The use of blood components represents the only therapy available for many seriously ill patients who suffer from acute or chronic diseases.

To provide all those working in the field of transfusion medicine – from blood services to hospital departments to regulators – with a compendium of measures designed to ensure the safety, quality and efficacy of blood components, the Council of Europe has developed a guide as a technical annex to its Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components. The Guide contains recommendations on blood collection, blood components, technical procedures, transfusion practices and quality systems for blood establishments. It represents the basis for a large number of national regulations, as well as for the blood directives of the European Commission.

This is the 16th Edition of the Guide, compiled by leading European experts under the aegis of the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS). This Steering Committee was created in 2007 by the Council of Europe to pursue its activities in the field of blood transfusion following the transfer of these activities to the European Directorate for the Quality of Medicines & HealthCare (EDQM).

The EDQM is a Directorate of the Council of Europe, an international organisation founded in 1949 that covers almost the entire continent of Europe. The Council of Europe aims to develop common democratic and legal principles based on the European Convention on Human Rights and other reference texts on the protection of individuals.
Guide to the Preparation, Use and Quality Assurance of Blood Components

Recommendation No. R (95) 15

16th Edition
Guide to the preparation, use and quality assurance of blood components

Foreword

Founded in 1949, the Council of Europe is the oldest and largest of all European institutions and now numbers 47 member states. One of its founding principles is that of increasing co-operation between member states to improve the quality of life for all Europeans.

Within this context of intergovernmental co-operation in the field of health, the Council of Europe has consistently selected ethical problems for study. The most important such ethical issue relates to the non-commercialisation of human substances i.e. blood, organs and tissues.

With regard to blood transfusion, co-operation among member states started back in the 1950s. From the outset, the activities were inspired by the following guiding principles: promotion of voluntary, non-remunerated blood donation, mutual assistance, optimal use of blood and blood products and protection of the donor and the recipient.

The first result of this co-operation was the adoption of the European Agreement on the Exchange of Therapeutic Substances of Human Origin (European Treaty Series, No. 26) in 1958. It was followed by the European Agreement on the exchange of blood grouping reagents (European Treaty Series, No. 39) and of tissue-typing reagents (European Treaty Series, No. 84) in 1962 and 1976 respectively.

1 Albania, Andorra, Armenia, Austria, Azerbaijan, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, Monaco, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey, Ukraine, United Kingdom.
Around these three Agreements, the Council of Europe has established a blood transfusion programme, the aim of which is to ensure good quality of blood and blood products.

Since then, the Council of Europe has adopted a number of recommendations covering ethical, social, scientific and training aspects of blood transfusion. Whereas Agreements are binding on the States that ratify them, recommendations are policy statements to governments proposing a common course of action to be followed. Major recommendations include Recommendation No. R (88) 4 on the responsibilities of Health Authorities in the field of blood transfusion or this Recommendation, No. R (95) 15, which contains 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 guide on blood components in 1995. The immediate success and acceptability of this document was such that the Committee of Ministers adopted it as a technical appendix to what then became Recommendation No. R (95) 15.

Recommendation No. R (95) 15 also states that its technical appendix will be regularly up-dated to keep it in line with scientific progress and to this end, the Committee was charged with producing annual up-dates in the form of a guide. During the elaboration of the 4th Edition a public consultation procedure was introduced for the first time with great success. It is on the basis of this procedure that the publication of future editions was envisaged.

This is the 16th Edition of the Guide containing amendments which take into account comments made during the consultation procedure of the draft 15th and 16th Editions where National Health Authorities as well as interested parties were invited to comment on the proposed text.
The members of the Experts working group (GTS) who worked on this 16th Edition of the Guide are listed in the acknowledgements.

They operate under the aegis of the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS), a Steering Committee of the Council of Europe pursuing activities in the field of blood transfusion in the frame of the European Directorate for the Quality of Medicines and HealthCare (EDQM).2

As of the 15th Edition of the Guide, the content has been separated into two sections. The first, entitled Principles, encompasses background information that has to be considered in forming policy decisions as well as educational aspects. The second section, entitled Standards, contains the matters that are considered to be “minimum standards” aligning closely to the European Pharmacopoeia and European Commission Directives. It is intended to assist other jurisdictions to transpose these into legislation. The Standards Section states “what must be done”.

The Principles Section provides information on the “why and how”. It also refers to developments that are not yet incorporated into standards, thus providing advance information about technical changes in the field. It was anticipated that in the next editions of the Guide, apart from changes to its technical content, the Principles Section would be further expanded.

In view of the good acceptance of this new format for the 15th Edition, the 16th Edition has been prepared along the same lines.

Special thanks should be made to the chairman, Dr van der Poel and to the other members of GTS, Dr Flanagan, Dr Klüter, Dr Lozano, Dr MacLennan, Dr M’Clelland, Dr O’Riordan, Dr Sondag-Thull who were involved in the redrafting of the guide for the 15th and 16th Editions.

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2 EDQM is a Directorate of the Council of Europe, created in 1964 on the legal basis of the Convention on the Elaboration of a European Pharmacopoeia. 36 member states, the European Union and 23 observers co-operate in this frame.
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The experts having prepared this edition are gratefully acknowledged for their valuable contributions. The members and the chairman of the drafting group – Dr Flanagan, Dr Klüter, Dr Lozano, Dr O’Riordan, Dr MacLennan, Dr Sondag-Thull and Dr van der Poel (chair) – who have been in charge of the management of the restructuring process of the guide are especially acknowledged. Dr McClelland who has performed the editorial review. The participants to the public enquiry and the representatives from CD-P-TS who have submitted many constructive comments are also acknowledged.

The drafting and the publication of the 16th Edition of the guide was coordinated by Dr Marie-Emmanuelle Behr-Gross (Scientific Officer, EDQM) supported by Ms Ahlem Sanchez (secretarial assistant, EDQM) and Ms Ioulia Iankova (editorial assistant, EDQM).
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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 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 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.
APPENDIX

to Recommendation No. R (95) 15
on the preparation, use and quality
assurance of blood components
Introduction

The purpose of this recommendation is to provide transfusion services with a set of standards and principles relating to the preparation, use and quality assurance of blood components. These guidelines should form the basis for standard operating procedures (SOPs).

These guidelines and descriptions of the different blood components should also be of value to hospital blood banks and the clinical users of these therapeutic products. As these guidelines were originally and primarily designed to provide information on quality assurance, some emphasis is to be expected on this aspect including the selection of donors, the control of laboratory reagents and competency testing of staff carrying out the procedures necessary for the safe preparation, selection and transfusion of blood and its components.

