4511	4533	4555	4577	4599	4620
177 cm	4415	4438	4461	4484	4506	4529	4551	4574	4596	4618	4639
178 cm	4433	4456	4479	4502	4525	4547	4570	4592	4614	4636	4658
179 cm	4451	4474	4497	4520	4543	4566	4588	4611	4633	4655	4677
180 cm	4468	4492	4515	4538	4561	4584	4607	4629	4651	4674	4696
181 cm	4486	4510	4533	4556	4579	4602	4625	4648	4670	4692	4714
182 cm	4504	4528	4551	4574	4598	4621	4643	4666	4689	4711	4733
183 cm	4522	4546	4569	4592	4616	4639	4662	4684	4707	4729	4752
184 cm	4540	4563	4587	4610	4634	4657	4680	4703	4725	4748	4770
185 cm	4557	4581	4605	4628	4652	4675	4698	4721	4744	4767	4789

Table 2. Blood volume of males in mL as calculated according to the ICSH formula

kg	50	51	52	53	54	55	56	57	58	59
160 cm	3774	3813	3852	3890	3927	3965	4001	4038	4074	4110
161 cm	3795	3834	3873	3911	3949	3986	4023	4060	4096	4132
162 cm	3816	3855	3894	3932	3970	4008	4045	4082	4118	4154
163 cm	3837	3876	3915	3954	3992	4030	4067	4104	4140	4177
164 cm	3858	3897	3936	3975	4013	4051	4089	4126	4162	4199
165 cm	3878	3918	3957	3996	4035	4073	4110	4148	4184	4221
166 cm	3899	3939	3978	4017	4056	4094	4132	4169	4206	4243
167 cm	3919	3960	3999	4038	4077	4116	4154	4191	4228	4265

kg	50	51	52	53	54	55	56	57	58	59
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

kg	60	61	62	63	64	65	66	67	68	69
160 cm	4145	4180	4215	4249	4283	4317	4350	4384	4417	4449
161 cm	4168	4203	4238	4272	4306	4340	4374	4407	4440	4473
162 cm	4190	4225	4260	4295	4329	4363	4397	4431	4464	4497
163 cm	4212	4248	4283	4318	4352	4387	4421	4454	4488	4521
164 cm	4235	4270	4306	4341	4375	4410	4444	4478	4511	4544
165 cm	4257	4293	4328	4364	4398	4433	4467	4501	4535	4568
166 cm	4279	4315	4351	4386	4421	4456	4490	4525	4558	4592
167 cm	4302	4338	4374	4409	4444	4479	4514	4548	4582	4615
168 cm	4324	4360	4396	4432	4467	4502	4537	4571	4605	4639
169 cm	4346	4383	4419	4454	4490	4525	4560	4594	4629	4663
170 cm	4368	4405	4441	4477	4513	4548	4583	4618	4652	4686
171 cm	4390	4427	4464	4500	4535	4571	4606	4641	4675	4710
172 cm	4413	4449	4486	4522	4558	4594	4629	4664	4699	4733
173 cm	4435	4472	4508	4545	4581	4617	4652	4687	4722	4756
174 cm	4457	4494	4531	4567	4603	4639	4675	4710	4745	4780
175 cm	4479	4516	4553	4590	4626	4662	4698	4733	4768	4803
176 cm	4501	4538	4575	4612	4649	4685	4721	4756	4792	4826
177 cm	4522	4560	4598	4635	4671	4708	4744	4779	4815	4850
178 cm	4544	4582	4620	4657	4694	4730	4766	4802	4838	4873
179 cm	4566	4604	4642	4679	4716	4753	4789	4825	4861	4896
180 cm	4588	4626	4664	4701	4739	4775	4812	4848	4884	4919
181 cm	4610	4648	4686	4724	4761	4798	4835	4871	4907	4942
182 cm	4632	4670	4708	4746	4783	4820	4857	4894	4930	4966
183 cm	4653	4692	4730	4768	4806	4843	4880	4916	4953	4989
184 cm	4675	4714	4752	4790	4828	4865	4902	4939	4975	5012
185 cm	4697	4736	4774	4812	4850	4888	4925	4962	4998	5035
186 cm	4718	4757	4796	4834	4872	4910	4947	4984	5021	5058
187 cm	4740	4779	4818	4856	4895	4932	4970	5007	5044	5080
188 cm	4761	4801	4840	4878	4917	4955	4992	5030	5067	5103
189 cm	4783	4822	4862	4900	4939	4977	5015	5052	5089	5126
190 cm	4804	4844	4883	4922	4961	4999	5037	5075	5112	5149
191 cm	4826	4866	4905	4944	4983	5021	5060	5097	5135	5172

kg	60	61	62	63	64	65	66	67	68	69
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

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

kg	70	71	72	73	74	75	76	77	78	79
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

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
163 cm	4 868	4 898	4 928	4 957	4 987	5 016	5 045	5 074	5 103	5 131
164 cm	4 893	4 923	4 953	4 983	5 013	5 042	5 071	5 100	5 129	5 158
165 cm	4 918	4 948	4 979	5 009	5 038	5 068	5 097	5 127	5 155	5 184
166 cm	4 943	4 974	5 004	5 034	5 064	5 094	5 123	5 153	5 182	5 211
167 cm	4 968	4 999	5 030	5 060	5 090	5 120	5 149	5 179	5 208	5 237
168 cm	4 994	5 024	5 055	5 085	5 116	5 145	5 175	5 205	5 234	5 263
169 cm	5 019	5 050	5 080	5 111	5 141	5 171	5 201	5 231	5 260	5 290

170 cm	5 044	5 075	5 106	5 136	5 167	5 197	5 227	5 257	5 286	5 316
171 cm	5 069	5 100	5 131	5 162	5 192	5 223	5 253	5 283	5 312	5 342
172 cm	5 094	5 125	5 156	5 187	5 218	5 248	5 278	5 309	5 338	5 368
173 cm	5 119	5 150	5 181	5 212	5 243	5 274	5 304	5 334	5 364	5 394
174 cm	5 144	5 175	5 206	5 238	5 269	5 299	5 330	5 360	5 390	5 420
175 cm	5 168	5 200	5 232	5 263	5 294	5 325	5 355	5 386	5 416	5 446
176 cm	5 193	5 225	5 257	5 288	5 319	5 350	5 381	5 412	5 442	5 472
177 cm	5 218	5 250	5 282	5 313	5 345	5 376	5 407	5 437	5 468	5 498
178 cm	5 243	5 275	5 307	5 338	5 370	5 401	5 432	5 463	5 494	5 524
179 cm	5 267	5 300	5 332	5 363	5 395	5 426	5 458	5 488	5 519	5 550
180 cm	5 292	5 324	5 357	5 388	5 420	5 452	5 483	5 514	5 545	5 576
181 cm	5 317	5 349	5 381	5 414	5 445	5 477	5 508	5 540	5 571	5 601
182 cm	5 341	5 374	5 406	5 438	5 470	5 502	5 534	5 565	5 596	5 627
183 cm	5 366	5 399	5 431	5 463	5 495	5 527	5 559	5 590	5 622	5 653
184 cm	5 390	5 423	5 456	5 488	5 521	5 553	5 584	5 616	5 647	5 678
185 cm	5 415	5 448	5 481	5 513	5 545	5 578	5 610	5 641	5 673	5 704
186 cm	5 439	5 472	5 505	5 538	5 570	5 603	5 635	5 667	5 698	5 730
187 cm	5 464	5 497	5 530	5 563	5 595	5 628	5 660	5 692	5 724	5 755
188 cm	5 488	5 521	5 555	5 588	5 620	5 653	5 685	5 717	5 749	5 781
189 cm	5 512	5 546	5 579	5 612	5 645	5 678	5 710	5 742	5 774	5 806
190 cm	5 537	5 570	5 604	5 637	5 670	5 703	5 735	5 767	5 800	5 831
191 cm	5 561	5 595	5 628	5 662	5 695	5 728	5 760	5 793	5 825	5 857
192 cm	5 585	5 619	5 653	5 686	5 719	5 752	5 785	5 818	5 850	5 882
193 cm	5 609	5 643	5 677	5 711	5 744	5 777	5 810	5 843	5 875	5 907
194 cm	5 633	5 668	5 702	5 735	5 769	5 802	5 835	5 868	5 900	5 933
195 cm	5 658	5 692	5 726	5 760	5 793	5 827	5 860	5 893	5 925	5 958
196 cm	5 682	5 716	5 750	5 784	5 818	5 851	5 885	5 918	5 951	5 983
197 cm	5 706	5 740	5 775	5 809	5 842	5 876	5 909	5 943	5 976	6 008
198 cm	5 730	5 764	5 799	5 833	5 867	5 901	5 934	5 968	6 001	6 033
199 cm	5 754	5 788	5 823	5 857	5 891	5 925	5 959	5 992	6 026	6 059
200 cm	5 778	5 813	5 847	5 882	5 916	5 950	5 984	6 017	6 051	6 084

kg	**90**	**91**	**92**	**93**	**94**	**95**	**96**	**97**	**98**	**99**
160 cm	5 080	5 107	5 135	5 163	5 190	5 217	5 244	5 271	5 297	5 324

kg	90	91	92	93	94	95	96	97	98	99
161 cm	5 106	5 134	5 162	5 190	5 217	5 244	5 271	5 298	5 325	5 352
162 cm	5 133	5 161	5 189	5 217	5 244	5 272	5 299	5 326	5 353	5 379
163 cm	5 160	5 188	5 216	5 244	5 271	5 299	5 326	5 353	5 380	5 407
164 cm	5 186	5 215	5 243	5 271	5 298	5 326	5 353	5 381	5 408	5 435
165 cm	5 213	5 241	5 270	5 298	5 325	5 353	5 381	5 408	5 435	5 462
166 cm	5 239	5 268	5 296	5 324	5 353	5 380	5 408	5 436	5 463	5 490
167 cm	5 266	5 295	5 323	5 351	5 379	5 407	5 435	5 463	5 490	5 518
168 cm	5 292	5 321	5 350	5 378	5 406	5 434	5 462	5 490	5 518	5 545
169 cm	5 319	5 348	5 376	5 405	5 433	5 461	5 489	5 517	5 545	5 573
170 cm	5 345	5 374	5 403	5 432	5 460	5 488	5 517	5 545	5 572	5 600
171 cm	5 371	5 400	5 429	5 458	5 487	5 515	5 544	5 572	5 600	5 627
172 cm	5 398	5 427	5 456	5 485	5 514	5 542	5 571	5 599	5 627	5 655
173 cm	5 424	5 453	5 482	5 511	5 540	5 569	5 597	5 626	5 654	5 682
174 cm	5 450	5 479	5 509	5 538	5 567	5 596	5 624	5 653	5 681	5 709
175 cm	5 476	5 506	5 535	5 564	5 594	5 622	5 651	5 680	5 708	5 736
176 cm	5 502	5 532	5 561	5 591	5 620	5 649	5 678	5 707	5 735	5 764
177 cm	5 528	5 558	5 588	5 617	5 647	5 676	5 705	5 734	5 762	5 791
178 cm	5 554	5 584	5 614	5 644	5 673	5 702	5 732	5 760	5 789	5 818
179 cm	5 580	5 610	5 640	5 670	5 700	5 729	5 758	5 787	5 816	5 845
180 cm	5 606	5 636	5 666	5 696	5 726	5 756	5 785	5 814	5 843	5 872
181 cm	5 632	5 662	5 693	5 723	5 752	5 782	5 811	5 841	5 870	5 899
182 cm	5 658	5 688	5 719	5 749	5 779	5 808	5 838	5 867	5 897	5 926
183 cm	5 684	5 714	5 745	5 775	5 805	5 835	5 865	5 894	5 923	5 953
184 cm	5 709	5 740	5 771	5 801	5 831	5 861	5 891	5 921	5 950	5 979
185 cm	5 735	5 766	5 797	5 827	5 857	5 888	5 917	5 947	5 977	6 006
186 cm	5 761	5 792	5 823	5 853	5 884	5 914	5 944	5 974	6 003	6 033
187 cm	5 786	5 818	5 848	5 879	5 910	5 940	5 970	6 000	6 030	6 060
188 cm	5 812	5 843	5 874	5 905	5 936	5 966	5 997	6 027	6 057	6 086
189 cm	5 838	5 869	5 900	5 931	5 962	5 992	6 023	6 053	6 083	6 113
190 cm	5 863	5 895	5 926	5 957	5 988	6 019	6 049	6 079	6 110	6 140
191 cm	5 889	5 920	5 952	5 983	6 014	6 045	6 075	6 106	6 136	6 166
192 cm	5 914	5 946	5 977	6 009	6 040	6 071	6 101	6 132	6 162	6 193

kg	90	91	92	93	94	95	96	97	98	99
193 cm	5 940	5 971	6 003	6 034	6 066	6 097	6 128	6 158	6 189	6 219
194 cm	5 965	5 997	6 029	6 060	6 092	6 123	6 154	6 185	6 215	6 246
195 cm	5 990	6 022	6 054	6 086	6 117	6 149	6 180	6 211	6 241	6 272
196 cm	6 016	6 048	6 080	6 112	6 143	6 175	6 206	6 237	6 268	6 298
197 cm	6 041	6 073	6 105	6 137	6 169	6 200	6 232	6 263	6 294	6 325
198 cm	6 066	6 099	6 131	6 163	6 195	6 226	6 258	6 289	6 320	6 351
199 cm	6 091	6 124	6 156	6 188	6 220	6 252	6 284	6 315	6 346	6 377
200 cm	6 117	6 149	6 182	6 214	6 246	6 278	6 310	6 341	6 372	6 403