This recommendation covers all of the components of blood which will be prepared at a routine blood transfusion establishment. It does not cover plasma products obtained by fractionation. In respect of plasma-derived products, technical matters are addressed by the European Pharmacopoeia whilst the European Union has a substantial body of legislation regarding pharmaceutical products including plasma-derived products.

On 27 January 2003, the European Union adopted Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. As regards technical requirements to be set under Article 29 of the said Directive, the European Commission and the Council of Europe work closely together to ensure that these requirements are compatible with the ones described in the Guide.
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 on the preparation, use and quality assurance of blood components through education and the provision of non-binding recommendations. These may differ in some respects from those contained in the European Commission Directives.

The Council of Europe wishes to express its gratitude to the European Commission which contributed a substantial amount of information to the revised Chapter on Haemovigilance by giving its approval to use information from the “Feasibility project on the establishment of a Haemovigilance Network in the European Community”.

This Guide provides information and additional guidance on best practices consistent with current scientific understanding and expert opinion. At any given time, implementation of these recommendations may vary among member states and individual blood establishments, and alternative procedures, practices and standards may be in place.

It is inevitable, even in the best facilities that some materials will fail some of the tests, and a strict protocol should be drawn up showing action to be taken in such an eventuality. It is essential that all staff in a blood transfusion service be trained to accept quality assurance as a welcome and necessary part of everyday work. It is useful to cultivate a positive attitude towards the detection and correction of errors though the emphasis is on the prevention of problems in the production of blood components. A scheme of rotation of junior staff between routine departments and the quality assurance department may help to foster such an attitude.

Due to the fact that the Council of Europe publishes a Guide on safety and quality assurance for organs, tissues and cells (now in its third edition) any reference to haematopoietic progenitor cells was deleted from this Guide (on the preparation, use and quality assurance of blood components).

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3 Carried out by the HAEMAN Consortium for the European Commission under Contract SOC 96 201709 05F01 (96PRVF1-036-0).
PRINCIPLES
Chapter 1

Principles of a quality system for blood establishments

Paragraph 1. Overview

Introduction

The specific requirements for a blood establishment quality system are identified in the Standards section of this Guide. This Principles section aims to provide advice and recommendations that might assist blood establishments to maintain and develop effective quality systems.

Quality is the responsibility of all persons involved in the processes of the blood establishments. Management is responsible for a systematic approach towards quality and the implementation and maintenance of a quality management system.

The quality assurance function should be involved in all quality-related matters and review and approve all appropriate quality related documents.

Paragraph 2. Personnel and organisation

An effective quality system requires a number of key personnel including:

- Responsible Person;
• Processing or Operations Manager;
• Quality Assurance Manager.

The Responsible Person should have appropriate qualifications.

The Quality Assurance Manager and Processing or Operations Manager should be different individuals, functioning independently.

The Quality Assurance Manager is responsible for ensuring that there are appropriate systems and protocols in place for the safe and secure release of all materials, equipment, reagents and blood and blood components.

Delegation of responsibilities should only be given to individuals who have been trained for the task. Delegation should be in written form and be reviewed on a regular basis.

**Paragraph 3. General requirements for premises, including mobile sites**

The workflow in an area should be arranged in a logical sequence to minimise the risk of errors.

A working area should not be used as a passageway.

The area for blood donors should be separated from all processing areas. The area for donor selection should allow confidential personal interviews with due regard for donor and personnel safety.

The premises used for the processing of blood components meant for transfusion in an open process should comply with Good Manufacturing Practice.

A less stringent environment may be acceptable if combined with additional safety measures, such as preparing the blood component within a specific time before transfusion or immediately after processing applying storage conditions that are unfavourable to bacterial growth, specific hygienic procedures, selected and specially trained personnel, etc.
Personnel performing open processing should wear appropriate clothing and should receive regular training in aseptic manipulations. Aseptic processing should be validated and performed in areas validated for that purpose.

Laboratory areas should be separated from the processing areas.

Ancillary areas should be separated from other areas.

Washing and toilet facilities and, if required, facilities for changing should be adequate.

**Paragraph 4. Documentation**

**General**

Procedures should be designed, developed, validated and personnel trained in a consistent manner.

The documentation should allow all steps and all data to be checked. All documentation should be traceable and reliable. It should include a distribution list.

**Computerised systems**

There should be procedures for each type of software and hardware, detailing the action to be taken when malfunctions or failures occur.

The purpose of user testing is to demonstrate that the system is correctly performing all its specified functions in its real world environment. Testing should be part of system installation. Testing also should be performed after any system modifications to ensure that the changes did not cause any unintended results. Testing should follow a written plan based on an expert assessment of the risks inherent in the system and their potential impact on the quality of blood components.

Maintenance activities apply to all elements of the system including hardware, software, peripheral devices, standard operating procedures and training. Maintenance activities include prevention, emergency management and quality assurance audits. At a minimum:
• The vendor’s recommendations should be followed for periodic use of utility and diagnostic software programs to test system integrity.
• All changes to documents should be acted upon promptly and should be reviewed, dated and signed by an authorised person.

Paragraph 5. Storage

There should be a system in place to maintain and control the storage of blood components during their shelf life, including any transportation that may be required. Temperature and hygienic conditions should be continuously monitored. Warning systems should be used where applicable. Autologous blood and blood components should be stored separately.

Paragraph 6. Self inspection, audits and improvement

Inter-institutional audits should be actively promoted.

External inspections and audits by approved and competent authorities are necessary.

Preventive and corrective actions should be documented and assessed for effectiveness after implementation.

The management of a Blood Establishment should demonstrate a commitment towards continuous quality improvement. Input for this process can come from various sources such as complaints, errors, inspections, audits and suggestions.

Paragraph 7. Validation and qualification

This Paragraph describes the general principles of validation and qualification which are applicable to systems, processes, storage and distribution of human blood and blood components.

Validation policy

A risk assessment approach should be used to determine the scope and extent of validation.
Planning for validation

All validation activities should be planned. The key elements of a validation programme should be clearly defined in a validation master plan. The plan should also include a summary document which is brief, concise and clear. The plan should contain data on at least the following:

i. validation policy;
ii. organisational structure of validation activities;
iii. summary of facilities, systems, equipment and processes to be validated;
iv. documentation format;
v. planning and scheduling;
vi. change control.

Documentation

A written plan and/or protocol should be established that specifies how validation and qualification will be conducted. The protocol should specify critical steps and acceptance criteria. The protocol should be reviewed and approved. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

Validation process

Validation should start when the decision is made to implement new processes, facilities, systems, equipment or tests. Change to an existing process should also initiate validation as part of the change control procedure.

The first steps involve the identification of the requirements for the procedure or process and documenting these specifications.
Performing risk assessments at various stages will help define requirements and alternatives, aid the supplier selection process, help determine the scope and extent of validation and determine any mitigation steps.

Equipment shall be selected to minimise any hazard to donors, personnel, or blood components. Only reagents and materials from approved suppliers that meet the documented requirements and specifications shall be used.

The strategy for validation will depend on the scope of the validation and the degree of risks involved in the implementation. It is mainly based on the different elements identified in the risk assessment and documents provided by the supplier.

Validation tasks that have to be performed when validating new facilities, systems or equipment can be classified to the following qualifications:

- Design qualification (DQ) is the first qualification element. It is the documented verification that the proposed design is suitable for the intended purpose.

- Installation qualification (IQ) is the documented verification that the facilities, systems and equipment, as installed and modified, comply with the approved design and the manufacturer’s recommendations.

- Operational qualification (OQ) is the documented verification that the facilities, systems and equipment, as installed and modified, perform as intended throughout the anticipated operation ranges.

- Performance qualification (PQ) is the documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification. It is desirable to establish the degree to which products in a controlled manufacturing environment are expected to meet their specifications by pre-defining the percent of expected product
conformance within statistically-defined confidence limits. These product specifications will then provide baseline level for quality control during actual production.

All results and documentation generated are reviewed upon completion of the validation process. The review should confirm that:

- documentation is complete;
- the qualifications prove, with a high degree of assurance, that the system will consistently meet its acceptance criteria; including percent conformance to pre-defined product specifications within pre-established confidence limits;
- any non-conformance was addressed through problem resolution;
- training requirements have been met;
- written procedures for operation, calibration, maintenance, etc. are in place;
- business continuity plans are in place;
- validation activities are approved by the person responsible for quality management.

**Change control**

Some changes may require notification to, or license amendment, from regulatory agencies.

**Validation state maintenance**

All processes, facilities, systems, equipment and laboratory tests should be constantly monitored and periodically evaluated to confirm that they remain valid. The following items are essential to maintaining the validated state:

- calibration and monitoring;
- preventive maintenance;
- training and competency;
- supplier re-qualification;
- periodic review;
• performance monitoring;
• system retirement.

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

**Paragraph 8. Control of equipment**

**Introduction**

Documented systems for equipment purchase should be available. These should identify the specific requirements for setting and review of contracts for supply of both equipment and materials. The contracting process should include:

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

Assessment of the performance of blood transfusion equipment should occur in the following situations:

• on commissioning of new equipment, which must include full validation data by the manufacturer, design, installation, operational and performance qualification;
• after any relocation, repairs or adjustments which may potentially alter the function of the equipment. Consideration should be given to the quality, safety and efficacy of any blood components processed before the repair or adjustment;
• if ever a doubt arises that a machine is not functioning properly.
The laboratory environment

The laboratory should be designed to provide a comfortable working environment for the laboratory staff and this must also comply with health and safety regulations. Benches as well as floor, ceiling and walls should be designed and constructed to be easy to clean. In addition, to the control of temperature and humidity, excess noise must be avoided by the removal to a separate site of all excessively noisy pieces of equipment. Volatile and toxic materials must be handled in appropriate exhaust cabinets to avoid atmospheric pollution. A temperature monitoring device should be installed and regularly checked by quality control personnel.

Implementation and validation of new equipment

Equipment should be selected to minimise any hazard to donors, personnel, or blood components. All collection, processing and testing equipment should be designed, qualified and maintained to suit its intended purpose. All equipment and technical devices should be used in accordance with validated procedures.

The extent of validation depends on the criticality and complexity of the equipment or system. For equipment such as automatic pipettes, centrifuges, balances and refrigerators it may be sufficient to perform installation qualification and calibration. More complex equipment that is critical for the process needs a more thorough qualification (e.g. measuring devices used in laboratory testing). For complex automated systems a holistic approach should be used i.e. an inclusive validation of the instrument(s) and the associated operation(s) and the software involved should be performed.

All qualification steps and results should be documented and approved before routine use of the equipment or system. Typical items included in an equipment qualification are listed in the following:

Installation qualification (IQ)

- installation of equipment checked to specifications, engineering drawings, etc.;
- power and grounding verification (wiring, utilities, UPS, etc.);
collection and collation of supplier operating and working instructions and maintenance requirements (including spare parts list);

- safety requirements;
- calibration requirements;
- hardware and software installation, backup and interface connections;
- environmental conditions (such as temperature, humidity).

**Operational qualification (OQ)**

- Operational parameters and checks;
- tests that have been developed from knowledge of the equipment and its use;
- tests to include a condition or a set of conditions encompassing upper and lower limits, sometimes referred to as “worst case conditions”;
- data integrity and security, backup and recovery, generation of reports (if relevant);
- calibration;
- operating procedures for use, calibration and maintenance;
- operator training.

**Performance qualification (PQ)**

- tests, using actual components, laboratory test methods, samples, materials, etc., that have been developed from knowledge of the process, systems and equipment and designed to represent the normal use of the system;
- tests for repeatability when different trained operators are involved;
- tests to include a condition or set of conditions encompassing upper and lower operating limits.

Based on the results of these activities monitoring, calibration and maintenance programs should be established to maintain the system in the validated state.
Maintenance of validation status

It is necessary to establish a mechanism for assuring the adequacy of the calibration and monitoring programmes and ensuring that qualified personnel are available for its 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.

Trending and analysis of calibration and monitoring results should be a continuous process. Calibration and monitoring intervals should be determined for each item of equipment to achieve and maintain a desired level of accuracy and quality. The calibration and monitoring procedure should be traceable to a recognised international standard. The calibration status of all equipment that requires calibration should be readily available.

To ensure proper performance of a system or equipment a monitoring plan should be developed and implemented. The plan should take into account the criticality of the system or equipment, outline monitoring, user notification and problem resolution mechanisms. If an unusual event is observed, personnel should follow standard response described in the monitoring plan. The standard response should involve notifying affected personnel and possibly initiating a resolution 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 backup plan may need to be implemented to keep the process or system operating.

In addition to testing that evaluates the correctness 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 were not adversely impacted.