kg	100	101	102	103	104	105	106	107	108	109
160 cm	5 350	5 376	5 402	5 428	5 454	5 479	5 505	5 530	5 555	5 580
161 cm	5 378	5 404	5 430	5 456	5 482	5 508	5 534	5 559	5 584	5 609
162 cm	5 406	5 432	5 459	5 485	5 511	5 536	5 562	5 588	5 613	5 638
163 cm	5 434	5 460	5 487	5 513	5 539	5 565	5 591	5 616	5 642	5 667
164 cm	5 462	5 488	5 515	5 541	5 567	5 593	5 619	5 645	5 671	5 696
165 cm	5 489	5 516	5 543	5 569	5 596	5 622	5 648	5 674	5 699	5 725
166 cm	5 517	5 544	5 571	5 597	5 624	5 650	5 676	5 702	5 728	5 754
167 cm	5 545	5 572	5 599	5 625	5 652	5 678	5 704	5 731	5 757	5 782
168 cm	5 572	5 600	5 626	5 653	5 680	5 706	5 733	5 759	5 785	5 811
169 cm	5 600	5 627	5 654	5 681	5 708	5 735	5 761	5 787	5 814	5 840
170 cm	5 628	5 655	5 682	5 709	5 736	5 763	5 789	5 816	5 842	5 868
171 cm	5 655	5 682	5 710	5 737	5 764	5 791	5 818	5 844	5 870	5 897
172 cm	5 682	5 710	5 737	5 765	5 792	5 819	5 846	5 872	5 899	5 925
173 cm	5 710	5 738	5 765	5 793	5 820	5 847	5 874	5 901	5 927	5 954
174 cm	5 737	5 765	5 793	5 820	5 848	5 875	5 902	5 929	5 955	5 982
175 cm	5 765	5 793	5 820	5 848	5 875	5 903	5 930	5 957	5 984	6 010
176 cm	5 792	5 820	5 848	5 876	5 903	5 930	5 958	5 985	6 012	6 039
177 cm	5 819	5 847	5 875	5 903	5 931	5 958	5 986	6 013	6 040	6 067
178 cm	5 846	5 875	5 903	5 931	5 958	5 986	6 014	6 041	6 068	6 095
179 cm	5 873	5 902	5 930	5 958	5 986	6 014	6 041	6 069	6 096	6 123
180 cm	5 901	5 929	5 957	5 986	6 014	6 041	6 069	6 097	6 124	6 151
181 cm	5 928	5 956	5 985	6 013	6 041	6 069	6 097	6 125	6 152	6 180

kg	100	101	102	103	104	105	106	107	108	109
182 cm	5 955	5 983	6 012	6 040	6 069	6 097	6 125	6 152	6 180	6 208
183 cm	5 982	6 010	6 039	6 068	6 096	6 124	6 152	6 180	6 208	6 236
184 cm	6 009	6 038	6 066	6 095	6 123	6 152	6 180	6 208	6 236	6 263
185 cm	6 035	6 065	6 093	6 122	6 151	6 179	6 207	6 236	6 264	6 291
186 cm	6 062	6 092	6 121	6 149	6 178	6 207	6 235	6 263	6 291	6 319
187 cm	6 089	6 118	6 148	6 177	6 205	6 234	6 263	6 291	6 319	6 347
188 cm	6 116	6 145	6 175	6 204	6 233	6 261	6 290	6 318	6 347	6 375
189 cm	6 143	6 172	6 202	6 231	6 260	6 289	6 317	6 346	6 374	6 403
190 cm	6 169	6 199	6 229	6 258	6 287	6 316	6 345	6 373	6 402	6 430
191 cm	6 196	6 226	6 255	6 285	6 314	6 343	6 372	6 401	6 430	6 458
192 cm	6 223	6 253	6 282	6 312	6 341	6 370	6 399	6 428	6 457	6 486
193 cm	6 249	6 279	6 309	6 339	6 368	6 398	6 427	6 456	6 485	6 513
194 cm	6 276	6 306	6 336	6 366	6 395	6 425	6 454	6 483	6 512	6 541
195 cm	6 302	6 333	6 363	6 392	6 422	6 452	6 481	6 510	6 539	6 568
196 cm	6 329	6 359	6 389	6 419	6 449	6 479	6 508	6 538	6 567	6 596
197 cm	6 355	6 386	6 416	6 446	6 476	6 506	6 535	6 565	6 594	6 623
198 cm	6 382	6 412	6 443	6 473	6 503	6 533	6 562	6 592	6 621	6 651
199 cm	6 408	6 439	6 469	6 500	6 530	6 560	6 589	6 619	6 649	6 678
200 cm	6 434	6 465	6 496	6 526	6 556	6 587	6 616	6 646	6 676	6 705

kg	110	111	112	113	114	115	116	117	118	119	120
160 cm	5 605	5 630	5 655	5 679	5 704	5 728	5 752	5 776	5 800	5 824	5 848
161 cm	5 634	5 659	5 684	5 709	5 733	5 758	5 782	5 806	5 830	5 854	5 878
162 cm	5 664	5 689	5 713	5 738	5 763	5 787	5 812	5 836	5 860	5 884	5 908
163 cm	5 693	5 718	5 743	5 767	5 792	5 817	5 841	5 866	5 890	5 914	5 938
164 cm	5 721	5 747	5 772	5 797	5 822	5 846	5 871	5 895	5 920	5 944	5 968
165 cm	5 750	5 776	5 801	5 826	5 851	5 876	5 901	5 925	5 950	5 974	5 998
166 cm	5 779	5 805	5 830	5 855	5 880	5 905	5 930	5 955	5 979	6 004	6 028
167 cm	5 808	5 834	5 859	5 884	5 910	5 935	5 960	5 984	6 009	6 034	6 058
168 cm	5 837	5 863	5 888	5 913	5 939	5 964	5 989	6 014	6 039	6 063	6 088
169 cm	5 866	5 891	5 917	5 943	5 968	5 993	6 018	6 043	6 068	6 093	6 118
170 cm	5 894	5 920	5 946	5 972	5 997	6 022	6 048	6 073	6 098	6 123	6 147

kg	110	111	112	113	114	115	116	117	118	119	120
171 cm	5 923	5 949	5 975	6 001	6 026	6 052	6 077	6 102	6 127	6 152	6 177
172 cm	5 951	5 978	6 004	6 029	6 055	6 081	6 106	6 132	6 157	6 182	6 207
173 cm	5 980	6 006	6 032	6 058	6 084	6 110	6 135	6 161	6 186	6 211	6 236
174 cm	6 009	6 035	6 061	6 087	6 113	6 139	6 165	6 190	6 215	6 241	6 266
175 cm	6 037	6 063	6 090	6 116	6 142	6 168	6 194	6 219	6 245	6 270	6 295
176 cm	6 065	6 092	6 118	6 145	6 171	6 197	6 223	6 248	6 274	6 300	6 325
177 cm	6 094	6 120	6 147	6 173	6 200	6 226	6 252	6 278	6 303	6 329	6 354
178 cm	6 122	6 149	6 175	6 202	6 228	6 255	6 281	6 307	6 332	6 358	6 384
179 cm	6 150	6 177	6 204	6 231	6 257	6 283	6 310	6 336	6 362	6 387	6 413
180 cm	6 179	6 206	6 232	6 259	6 286	6 312	6 338	6 365	6 391	6 417	6 442
181 cm	6 207	6 234	6 261	6 288	6 314	6 341	6 367	6 394	6 420	6 446	6 472
182 cm	6 235	6 262	6 289	6 316	6 343	6 370	6 396	6 422	6 449	6 475	6 501
183 cm	6 263	6 290	6 317	6 345	6 371	6 398	6 425	6 451	6 478	6 504	6 530
184 cm	6 291	6 318	6 346	6 373	6 400	6 427	6 454	6 480	6 507	6 533	6 559
185 cm	6 319	6 347	6 374	6 401	6 428	6 455	6 482	6 509	6 535	6 562	6 588
186 cm	6 347	6 375	6 402	6 430	6 457	6 484	6 511	6 538	6 564	6 591	6 617
187 cm	6 375	6 403	6 430	6 458	6 485	6 512	6 539	6 566	6 593	6 620	6 646
188 cm	6 403	6 431	6 458	6 486	6 513	6 541	6 568	6 595	6 622	6 649	6 675
189 cm	6 431	6 459	6 487	6 514	6 542	6 569	6 596	6 624	6 650	6 677	6 704
190 cm	6 459	6 487	6 515	6 542	6 570	6 597	6 625	6 652	6 679	6 706	6 733
191 cm	6 486	6 515	6 543	6 570	6 598	6 626	6 653	6 681	6 708	6 735	6 762
192 cm	6 514	6 542	6 570	6 598	6 626	6 654	6 682	6 709	6 736	6 763	6 791
193 cm	6 542	6 570	6 598	6 626	6 654	6 682	6 710	6 737	6 765	6 792	6 819
194 cm	6 569	6 598	6 626	6 654	6 683	6 710	6 738	6 766	6 793	6 821	6 848
195 cm	6 597	6 626	6 654	6 682	6 711	6 739	6 766	6 794	6 822	6 849	6 877
196 cm	6 625	6 653	6 682	6 710	6 739	6 767	6 795	6 823	6 850	6 878	6 905
197 cm	6 652	6 681	6 710	6 738	6 767	6 795	6 823	6 851	6 879	6 906	6 934
198 cm	6 680	6 709	6 737	6 766	6 794	6 823	6 851	6 879	6 907	6 935	6 962
199 cm	6 707	6 736	6 765	6 794	6 822	6 851	6 879	6 907	6 935	6 963	6 991
200 cm	6 735	6 764	6 793	6 821	6 850	6 879	6 907	6 935	6 963	6 991	7 019