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

The ability of a supplier to maintain its activities related to a system or equipment has to be re-qualified on a regular basis, notably to anticipate weaknesses in services or to manage changes in the system, equipment or supplier. The periodicity and the detail of the re-qualification process depend on the level of risk from using the system or equipment and should be planned for every supplier concerned.

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

**Control of equipment**

The Table below lists some of the equipment used routinely in blood transfusion practice and the minimum requirements for their control. Other items of equipment, for example automated blood grouping machines, automated blood processing systems, etc. require the design of specific quality control procedures.

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Method of control</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood bag refrigerator, cold room, Freezer containing transfusates</td>
<td>Continuous temperature recording plus independent audible and visual alarm for appropriate high and low temperature parameters</td>
<td>daily</td>
</tr>
<tr>
<td>Laboratory refrigerator, Laboratory freezer, incubators, water baths</td>
<td>(a) Thermometer</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>(b) Precision thermometer</td>
<td>every 6 months</td>
</tr>
<tr>
<td>Equipment</td>
<td>Method of control</td>
<td>Frequency of control</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Blood bag centrifuge</td>
<td>Precision RPM meter plus stopwatch to control speed, acceleration and retardation</td>
<td>at least once a year</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
<td>daily</td>
</tr>
<tr>
<td>Table centrifuge</td>
<td>RPM meter plus stopwatch to control speed, acceleration and retardation</td>
<td>occasionally</td>
</tr>
<tr>
<td>Antiglobulin test automatic washer</td>
<td>Anti-RhD sensitised cells</td>
<td>every run</td>
</tr>
<tr>
<td>Haemoglobin photometer</td>
<td>Calibration standard Hb quality control</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>Sample</td>
<td></td>
</tr>
<tr>
<td>Cell counters</td>
<td>Calibration: reference sample.</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>Drift: working standard</td>
<td></td>
</tr>
<tr>
<td>Automatic pipettes</td>
<td>Dye- or isotope-labelled protein</td>
<td>at least once a year</td>
</tr>
<tr>
<td>Balance</td>
<td>Analytical-control</td>
<td>every 6 months or after each</td>
</tr>
<tr>
<td></td>
<td>Weights 5 mg – 100 g</td>
<td>location change</td>
</tr>
<tr>
<td></td>
<td>Preparative control weights 100 mg – 100 g</td>
<td></td>
</tr>
<tr>
<td>pH meter</td>
<td>Control solutions pH 4-7,7-10</td>
<td>each time of use</td>
</tr>
<tr>
<td>Platelet agitator</td>
<td>Thermometer</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>Frequency of agitation</td>
<td>monthly</td>
</tr>
<tr>
<td>Laminar flow hood and sterile area filters</td>
<td>Air pressure meter</td>
<td>daily</td>
</tr>
<tr>
<td></td>
<td>Particle counter</td>
<td>tri-monthly</td>
</tr>
<tr>
<td></td>
<td>Bacteriological plates</td>
<td>monthly</td>
</tr>
<tr>
<td>Blood mixer (swing)</td>
<td>Control weighing and mixing</td>
<td>bi-monthly</td>
</tr>
<tr>
<td>Spring balance for bags</td>
<td>Control weighing</td>
<td>monthly</td>
</tr>
<tr>
<td>Sterile connecting device</td>
<td>Test and visual examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standardised tensile strength or pressure test</td>
<td>every 6 months</td>
</tr>
<tr>
<td>Blood transport container</td>
<td>In the absence of a validated transport system, minimum/maximum thermometer or a</td>
<td>every time of use (on receipt)</td>
</tr>
<tr>
<td></td>
<td>temperature recording device</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring of results

The results of tests obtained from equipment should be reviewed to ensure reproducibility. A check of reproducibility is based on two principal concepts:

a. the determination of accuracy of the equipment by the testing of a reference standard;
b. the determination of the drift occurring during the routine day by testing of working standards at intervals.

Since examination of reproducibility usually implies that the test concerned is quantitative in nature, it follows that numerical values can be obtained for each type of control applied. Graphic plotting of the results of tests for accuracy and drift should be carried out so that a gradual deterioration in performance can be quickly identified and corrected.

Where a numerical value cannot be ascribed to the result of quality control tests, reproducibility can best be assessed by the inclusion in the schedule of testing of appropriate strong and weak positive controls at regular intervals.

Proper education of the personnel using blood transfusion laboratory equipment is essential. The staff must know not only how the control tests are to be done, but why they must be done, and they should be fully instructed not only in the performance of quality control tests but in the rapid detection of departures from the norm. In almost every case, normal functioning of the machine is defined by the manufacturer and confirmed at assessment on installation. Meticulous charting of quality control results preferably combined with statistical process controls will be the best methods of quick recognition of deterioration in function.

Paragraph 9. Record keeping

International rules and national laws on data protection have to be taken into consideration.
With records of results of quality control procedures a distinction should be made between records of results which may require prompt or almost immediate correction, and records of results which can only be evaluated statistically or by summing up over a certain period.

Examples of the former are given throughout the Guide. Most typical examples are those where a quality control procedure is prescribed for each unit of a blood component or for each laboratory procedure.

Examples of the latter records (summary records) are given below. The director of the transfusion service or a specially designated person should evaluate statistical variations from the usual pattern or from given normal values. Evaluation may take place monthly or quarterly, and annually.

- Rejection or deferral of blood donors (numbers, reasons).
- Donor reactions (numbers, gender, age, reaction category).
- Unsatisfactory donations (numbers, category).
- Positive tests for infectious markers (numbers, specific, false).
- Discarded units of blood and blood components (numbers, categories, reasons).
- Outdating of units of blood and blood components (for each category, the outdating as a percentage of the number of usable units).
- Transfusion complications (numbers, category) including transfusion transmitted infection.
- External complaints (number, origin, category).
- Clerical errors (numbers, category).

There are a number of other records which are important in transfusion centres but which do not deal directly with quality control. Examples are: routine working documents, blood group documents for patients and donors, the proportion of cross-matched units to used (transfused) units of blood components, statistics of issue and return of blood units, etc. Many of these records are mainly used for administrative or organisational purposes.
Specific consideration must be given to the ability to determine rapidly:

- each patient’s history of transfusion including the reason for transfusion and the record of all components;
- the identity of the donors;
- each donor’s history of donation;
- the final disposition (including the identity of the recipient) of all components from every donation.

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

The manual entry of critical data such as laboratory tests results should require independent verification by a second authorised person.

Records of quality control procedures should be signed by the supervisor.

It is considered that the retention period should be at least fifteen years.

**Retention of samples**

Retention of donor samples for a period of time may provide useful information. The provision of such systems is contingent on the availability of adequate human and financial resources.

**Paragraph 10. Data processing systems**

**Introduction**

Electronic data processing systems are used extensively in blood establishments and hospital blood banks (referred to as the “user” in Paragraph 10). These systems are used as tools for operational control and decision-making. In addition they support information management and storage of information in order to ensure documentation and full traceability. Because these functions are
critical to product quality, these systems must be fully validated\textsuperscript{4,5,6}, to ensure that they meet predetermined specifications for their functions, that they correctly preserve data integrity, and that their use is properly integrated into the user’s operating procedures.

The developers of computer systems used in blood establishments and hospital blood banks should follow established principles of software engineering design to develop, document and validate all source codes. Therefore, quality certification (e.g. ISO) of suppliers/vendors/developers of information systems will be beneficial. Additional validation by the user, at a minimum, should include provision of a written description of the system elements and their functions, and on-line performance testing of the system under at least limiting and boundary conditions. A record should be kept of the validation testing.

**Planning of a system**

There are a variety of computer systems and software programs available and each has different functions. Prior to purchase, the user should:

a. establish a list of requirements that will meet the needs of the user including the duration of record keeping (in general 15 years in EU member states) and the duration of data keeping for traceability (30 years are required by EU Directive 2002/98/EC);

b. evaluate the different computer systems and choose the one that will meet the established requirements;

c. audit the developer/manufacturer to ensure they are able to provide a product that meets regulatory requirements;

d. establish responsibility between the user and the developer/supplier/manufacturer, to define roles and responsibilities with regard to

\textsuperscript{4} ISBT guidelines for validation of automated systems in blood establishments, Vox Sanguinis (2010),98;Suppl.1.

\textsuperscript{5} ISBT guidelines for information security in transfusion medicine, Vox Sanguinis (2009),91;Suppl.1,51-23.

\textsuperscript{6} ISBT guidelines for validation and maintaining the validation state of automated systems in blood banking, Vox Sanguinis (2003),85;Suppl.1,51-14.
testing, user instructions, maintenance, system improvements and access to source codes.

These steps ensure that the user has all the necessary information about the purchased system and has an established relationship with the developer. This course of action also minimises the need for “work-around” by the user, which can be a source of error.

**Defining the system**

A blood establishment’s or hospital blood bank’s computerised system includes: hardware, software, peripheral devices, and documentation (e.g. manuals and Standard Operating Procedures). To define the system, the user, in co-operation with the vendor or developer, should generate a written description of the system, the functions that it is designed to perform and all human interactions. The documentation should be current, effectively updated, accurate and as detailed as necessary to ensure proper operation of the system. The documentation should include:

a. a detailed specification (inventory) of the hardware, software and peripheral devices, including their environmental requirements and limitations;

b. diagrams or flow charts of the system’s operations describing all component interfaces, network diagram (if applicable) and all database structures, e.g. file sizes, input and output formats, etc.;

c. standard operating procedures (SOPs) describing how the system is used. The user should develop the SOPs based on the user instructions from the software developer and the user’s internal procedure. In particular, SOPs should address all manual and automated interactions with the system including:

i. routine backup, maintenance and diagnostic procedures, including assignment of responsibilities;

ii. “work arounds” for system limitations;

iii. procedures for handling errors, including assignment of responsibilities;
iv. procedures for handling disasters and contingency planning, including assignment of responsibilities;

v. procedures for supervisory change of incorrect data;

vi. procedures for validation of a change;

d. a training system including training manuals, documentation and procedures for training.

**Implementation and validation**

The provisions of Paragraph 8 on implementation and validation of new equipment should be taken into account.

Validation documents and results of tests performed and approved by the supplier/vendor/developer of the system should be presented to the user. The user then performs tests according to a predefined written test plan. The types of risk to consider include inadequate system design, errors that may occur in use (user error or system defects), and loss or compromise of data. Testing should involve the whole system, in the manner it is expected to perform in the blood centre. Testing may be performed by a third party, but shall then also include blood establishment personnel. The following types of basic testing should be conducted:

a. **Functional testing of components**

   The system components are presented with all types of expected interaction including normal value, boundary, invalid and special case inputs. The system shall produce the correct outputs, including error messages by control programs. It is useful to perform this testing in parallel with a reference or standard system.

   Each test case should include the input, expected output, acceptance criteria and whether the test passed or failed. For traceability purposes and to facilitate quality assurance review and follow-up, it is recommended that any supporting documentation, such as print-screens, be included to verify the specific test case.
b. Data migration

The process for data migration should be defined, documented and appropriately tested. This should ensure full maintenance of traceability including archiving of data where necessary.

c. Environmental testing

All qualification steps and results should be documented and approved before routine use of the system (Paragraph 8).

In the actual operating environment, functional tests are performed to demonstrate that:

a. the software systems work properly with the hardware;
b. all applications of the software perform properly with the operating system software;
c. proper information passes correctly through system interfaces, including appropriate data transfer to or from other laboratory and automated (e.g. apheresis machine) systems, if applicable;
d. accessories, such as barcode scanners, perform as expected with the blood centre's barcode symbols;
e. printed reports are formatted correctly and appropriately;
f. personnel are trained and use the system correctly;
g. the system performs properly at peak production times and with the maximum number of concurrent users;
h. backups restore data in a correct way;
i. if system includes wireless radio frequency (RF) technology, it should be evaluated for electromagnetic compatibility (EMC) and electromagnetic interference (EMI) in the setting in which it will be used.

Change control

In case of changes in the software, the validation status needs to be re-established. If a revalidation analysis is needed, it should be risk assessment based and conducted not only for validation of the
individual change, but furthermore to determine the extent and impact of that change on the entire computerised system.

**Maintenance of the system**

The database should be checked periodically and systematically to identify and remove unwanted data such as duplicate records, and to ensure that data entries are accurate and properly stored. Manual entry of critical data requires independent verification by a second authorised person.

Security of the database should be maintained by:

- an adequate change history of the system; including software and hardware (when necessary);
- periodically rearranging electronic passwords (without re-use) and by removing unnecessary or outdated access;
- creating records of all data changes, i.e. an audit trail, including a retained record of the previous data and the reason for the change;
- the appropriate use of programs to detect and remove computer viruses;
- the control of administrative security access to ensure that only authorised personnel can make changes to the software, to the system configuration, and to the data;
- regular testing to verify the proper integrity and accuracy of backed up data.

Data should be archived periodically using a long-term stable medium, and placed “off-site” at another location than the hardware, to ensure safety. Such archives should be challenged at least annually to verify data retrieval.