Appendix 2b

Example nomograms for collection volume

An example nomogram for collection volume of plasmapheresis for fractionation is included to allow for individualisation of the collection volume by sex/gender and BMI. Estimation of total blood volume (TBV) is based on Pearson TC *et al.*[2]

The nomogram must contribute to donor safety while being easy for staff to interpret and handle. The nomogram below includes BMI and identifies too low a BMI (< 17), an adaptation to BMI > 30, and incremental volumes for BMI from 17 to 30. The maximum collection volume is 880 mL (including anticoagulant).

Example nomogram for collection volume in mL (including anticoagulant) for females

kg	50	55	60	65	70	75	80	85	90	95
150 cm	563	586	607	628	638	638	638	638	638	638
155 cm	576	599	622	643	663	671	671	671	671	671
160 cm	589	613	636	658	679	698	705	705	705	705
165 cm	602	627	650	672	694	714	734	740	740	740
170 cm	615	640	664	687	709	729	750	769	775	775
175 cm	BMI < 17	654	678	701	723	745	765	785	803	810
180 cm	BMI < 17	BMI < 17	692	716	738	760	781	800	810	839
185 cm	BMI < 17	BMI < 17	706	730	753	775	796	816	836	855
190 cm	BMI < 17	BMI < 17	BMI < 17	744	767	790	811	832	850	872
195 cm	BMI < 17	BMI < 17	BMI < 17	757	782	800	826	848	868	880
200 cm	BMI < 17	BMI < 17	BMI < 17	BMI < 17	796	800	841	863	880	880

2 Pearson TC, Guthrie DL, Simpson J *et al.* Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. *Br J Haematol*. 1995;89:748-56.

Example nomogram for collection volume in mL (including anticoagulant) for males

kg	50	55	60	65	70	75	80	85	90	95	100
150 cm	622	654	684	712	726	726	726	726	726	726	726
155 cm	641	673	704	733	761	772	772	772	772	772	772
160 cm	659	692	723	754	782	809	819	819	819	819	819
165 cm	677	711	743	774	802	831	858	858	858	858	858
170 cm	694	730	762	794	823	852	880	880	880	880	880
175 cm	BMI < 17	748	782	813	845	873	880	880	880	880	880
180 cm	BMI < 17	BMI < 17	800	833	864	880	880	880	880	880	880
185 cm	BMI < 17	BMI < 17	819	852	880	880	880	880	880	880	880
190 cm	BMI < 17	BMI < 17	BMI < 17	872	880	880	880	880	880	880	880
195 cm	BMI < 17	BMI < 17	BMI < 17	880	880	880	880	880	880	880	880
200 cm	BMI < 17	BMI < 17	BMI < 17	BMI < 17	880	880	880	880	880	880	880

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 marker 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 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 revalidation 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 whether the actual failure rate lies above the 'target failure rate'.

Frequency of control sampling

There are a number of challenges in developing statistically based quality control testing programmes for labile blood components. Due to the complexity of the transfusion system, blood facilities

should consult statistics experts when designing process control systems. Issues include the very large variation in volumes of blood components at different blood establishments, the need to minimise losses of blood components through testing at small centres, the 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 that may affect the final quality of the blood components, 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 % to detect the target failure rate, while giving a false-positive result in fewer than 5 % 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 predefined 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);

1 Beckman N, Nightingale MJ, Pamphilon D. Practical guidelines for applying statistical process control to blood component production. *Transfus Med* 2009;19: 329-39.

- 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:

- 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 of the parameter in question on the sample, 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, and the location statistic is 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 (although 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 reestablishment of 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 to 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 by 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 reestablishment 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 are a reliable and sensitive means of detecting that a change has taken place in the process, warranting investigation 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, etc. 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 revalidation might be expected to occur because of process modifications (e.g. equipment replacement, software upgrades). The size of the moving window can then 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

2 Glaz J, Naus J, Wallenstein S. Scan Statistics. New York, USA: Springer; 2001.

the target failure rate to be detected as indicating a non-conforming process. Table 1 shows the minimum failure rate that can be detected at ≥ 80 %power in any single window of control tests for test criteria with false-positive rates below 5 %.

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 %. The facility sets an action trigger at 5 % as a means to detect a defective lot of filters. The quality control standard is established to ensure, with at least 80 % confidence, that a true failure rate of 5 % would be detected, but at a false-positive rate below 5 % 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 % to detect a true rate of non-conformance of 5 % 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 %.

If the number of quality control tests is 1200 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 %. The power is 80.7 % to detect a non-conformance rate of 4.6 % (the power is 85.6 % to detect a 5 % 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 %

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
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 % 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]

Statistical quality control based upon a hypergeometric distribution is applicable for cycle sizes between $n = 30$ and $n = 4500$.[4] Successful control requires that pre-determined random sample sizes be

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 blood component standard, such as component content, where standardisation is desirable, but is not directly related to recipient safety.

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. $\leq n = 1$ non-conforming units 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:

$$\frac{28}{30}\times\frac{27}{29}\times\frac{26}{28}\cdots\frac{9}{11}\times\frac{8}{10}\times\frac{7}{9}=\frac{8\times 7}{30\times 29}=0.064$$

So the null hypothesis cannot be rejected at the 5 % significance level, which corresponds to 'with 95 % confidence'.

assessed with an outcome of zero, one or two failures, depending on the cycle size.

For cycle sizes above n = 4500, 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 two failures.

The table below provides random sample sizes across a range of cycle sizes. With a larger cycle size, one or two occurrences of non-conformance are allowed in conjunction with a larger pre-specified sample size.

For example, if the cycle size is 65 (95 %/95 %), there are three options that need to be pre-determined: a sample size of 34 without any failure, a sample size of 49 with one failure or a sample size of 59 with two 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 % quality control can still be done to make the final determination, whether or not greater than 95 % of the components meet the standard.

After the cycle size reaches 7000 for 95 %/95 % and 13 000 for 95 %/75 %, the results based on the hypergeometric distribution are the same as those based on a binomial distribution.

Under the null hypothesis stated above, the probability that the first 23 units are all good is 4.8 %:

$$\frac{28}{30}\times\frac{27}{29}\times\frac{26}{28}\cdots\frac{8}{10}\times\frac{7}{9}\times\frac{6}{8}=\frac{7\times 6}{30\times 29}=0.048$$

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.