Procedures should be defined for:

- investigation and correction of discrepancies in the database;
- corrective actions to be taken when validation testing yields unexpected results;
• handling, reporting, documenting and if needed correcting real-time problems, errors and alarms;
• manual operations (contingency plan) in the event of any system outage (even partial).

Quality assurance

The quality assurance programme should exercise oversight of the electronic data processing systems that affect product quality. At a minimum, such oversight should include:

a. assuring the ongoing accuracy and completeness of all documentation on equipment, software maintenance, and operator training;
b. performing audits periodically to verify proper accomplishment of all performance tests, routine maintenance, change procedures, data integrity checks, error investigations, and operator competency evaluations.

Paragraph 11. Statistical process control

Introduction

Statistical Process Control (SPC) is a tool which enables an organisation to detect change in the process and procedures which it carries out, monitoring collected data over a period of time in a standardised fashion. SPC became mandatory in 2005 for blood establishments in the EU (Directive 2004/33/EC), and has been implemented in other industries. Consequently, methods and standards for application of SPC to quality assurance of blood components should be further developed. The technique can be applied to all activities in a blood centre, administrative and clerical as well as scientific and technical. It is important to prioritise the processes to which it will be applied due to the amount of work involved. The most valuable uses currently would be in monitoring the performance of testing of infectious markers and leucocyte depletion. SPC is one of the few methods by which it can be shown that an improvement to a process has achieved the desired result, and enables decision-making to be placed on a much more rational and scientific basis.
Feedback to the staff on their performance is essential for continuing quality.

**Implementation of SPC**

Alongside all other aspects of quality, implementation of SPC demands understanding and commitment on the part of the management of the centre. It must be included in the Quality Policy of the centre, and a training programme introduced for senior management as well as operational staff. Plans must be made for data collection, including of charts, and all matters dealing with changes detected in the process, especially sudden “out-of-control” situations. Regular review of processes against charted data should take place, with the specific objective of improvement on a continuous basis.

**Strategy for statistical sampling**

As far as possible, the number and frequency of components sampled for quality control and the number of test failures per sample that will trigger an appropriate response (e.g. investigation, or revalidation of materials and procedures) should be based on the following considerations:

a. **Tolerance of failure**

   A “target failure rate” should be established as the failure rate that should not be exceeded. This will assure that monitoring of aspects of quality is continuous and that a failure rate exceeding target values will trigger appropriate corrective action.

b. **Confidence level**

   A confidence level should be set for detection of an actual failure rate which lies above the “target failure rate”.

   Determining that the actual failure lies above the “target failure rate” should be estimated using a valid method of statistical analysis.

**Frequency of control sampling**

A number of challenges arise in framing statistically based quality control testing programs for labile blood components. Due to the complexity of the issues, blood centers should consult statistical
experts when designing process control systems. Issues include the very large variation in volume of production at different blood establishments, the need to minimize product losses through testing at small centers, the very low expected rate of non-conformance for some processes, and the number of discrete conditions that arise in manufacture of otherwise similar components. These may include:

- number of sites, operators, and work shifts;
- different collection and processing systems and equipment;
- use of multiple reagent lots;
- alternative preparation times and temperatures;
- donor-related variables may affect final product quality even in a fully-controlled process (e.g. for HbS donor blood with poor leucofiltration properties);
- products may be used for more than one clinical indication with different levels of control needed (e.g. Leucoreduced RBC for neonate vs. for general transfusion).

Additionally, in many cases, the medical basis for currently accepted quality standards has not been established rigorously, making it difficult to determine the level of deviation from the expected level of conformance that can be tolerated. Nevertheless, to implement statistical process control, the blood establishment needs to establish the "target rate" of failure that should not be exceeded for each control test. Additionally, it is desirable that the criterion for non-conformance should have at least a power of 80% to detect the target rate of failure, while giving a false positive result in fewer than 5% of determinations.

Consideration also must 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.) Sample numbers specified for statistically valid process control are minimum samples. In circumstances where there are multiple manufacturing conditions,
and in blood establishments with large volumes of production, 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:

a. the public health importance of the standard being controlled (i.e. the period of time during which a process deviation could be tolerated prior to detection and correction);

b. the overall production volume;

c. the sampling and quality control testing capacity of the facility; including whether the quality control testing is ablative (i.e. destructive of the manufactured product);

d. the target failure rate of a process that is in control;

e. a pre-defined strategy for managing non-process failures, e.g. a failed leucocyte depletion procedure where further evaluation determined that the donor was HbS positive.

Three methods of statistical process control are provided below as examples.7

**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);

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- calculation of statistical control limits for the location and variation statistics;
- constructions of the chart;
- plotting of prospective data.

Two types of data are conventionally collected:
- variable data, appropriate to anything which is measured directly such as cell count, pH, time taken for a process, etc.;
- attribute data, appropriate to anything which 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**

The major applications in a blood centre are likely to be Individual/Moving Range charts, and Average/Range charts.

1. **Individual/Moving Range charts** are used where a process is monitored by a single measurement on the sample, of the parameter in question e.g. residual leucocyte count on a platelet preparation. The steps for constructing an SPC chart are as follows:

   - Historical data are collected by measuring a random sample each day, and the moving range established by taking the difference between each sample and its predecessor.
   - The location statistic is the average of the individual counts; the variation statistic is the average moving range.
   - The natural variation in a process has been defined as the process average plus or minus 3 standard deviations. Hence the Upper Control Limit (UCL) and Lower Control Limit (LCL) for the location statistic and variation statistics are determined as the appropriate average plus and minus 3 standard deviations.
   - The SPC chart conventionally has 2 distinct parts: 1 for the location statistic which appears above the other for the variation statistic. For each, the average is drawn as a solid line between 2 dotted lines signifying the UCL and LCL.
Prospective data are plotted on the charts in a similar way.

2. **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 the repeated use of a control sample during the daily use of a cytometer. In this situation, the average daily count on the control sample will be calculated, the location statistic being the average of the average. Each day will show 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 will, in general, fall into 1 of 2 groups – 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 latter case being classified as a defect. For example, a completed form will be classified as defective if it contains even 1 non-conformance, even though it may in fact contain multiple defects.

1. **Attribute charts for 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. 1 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 defectives 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 defective 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 before. 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, so that an
increase or decrease in the set of units sampled will necessitate resetting of the UCL and LCL. An increase in sampling size will generally result in convergence of UCL and LCL, making the system more sensitive to change in the process.