Table 2. Sizes of random samples needed at various quality control cycle sizes to assess 95%, 90% 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

	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*
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

	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*
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

	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*
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

	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*
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

	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*
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
10 000	499	59	93	124	999	29	46	61	2499	11	17	23
11 000	549	59	93	124	1099	29	46	61	2749	11	17	23
12 000	599	59	93	124	1199	29	46	61	2999	11	17	23
13 000	649	59	93	124	1299	29	46	61	3249	11	18	23
14 000	699	59	93	124	1399	29	46	61	3499	11	18	23
15 000	749	59	93	124	1499	29	46	61	3749	11	18	23

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 (BTS), 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, benchmarking, 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 benchmarking 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 (buildings, equipment, training, furniture, vehicles, etc.) and recurrent costs (personnel, supplies, transportation, utilities, administration, insurance, etc.).

Managers of blood transfusion services 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 BTSs, 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 expenditure 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.

ABBREVIATIONS

AABB	Association for the Advancement of Blood and Biotherapies
AE	Adverse event
Ag	Antigen
AIDS	Acquired immune deficiency syndrome
AML	Acute myeloid leukaemia
AR	Adverse reaction
AS	Additive solution
AS-BCR	Additive solution-buffy coat removed
BCG	Bacillus Calmette–Guérin
BCR	Buffy coat removed
BE	Blood establishment
BMI	Body mass index
BPAT	Batch pre-acceptance testing
BSE	Bovine spongiform encephalopathy
B-SCEP	Blood supply contingency and emergency plan
BTHC	Butyryl trihexyl citrate
BTS	Blood transfusion services
CAPA	Corrective and preventive action
CD-P-TS	European Committee (Partial Agreement) on Blood Transfusion
CJD	Creutzfeldt–Jakob disease
CMV	Cytomegalovirus
CPP	Critical process parameter
CQA	Critical quality attribute
CS	Cell salvage
DAT	Direct antiglobulin test

DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DQ	Design qualification
EBMP	Emergency blood management plan
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
ET	Exchange Transfusion
ETS	European Treaty Series
EU	European Union
FAT	Factory acceptance testing
FFP	Fresh frozen plasma
G-CSF	Granulocyte colony-stimulating factor
GMP	Good manufacturing practice
GPG	Good practice guidelines
GTS	*Ad hoc* working group on the *Guide to the preparation, use and quality assurance of blood components*
HAV	Hepatitis A virus
Hb	Haemoglobin
HbA	Haemoglobin
HbS	Sickle haemoglobin
HBc	Hepatitis B core antigen
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

Hct	Haematocrit
HCV	Hepatitis C virus
HDFN	Haemolytic disease of the foetus and newborn
HES	Hydroxyethyl starch
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
HPA	Human platelet antigen
HTC	Hospital transfusion committee
HTLV	Human T-lymphotropic virus
IA	Immunoassay
ICSH	International Council for Standardization in Haematology
IgG	Immunoglobulin G
IHN	International Haemovigilance Network
IOQ	Installation/operation qualification
IQ	Installation qualification
ISBT	International Society of Blood Transfusion
ISO	International Organization for Standardization
IU	International unit
IUT	Intrauterine transfusion
KPI	Key performance indicators
LCL	Lower control limit
LD	Leucocyte-depleted
LoQ	Limit of quantification
MCV	Mean corpuscular volume

MDS	Myelodysplasia
NAT	Nucleic acid amplification technique
OQ	Operational qualification
PAD	Pre-deposit autologous donation
PAS	Platelet additive solution
PBM	Patient blood management
PBSC	Peripheral blood stem cell
PDI	Post-donation information
PIT	Pathogen inactivation technologies
PQ	Performance qualification
PR	Pathogen reduced
PRF	Platelet-rich fibrin
PRP	Platelet-rich plasma
QA	Quality assurance
QALY	Quality adjusted life year
QC	Quality control
RBC	Red blood cell
RhD	Rhesus D antigen
SAE	Serious adverse event
SAR	Serious adverse reaction
SAT	Site acceptance testing
SI	International System of Units
SOP	Standard operating procedure
SPC	Statistical process control
SU	Single Unit
TA	Transfusion-associated

TACO	Transfusion-associated circulatory overload
TA-GVHD	Transfusion-associated graft-versus-host disease
TBV	Total blood volume
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-transmissible infection
UCL	Upper control limit
URS	User requirements specification
vCJD	Variant Creutzfeldt–Jakob disease
VMP	Validation master plan
vWF	Von Willebrand factor
WB	Whole blood
WHO	World Health Organization
WNV	West Nile virus

DEFINITIONS OF TERMS

Additive solution	Solution specifically formulated to maintain beneficial properties of cellular components during storage.
Adverse event	Any incident or error associated with activities that may affect the quality or safety of blood or blood components in such a way that involves a risk of harm to a blood donor or to a blood recipient.
Adverse reaction	Any incident that could be reasonably associated with the quality or safety of blood or blood components, or its collection or application to a recipient, that caused harm to a blood donor or to a blood recipient.

Affected area	An area with ongoing transmission of an infection to humans. This means that there has been at least one autochthonous case as a result of local transmission in the area according to the agreed, standardised and disease-specific case definition. Under exceptional circumstances, a probable case can be used to determine transmission but only in specific and agreed situations when case confirmation cannot be performed within a reasonable time.
Allogeneic donation	Blood and blood components collected from an individual and intended for transfusion to another individual, for use in medical devices or as starting material/raw material for manufacturing into medicinal products.
Antiglobulin testing technique	The direct antiglobulin test (direct Coombs' test) and the indirect antiglobulin test. It detects antibody or complement bound to red cells *in vivo*.
Apheresis	Method of obtaining one or more blood components by machine processing of whole blood, in which the residual components of the blood are returned to the donor during or at the end of the process.
Audit programme	A systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.
Autologous collection	Blood and blood components collected from an individual and intended solely for subsequent autologous transfusion or other human application to that same individual.

Autologous donors	Individuals who give blood for their own use if the need for blood can be anticipated and a collection plan developed.
Autologous transfusion	Transfusion in which the donor and the recipient are the same person and in which pre-deposited blood and blood components are used.
Biometrics	A method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
Blood	Whole blood collected from a donor and processed either for transfusion or for further manufacture.
Blood bag system	A disposable medical device used for the preparation and transfusion of blood and blood components. The system consists of a single or multiple bags connected with integral blood bag collection tubing, needle, needle cover, clamp, etc.
Blood components	Therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration and freezing using conventional methodologies in blood establishments.
Blood component release	Procedure which enables a blood component to be released from a quarantine status by the use of systems and procedures to ensure that the finished product meets its release specifications.
Blood container	A blood bag, bottle or other medical device which contains blood or blood components.

Blood establishment	Any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage and distribution if intended for transfusion. This does not include hospital blood banks.
Blood product	Any therapeutic product derived from human blood or plasma.
Blood supply	The blood and blood components in blood establishments, hospital blood banks and clinical transfusion services that are available for use by the healthcare community.
Blood system	Blood regulatory systems, blood supply systems or 'services', blood transfusion systems including hospital blood banks and clinical transfusion services, related laboratories and allied industries, including providers of related substances, reagents and medical devices. A blood system comprises all stakeholders involved in ensuring the provision of safe blood and blood components, clinical transfusion and patient blood management.
Buffy coat	The layer between plasma and red cells after centrifugation of whole blood.
Calibration	Set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument/system or values represented by a material measure and the corresponding known values of a reference standard.
Case	A particular disease, health disorder or condition under investigation found in an individual or within a population or study group.