Construction of the chart is carried out as above.

2. **Attribute charts for defects** (sometimes known as u-charts) are generally useful when the object under investigation often has more than 1 non-conformance with requirements. They thus lend themselves well to the control of clerical procedures. Collection of historical data involves counting the number of defects in each unit of a set of samples, repeated at intervals.

The location statistic is the average number of defects per unit, calculated by dividing the total number of defects in the total number of historical samples. As before, there is no variation statistic for attribute data.

Once again, UCL and LCL is calculated on the basis of the location statistic plus and minus 3 standard deviations. Standard deviation in this system will again depend on sample size, and any prospective increase will require resetting of UCL and LCL.

The likely result will be 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, when plotting prospective data on the control chart follows the pattern established by the use of historical data in its construction, the process may be assumed to be “in control”. Changes in the pattern form a reliable and sensitive means of detecting that change has taken place in the process, warranting investigations into the cause. Rules have been established to give guidance to users as to when change has occurred, those usually employed being:
• 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. 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” were set at 60 observations, the first test set would include observations 1 through 60. The second test set would include observations 2 through 61; the third test set would include observations three through 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 center must identify a reasonably large “universe” of ultimate test samples, typically representing a year or more of testing, or a period after which routine re-validation might be expected.

to occur because of process modifications (e.g. equipment replacement, software upgrades, etc.) 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 chapter), the size of the test “universe,” and the “target rate” of failure to be detected as indicating a non-conforming process. The Table hereafter shows the minimum failure rate that can be detected at 80% or greater 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 centre seeks to monitor the failure rate of leucocyte reduction. The expected failure rate (rate of non-conforming tests for a conforming process) is taken to be 0.1%. The centre sets an action trigger at 5% as a means to detect a defective lot of filters. The quality control standard is set to assure, with at least 80% confidence, that a true failure rate of 5% would be detected, but at a false-positive rate below 5% for declaration of non-conformance.

For a blood centre with 400 QC tests per year (approximately 34 per month), a non-conforming process can be declared if in any “moving window” of 60 consecutive QC tests, 2 or more non-conforming test results are found (i.e. the “trigger” is greater than 1 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 QC tests is 1200 per year (100 per month), a non-conforming process can be declared if in any “moving window” of 120 sequential QC tests, 3 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% (power is 85.6% to detect a 5% failure rate) for any window of 120 tests, and near certainty over 1 year.
Sample size ("window") and maximum number of failed tests allowed for a conforming process based on scan statistics

<table>
<thead>
<tr>
<th>Allowed failure rate for a conforming process</th>
<th>Number of tests in &quot;universe&quot; (e.g. the number of tests per year)</th>
<th>Sample size (i.e. the fixed number of tests in a moving &quot;window&quot;)</th>
<th>Maximum allowed number of failed tests in window</th>
<th>False positive rate of test criterion</th>
<th>Minimum failure rate of a non-conforming process detectable at &gt; 80% power in any single &quot;window&quot;</th>
<th>Power to detect non-conforming process in any window of QC tests</th>
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Example 3

Statistical process control for dichotomous outcomes: an approach based upon hypergeometric/binomial distributions

The 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. The binomial distribution is very similar to the hypergeometric, but is based upon sampling with replacement. At sampling levels $n \geq 59$ to meet the 95% criterion, the 2 distributions are essentially identical.

For statistical quality control using the hypergeometric/binomial approach, a cycle is defined as the production 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.\(^9\)

Statistical quality control based upon a hypergeometric distribution is applicable for cycle sizes between $n = 30$ and $n = 4500^{10}$. Successful

\(^9\) For example, 95% conformance (and the resulting high level of quality control testing) would be appropriate for a safety-related product standard such as residual leucocytes in a leukoreduced component. However, 75% conformance may be acceptable for a standard such as components content, where standardization is desirable, but is not directly related to recipient safety.

\(^{10}\) For a cycle size of 30, greater than 95% conformance would be reflected by at most nonconforming unit because $29/30 = 96.7\%$ and $28/30 = 93.3\%$. To define this conformance statistically, we would need to be able to conclude with 95% confidence that greater than 95% of the units are conforming (i.e. $\leq n = 1$ nonconforming unit for a cycle size of $n = 30$). Using a null hypothesis that there are at least 2 nonconforming units among these 30 units, the alternative hypothesis would be that there are less than 2 nonconforming units among these 30 units. Under this null hypothesis, the probability that the first 22 units are all good is 6.4%, which is calculated as:

\[
\frac{28 \times 27 \times 26 \times 9 \times 8 \times 7}{30 \times 29 \times 28 \times 11 \times 10 \times 9} = 0.064
\]
control requires that pre-determined random sample sizes be assessed with an outcome of 0, 1, or 2 failures, depending on the cycle size. For cycle sizes above \( n = 4500 \), the hypergeometric distribution approaches the binomial distribution and the traditional binomial approach applies, i.e., assessing \( n = 60 \) random samples per cycle with an outcome of zero failures; \( n = 93 \) with 1 failure; or \( n = 124 \) with 2 failures.

- The Table hereafter provides sizes for random samples across a range of cycle sizes. With a larger cycle size, 1 or 2 occurrences of nonconformance 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 1 failure, or a sample size of 59 with 2 failures. If we (i) choose a sample size of 34 and observe 1 failure, or (ii) choose a sample size of 49 and observes 2 failures, we still could do 100% QC to make the final determination whether 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 the hypergeometric distribution is same as these based on the binomial distribution.

So the null hypothesis can not be rejected at 5% significance level which corresponds to "with 95% confidence".

Under null hypothesis above, the probability that the first 23 units are all good is 4.8%:

\[
\frac{28}{30} \cdot \frac{27}{29} \cdot \frac{26}{28} = 0.048
\]

So the null hypothesis can be rejected at 5% significance level which corresponds to "with 95% confidence". Thus 23 samples without nonconformance are needed to conclude with 95% confidence that greater than 95% of the units are conforming.
## Sizes of random samples needed at various quality control cycle sizes to assess 95%, 90% or 75% conformance to a standard with 95% confidence

<table>
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<th>Lot size</th>
<th>95% / 95% 95% confidence that &gt; 95% of the components meet the standard</th>
<th>Sample size</th>
<th>Failures allowed in lot</th>
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Chapter 2

Principles of donor selection

Paragraph 1. Overview

Principles of self-sufficiency from voluntary and non-remunerated donations have been recommended and promoted by the Council of Europe and have been defined in Article 2 of Council of Europe Recommendation No. R (95) 14 as follows:

The definition of voluntary and non-remunerated donation is:

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

They have also been adopted by the Council of the European Communities in Directive 2002/98 EC which in the preamble (23) states: “The definition of voluntary and unpaid donation of the Council of Europe should be taken into account”, and, in Article 20 paragraph 1: “Member states shall take the necessary measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible provided from such donations.”