Cell-free plasma	Plasma obtained by cross-flow filtration, where blood flows along a membrane with a pore size allowing free passage of plasma proteins, but not of blood cells.
Cell separator	An instrument for apheresis.
Change control	A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that may affect the validated status of facilities, systems, equipment or processes. The objective is to determine the need for action that would ensure and document that the system is maintained in a validated state.
Complaint	An act of expressing customer dissatisfaction with the quality of products or services provided by the responsible organisation.
Computerised system	A system comprising the input of data, electronic processing and the output of information to be used either for reporting, automatic control or documentation.
Consent	To give assent or approval, such as consent to be transfused.
Contingency planning	Contingency planning ensures that, when faced with disruptions, the capability to continue the delivery of blood, blood components and associated services is maintained.
Cryopreservation	Prolongation of the storage life of blood components by freezing.
Distribution	Act of delivery of blood and blood components to other blood establishments, hospital blood banks, and manufacturers of blood- and plasma-derived products. It does not include issuing blood or blood components for transfusion.

Donor	A person in normal health with a good medical history who voluntarily gives blood or blood components for therapeutic use.
Donor deferral	Suspension of the eligibility of an individual to donate blood or blood components; such suspension is either permanent or temporary.
Emergency	A serious, unexpected and potentially dangerous situation requiring immediate action.
Emergency preparedness	The development, implementation and maintenance of plans through which the impact of an unexpected event is managed, which enables the required blood, blood components and associated services to be provided to the healthcare community throughout the ongoing emergency/disruption. A cornerstone of emergency preparedness is training and exercising of such plans
Endemic area	A risk area where an infectious disease lingers at around the same incidence for a long time.
Epidemiological surveillance	The continuous gathering, analysis and interpretation of data about diseases, and dissemination of conclusions of the analyses to relevant organisations and audiences.
Extended red cell phenotype	The determination of the red blood cell antigen profile by serology or predicted antigen profile by molecular-based testing for red blood cell antigens other than ABO and RhD.
Facilities	Hospitals, clinics, manufacturers and biomedical research institutions to which blood or blood components may be delivered.
Febrile transfusion reactions	A febrile response associated with the administration of blood or blood components.

First-time donor	Someone who has never donated either blood or a blood component.
Frozen storage	A temperature at or less than – 25 °C.
Full blood count	Analysis of haematological parameters including Hb and RBC indices as well as counts of RBCs, white cells and platelets.
Glycerol	Propanetriol, used as a cell-cryoprotective agent for the storage of red cells in the frozen state.
Good practice	All elements in established practice that collectively lead to final blood or blood. components that consistently meet predefined specifications and compliance with defined regulations.
Haematocrit	Result obtained by the measurement of the volume of red cells in blood, after centrifugation, expressed as a percentage or as a ratio in the SI system.
Haematopoietic progenitor cells (HPC)	Primitive pluripotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages. They are found in bone marrow (bone marrow cells; BMC), in the mononuclear cells of circulating blood (peripheral blood stem cells; PBSC) and in umbilical cord blood (umbilical stem cells; USC).
Haemovigilance	Organised surveillance procedures related to serious adverse or unexpected events or reactions in donors or recipients, and the epidemiological follow-up of donors.
Hospital blood bank	Hospital unit which stores and distributes and may perform compatibility tests on blood and blood components exclusively for use within the hospital facilities, including hospital-based transfusion activities.

Imputability	The likelihood that an adverse reaction in a blood donor is associated with the collection process or, in a blood recipient with the application of the blood and blood components.
Incident	Any deviation from usual medical care that either causes an injury to the recipient or donor or poses a risk of harm, including errors, preventable adverse events and hazards.
Inspection	Formal and objective control according to adopted standards to assess compliance with a given directive and other relevant legislation and to identify problems.
Issue	The provision of blood or blood components by a blood establishment or a hospital blood bank for transfusion to a recipient (Directive 2005/61/EC).
Leucocyte depletion	The removal of leucocytes from blood.
Medicinal product	Any substance or combination of substances presented as having properties for treating or preventing disease in human beings (Directives 2001/83/EC, 2003/94/EC).
Mobile site	A temporary or movable place used for the collection of blood and blood components which is in a location outside of, but under the control of, the blood establishment.
Near-miss event	An error or deviation from standard procedures or policies that is recognised before transfusion. These can be considered a subgroup of adverse events.
Open system	A system in which a breach has occurred but every effort is made to prevent microbial contamination by operating in a clean environment using sterilised materials and aseptic handling techniques.

Pathogen inactivation technologies (PIT)	Procedures that irreversibly impede proliferation of pathogens, either by removal or inactivation with physical and/or chemical methods.
Pathogen-reduced (PR)	A term applied to a blood component that has been prepared following the use of PIT.
Peripheral blood stem cells (PBSC)	Primitive pluripotent cells capable of self-renewal as well as differentiation and maturation into all haematopoietic lineages, and found in the mononuclear cells of circulating blood (see haematopoietic progenitor cells).
Physician	A medical doctor who has day to day responsibility for supporting donor eligibility and safe collection practices.
Plasma	The liquid portion of the blood in which the cells are suspended. Plasma may be separated from the cellular portion of whole blood for therapeutic use as fresh frozen plasma or further processed to cryoprecipitate and cryoprecipitate-depleted plasma for transfusion. It may be used for the manufacture of medicinal products derived from human blood and human plasma or used in the preparation of pooled platelets, or pooled leucocyte-depleted platelets. It may also be used for resuspension of red cell preparations for exchange transfusion or perinatal transfusion.
Platelet standard adult dose	A dose of platelets derived from 4-6 whole blood donations or obtained by apheresis, with a minimum platelet content of 200×10^9 platelets.
Preparation	Preparation of a blood component includes the steps of collection, processing, testing, release and storage.

Preservation	The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of blood or blood components.
Pre-transfusion sampling	Procedure for taking blood samples from the patient requiring a transfusion, for compatibility investigation.
Procedure	A procedure controls a distinct process or activity, including the associated inputs and outputs. A series of tasks usually performed by one person according to instructions.
Process	A set of related tasks and activities that accomplish a work goal.
Procurement	A process by which blood or blood components are made available (Directive 2004/23/EC).
Proficiency testing	The evaluation of participant performance against pre-established criteria by means of an external quality assessment scheme involving inter-laboratory comparisons with externally sourced samples or panels.
Qualification	Part of validation and the act of verifying that any personnel, premises, equipment or material works correctly and delivers the expected results.
Qualified healthcare professional	A healthcare professional who is qualified, trained and deemed competent to carry out their assigned duties.
Quality	Totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs. Consistent and reliable performance of services or products in conformity with specified standards.

Quality assurance	All the activities from blood collection to distribution made with the object of ensuring that blood and blood components are of the quality required for their intended use.
Quality control	Part of a quality system focused on fulfilling quality requirements.
Quality management	The co-ordinated activities to direct and control an organisation with regard to quality at all levels within the blood establishment.
Quality monitoring	The part of a quality assurance programme concerned with maintenance and improvement of quality, which deals with the identification and use of indicators to detect variations from standards or specifications.
Quality system	The organisational structure, responsibilities, procedures, processes and resources for implementing quality management.
Quarantine	The physical isolation of blood components or incoming materials/reagents over a variable period of time while awaiting acceptance, issuance or rejection of the blood components or incoming materials/reagents.
Recipient	Someone who has been transfused with blood or blood components.
Reconciliation	Comparison and assessment of any discrepancy between the amount of material entering and leaving a given operation or series of operations.
Record	Written or electronically captured evidence that an event has occurred or an outcome has been achieved. A document that contains objective evidence that shows how well activities are being performed or what kind of results are being achieved.

Red cell genotype	The predicted red cell antigens present on the red cell surface, determined using molecular-based testing.
Red cell phenotype	The red cell antigens expressed on the red cell surface, determined using serological testing.
Refrigerated storage	A temperature at or between + 2 and + 6 °C.
Regular donor	Someone who routinely donates their blood or plasma (i.e. within the last 2 years), in accordance with minimum time intervals, in the same donation centre.
Regulatory oversight body	A dedicated body responsible for regulatory functions (e.g. inspection, authorisation, vigilance, monitoring or reporting) under the applicable blood regulatory framework. This can include national competent authorities, regional authorities, inspectorates, haemovigilance or authorising bodies.
Repeat donor	Someone who has donated before, but not within the last 2 years in the same donation centre.
Replacement donor	Donor recruited by a patient to enable them to undergo elective surgery.
Reporting establishment	The blood establishment, the hospital blood bank or facilities where the transfusion takes place that reports serious adverse reactions and/or serious adverse events to the competent authority.
Resources	People, money, information, knowledge, skills, energy, facilities, machines, tools, equipment, technologies and techniques.
Responsible physician	A medical doctor who is responsible for setting blood establishment policies which support donor and blood component safety. Thereby has the responsibility for ensuring the safety of donors.

RhD immunoglobulin	Immunoglobulin specific for RhD antigen is given routinely to RhD-negative mothers bearing RhD-positive infants to protect them from red cell exposure during pregnancy and delivery, and so prevent alloimmunisation.
Risk area	An area where individuals are exposed to the risk (which can be small or large) of being infected with a locally acquired infection. This is a generalised use of the term 'risk area' to prevent the imprecision linked to this term due to its use to signify a specific level of risk in an area.
Risk assessment	Method to assess and characterise the critical parameters in the functionality of equipment, systems or processes.
Room temperature storage	A temperature at or between + 20 and + 24 °C.
Self inspection	An audit carried out by people from within the organisation to ensure compliance with GPG and regulatory requirements.
Serious adverse event	An adverse event that involves a risk of any of the following: inappropriate distribution of blood or blood components, a defect posing a potential risk to recipients or donors detected in a blood establishment (BE)/ hospital blood bank (HBB) that could have implications for other recipients or donors because of shared practices, services, supplies or critical equipment, loss of a quantity of blood or blood components that causes human applications to be postponed or cancelled, loss of highly matched or autologous blood or blood components, event resulting in loss of the traceability of blood or blood components.

Serious adverse reaction	An adverse reaction that results in any of the following: death, life threatening, disabling or incapacitating condition, including transmission of a pathogen or a toxic substance that might cause such a condition, hospitalisation or prolongation of hospitalisation, the need for a major clinical intervention to prevent or reduce the effects of any of the above, prolonged sub-optimal health of a donor following single or multiple donations.
Seriousness	The degree of severity of an adverse reaction, involving harm to a blood donor, a blood recipient or for public health in general, or the degree of severity of an adverse event involving a risk of such harm.
Specification	Description of the criteria that must be fulfilled in order to achieve the required quality standard.
Standard	The requirements that serve as the basis for comparison.
Standard operating procedures (SOPs)	Detailed written procedures that give direction for performing certain operations.
Statistical process control	Method of quality control of a product or a process that relies on a system of analysis of an adequate sample size, without the need to measure every product of the process.
Sterile connecting device	A device that connects two tubes without breaching the sterility of their interior.
Storage	Maintaining the product under appropriate controlled conditions until distribution.
Surveillance	Systematic and continuous collection, analysis and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken.

Traceability	The ability to trace each individual unit of blood or blood component derived thereof from the donor to its final destination, whether this is a recipient, a manufacturer of medicinal products or disposal, and vice versa.
Trace-back	The process of investigating a report of a suspected transfusion-associated adverse reaction in a recipient to identify a potentially implicated donor.
Unique donation (identity) number	A unique donation number should be used to identify each donor. The unique donation number is used to link the donor, the related donation and all of its associated components, samples and records, as well as to link each one to each of the others.
Unique unit (identity) number	A unique number should be used to identify each unit. Where a donor's blood donation is prepared into more than one unit of the same type, for example where a plateletpheresis donation is split into two therapeutic doses, or a red cell donation is manufactured into paediatric red cells, each unit is identified by a unique unit (identity) number. Where the blood components from more than one donor are pooled together, such as pooling four whole blood platelets to prepare a Pooled Platelet, a unique unit (identity) number on the final product provides traceability to all donors included in the pool.
Validation	Refers to establishment of documented and objective evidence that the predefined requirements for a specific procedure or process can be fulfilled consistently.

Validation plan	Description of validation activities, responsibilities and procedures. It describes specifically how a certain validation is to be done.
Washed	A process of removing plasma or storage medium from cellular components by centrifugation, decanting of the supernatant liquid from the cells and addition of an isotonic suspension fluid, which in turn is generally removed and replaced following further centrifugation of the suspension. The centrifugation, decanting and replacement process may be repeated several times.
Washed red cells	A component derived from whole blood by centrifugation and removal of plasma, with subsequent washing of the red cells in an isotonic solution.
Whole blood	Blood collected from a single donor and processed either for transfusion or further manufacturing.
Written procedures	Controlled documents that describe how specified operations are to be carried out.
Xenotransplantation	Any procedure that involves transplantation or infusion into a human recipient of live animal cells, tissues or organs, or human body fluids, cells, tissues or organs that have *ex vivo* contact with live animal cells, tissues or organs.

RECOMMENDATIONS, RESOLUTIONS AND PUBLICATIONS

Recommendations and resolutions of the Council of Europe in the field of blood transfusion

Resolution (78) 29	on harmonisation of legislations of member states relating to removal, grafting and transplantation of human substances
Recommendation No. R (79) 5	concerning international exchange and transportation of human substances
Recommendation No. R (80) 5	on blood products for the treatment of haemophiliacs
Recommendation No. R (81) 5	concerning antenatal administration of anti-D immunoglobulin
Recommendation No. R (81) 14	on preventing the transmission of infectious diseases in the international transfer of blood, its components and derivatives
Recommendation No. R (83) 8	on preventing the possible transmission of acquired immune deficiency syndrome (AIDS) from affected blood donors to patients receiving blood or blood products
Resolution 812 (1983)	of the Parliamentary Assembly on acquired immune deficiency syndrome (AIDS)
Recommendation No. R (84) 6	on the prevention of the transmission of malaria by blood transfusion
Recommendation No. R (85) 5	on a model curriculum for the training of specialists in blood transfusion
Recommendation No. R (85) 12	on the screening of blood donors for the presence of AIDS markers
Recommendation No. R (86) 6	on guidelines for the preparation, quality control and use of fresh frozen plasma (FFP)
Recommendation No. R (87) 25	concerning a common European public health policy to fight the acquired immunodeficiency syndrome (AIDS)
Recommendation No. R (88) 4	on the responsibilities of health authorities in the field of blood transfusion
Recommendation No. R (90) 3	concerning medical research on human beings
Recommendation No. R (90) 9	on plasma products and European self-sufficiency
Recommendation No. R (93) 4	concerning clinical trials involving the use of components and fractionated products derived from human blood or plasma

Recommendation No. R (95) 14	on the protection of health of donors and recipients in the area of blood transfusion
Recommendation No. R (95) 15	on the preparation, use and quality assurance of blood components
Recommendation No. R (96) 11	on documentation and record-keeping to guarantee the traceability of blood and blood products , especially in hospital
Recommendation No. R (98) 2	on provision of haematopoietic progenitor cells
Recommendation No. R (98) 10	on the use of human red blood cells for the preparation of oxygen-carrying substances
Recommendation Rec (2001) 4	on the prevention of the possible transmission of variant Creutzfeldt–Jakob disease (vCJD) by blood transfusion
Recommendation Rec (2002) 11	on the hospital's and clinician's role in the optimal use of blood and blood products
Recommendation Rec (2003) 11	on the introduction of pathogen inactivation procedures for blood components
Recommendation Rec (2004) 8	on autologous cord blood banks
Recommendation Rec (2004) 18	on teaching transfusion medicine to nurses
Resolution CM/Res (2008) 5	on donor responsibility and limitation of donation of blood and blood components
Resolution CM/Res (2013) 3	on sexual behaviours of blood donors that have an impact on transfusion safety
Resolution CM/Res (2015) 2	on principles concerning human immunoglobulin therapies for immunodeficiency and other diseases
Resolution CM/Res (2015) 3	on principles concerning haemophilia therapies
Resolution CM/Res (2017) 43	on principles concerning haemophilia therapies (replacing Resolution CM/Res (2015) 3)

N.B. The figure in parentheses indicates the year of adoption.

Council of Europe publications in the field of blood transfusion

1976	Production and use of cellular blood components for transfusion. Study Director: B. Bucher with M. Benbunan, H. Heisto, U. Reesink
1978	Indications for the use of albumin, plasma protein solutions and plasma substitutes. Study Director: J. O'Riordan with M. Aebischer, J. Darnborough and I. Thoren
1980	Preparation and use of coagulation factors VIII and IX for transfusion. Study Director: R. Masure with G. Myllyla, I. Temperley and K. Stampli
1981	Assessment of the risks of transmitting infectious diseases by international transfer of blood, its components and derivatives. Study Director: W. Weise with T. Nielsen, P. Skinhot, J. P. Saleun
1982	European Co-operation in the field of blood: miscellany reports on the occasion of the 20th anniversary of the Committee of Experts on Blood Transfusion and Immuno-haematology 1962–1982. P. Cazal, A. André, P. Lundsgaard-Hansen, W. Weise, R. Butler, C. P. Engelfriet, and A. Hässig
1983	Essential aspects of tissue typing. B. Bradley and S. Gore
1985	Study on the current position of training programmes for future specialists in blood transfusion in Council of Europe member states and in Finland. Study Director: E. Freiesleben with A. André, A. Franco, B. Baysal, J. Cash
1986	Quality control in blood transfusion services. Study Director: E. Freiesleben, R. Butler, C. Hogman, W. Wagstaff
1987	Renal transplantation: sense and sensitisation. B. Bradley and S. Gore, Martinus Nijhoff Publishers
1988	First European Symposium on quality in blood transfusion Résumé of lectures (publication of the Health Division of the Council of Europe)
1989	European Course on Blood transfusion (Athens, March 1988) Compendium of lecturers (publication of the Health Division of the Council of Europe)
1990	Blood transfusion: 2nd European Course (Madrid 1990) Compendium of lecturers (publication of the Health Division of the Council of Europe)

1992	Impact of the Aids epidemic on health care services and planning in Europe (publication of the Health Division of the Council of Europe)
	Plasma products and European self-sufficiency: collection, preparation and use. Study Director: J. Leikola with W. van Aken, C. Hogman, D. Lee, M. Muglia, H. Schmitt
1993	Blood transfusion in Europe: a 'white paper'. Safe and sufficient blood in Europe by Piet J. Hagen
	Survey of blood transfusion services of central and eastern European countries and their co-operation with western transfusion services. Report by H. T. Heiniger
	The collection and use of human blood and plasma in Europe. Prof. Dr W.G. van Aken
1995	Guide on the preparation, use and quality assurance in blood components (appendix to Recommendation No. R (95) 15)
1997	Collection and use of blood and plasma in Europe (member States of the Council of Europe not members of the European Union). Study 1995, report by Dr Rejman
	Activities of blood banks in relation to bone marrow transplantations. Study Director: I.M. Francklin; Group members S. Koskimies, R. Kroczek, M. Reti, L. de Waal, R. Arrieta, F. Carbonell-Uberos
1998	Blood transfusion: half a century of contribution by the Council of Europe. Report by Prof. Dr B. Genetet
2000	Collection and use of human blood and plasma in the non-European Union Council of Europe member states in 1997. Report by Dr Rejman
	Autologous blood donation and transfusion in Europe – 1997 data. Report by Prof. Politis
2001	Pathogen inactivation of labile blood products. Study Director: Prof. A. Morell
2002	Autologous blood donation and transfusion in Europe – 2000 data. Report by Prof. Politis
2004	Collection, testing and use of blood and blood products in Europe – 2001 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
2005	Collection, testing and use of blood and blood products in Europe – 2002 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
2007	Collection, testing and use of blood and blood products in Europe – 2003 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross

2008	Collection, testing and use of blood and blood products in Europe – 2004 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
2011	Trends and observations on the collection, testing and use of blood and blood components in Europe – 2001-2005 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
	Collection, testing and use of blood and blood products in Europe – 2006 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
	Collection, testing and use of blood and blood products in Europe – 2007 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
	Collection, testing and use of blood and blood products in Europe – 2008 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
2013	Trends and observations on the collection, testing and use of blood and blood components in Europe – 2001-2008 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
	Collection, testing and use of blood and blood products in Europe – 2009 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
	Collection, testing and use of blood and blood products in Europe – 2010 data. Report by Drs C.L. van der Poel, M.P. Janssen and M.E. Behr-Gross
2014	Collection, testing and use of blood and blood products in Europe – 2011 data. Report by Drs L.R. van Hoeven, M.P. Janssen and G. Rautmann
2015	Trends and observations on the collection, testing and use of blood and blood components in Europe – 2001–2011 data. Report by Drs L.R. van Hoeven, M.P. Janssen and G. Rautmann
	Collection, testing and use of blood and blood products in Europe – 2012 data. Report by Drs L.R. van Hoeven, M.P. Janssen and G. Rautmann
2016	Collection, testing and use of blood and blood products in Europe – 2013 data. Report by Drs L.R. van Hoeven, M.P. Janssen and G. Rautmann
2017	Collection, testing and use of blood and blood products in Europe – 2014 data. Report by Drs M.P. Janssen and G. Rautmann
2018	Collection, testing and use of blood and blood products in Europe – 2015 data. Report by Drs M.P. Janssen and G. Rautmann

2020	Collection, testing and use of blood and blood products in Europe – 2016 data. Report by Drs C. Scrofani, D. le Tallec and G. Rautmann
2022	Collection, testing and use of blood and blood products in Europe – 2017 - 2019 data. Report by Dr Linda Larsson, D. le Tallec and R. Forde
2023	Variant Creutzfeldt–Jakob disease: deferral criteria for blood donors in European countries. Report by R. Forde
2025	EDQM Blood Conference Innovation in blood establishment processes. Abstract book by M. Pflieger, A. Sepich, Dr RM Grubovic Rastvorceva, R. Forde and M. Emery

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