Specific immunisation programmes are not considered in this document but donors enrolled for this purpose should at least fulfil the minimum
criteria outlined above (see also Annex 2, Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives, WHO Technical Report Series, No. 840, 1994).

Some criteria for the selection of donors vary according to the type of donation involved.

This chapter considers the principles on the selection of donors of whole blood and also donors of components obtained by different apheresis procedures. The selection of donors of haematopoietic progenitor cells is to be found in the “Guide to safety and quality assurance for organs, tissues and cells” (Council of Europe publications, ISBN 978-92-871-6037-9).

There are general principles which apply to all donors. There are also further requirements specific to donors of different components collected by different methods. The main purpose of selecting individuals for blood and component donation is to determine whether the person is in good health, in order to safeguard the health of both donor and recipient. All donors undergo a screening process to assess their suitability (see Standards).

The screening process involves:

- the provision of pre-donation educational material to be provided to all donors. This educational material should be understandable by the donors and explain the donation process, the transmission of blood borne infections and the donor’s responsibility in preventing such transmission, including the instruction to inform the blood establishment in case of post-donation information (see Standards);
- an assessment of each donor carried out by a suitably qualified individual, trained to use accepted guidelines and working under the direction of a physician. This assessment involves a questionnaire and an interview, followed by further direct questions if necessary.

Since blood establishments are ultimately responsible for the quality and safety of the blood and blood components collected, blood establishments are entitled to decide on the final acceptance or deferral of a donor or a prospective donor (Resolution CM/Res (2008) 5 on donor responsibility and on limitation to donation of blood and blood
components, adopted by the Committee of Ministers on 12 March 2008 at the 1021st meeting of the Ministers’ Deputies).

**Paragraph 2. Donor screening**

A complete medical and physical examination of the donors is generally not possible in practice. It is necessary to rely on the donor’s appearance, their answers to simple questions concerning their medical history, general health, relevant risk factors such as lifestyle and travel history and on simple laboratory tests.

An interview may be conducted with specifically trained staff who may ask further direct questions to supplement the information in the questionnaire. The interview should be conducted in privacy. The main issues to be covered either by the questionnaire or by direct questions are included in the example questionnaire given below.

In order to obtain relevant and consistent information about the donor’s medical history and general health, a pre-printed questionnaire is completed at each donation. Adaptation of the questionnaire to the type of donor (first time, regular, apheresis donor, etc.) is recommended.

Abnormal conditions not covered by guidelines for specifically qualified persons, must be referred to the physician in charge who has the responsibility of making the final decision.

**Age of the donor**

The Standards define age limits for donation and provide discretion for the responsible physician to accept donors outside of these limits. This medical discretion can be applied either on an individual basis for a given donor or else through a systematic approach based on an appropriate risk assessment.

**Hazardous occupations**

Hazardous occupations or hobbies should normally require that there is 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 operating, climbing of ladders or scaffolding, gliding, climbing and diving.
Guide to the preparation, use and quality assurance of blood components

Donor appearance, pulse and blood pressure

Special note should be taken of the appearance of the donor (see Standards).

If pulse and blood pressure is tested then the pulse should be regular and between 50 and 100 beats per minute. It is recognised that recording the blood pressure may be subject to several variables but as a guide the systolic blood pressure should not exceed 180 mm of mercury and the diastolic pressure 100 mm.

Donor deferral

Based on the information obtained by the application of the questionnaire and interview the following guidelines should be followed. See also Standards.

Persons clearly under the influence of alcohol should be deferred until sober. Illicit parenteral drug taking if admitted or suspected must lead to permanent deferral.

Abnormal conditions should be referred to the physician in charge who has the responsibility of making the final decision. If the physician has any doubt about the donor’s suitability they should be deferred.

Taking into account the requirement that only healthy people are acceptable as blood donors, deferral criteria are grouped into:

- conditions requiring permanent deferral;
- conditions requiring temporary deferral for defined time periods;
- conditions requiring individual assessment;
- infectious diseases.

Conditions leading to permanent deferral (rejection)

See Standards.

Conditions leading to temporary deferral (suspension)

See Standards.
Principles. Chapter 2

Prophylactic immunisations
See Standards.

Conditions requiring individual assessment
As donors may present with a variety of medical problems, past or present only some of the more common examples are considered here.

<table>
<thead>
<tr>
<th>Condition requiring individual assessment</th>
<th>Criteria for deferral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>Individuals with a documented history of anaphylaxis should not be accepted as donors.</td>
</tr>
<tr>
<td>Auto-immune diseases</td>
<td>If more than one organ is affected this leads to permanent deferral.</td>
</tr>
<tr>
<td>Beta thalassaemia trait</td>
<td>Heterozygote carriers of beta-thalassaemia trait may give blood provided they are in good health and have a haemoglobin level within acceptable values.</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>Persons with symptoms of severe chronic bronchitis should not be accepted as donors.</td>
</tr>
<tr>
<td>Common cold</td>
<td>Accept, if asymptomatic and feels well on the day of donation.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>A person who presents with a systolic blood pressure of more than 180 mm Hg or a diastolic blood pressure of more than 100 mm Hg should not be accepted as a blood donor. A mild hypertensive whose diastolic blood pressure is maintained at less than 100 mm Hg may be accepted.</td>
</tr>
<tr>
<td>Jaundice and hepatitis</td>
<td>Hospital staff coming into direct contact with patients with hepatitis are accepted at the discretion of the physician in charge of the blood-collecting unit providing they have not suffered an inoculation injury or mucous membrane exposure, in which case they must be deferred.</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>In some countries, donors who were born or have been transfused in areas where the disease is endemic are deferred or tested. The blood of persons who were born or have been transfused in areas where the disease is endemic should be used only for plasma fractionation products unless a validated test for infection with <em>T. cruzi</em> is negative.</td>
</tr>
</tbody>
</table>
Post donation information

Blood donors must be instructed to inform the blood establishment when signs or symptoms occur after a donation, indicating that the donation may have been infectious (see Standards). A donor may also inform the blood establishment that he or she previously donated blood, but should not have done so in the light of donor selection criteria aimed at the health protection of recipients, e.g. in retrospect did not fulfil criteria mentioned in the donor questionnaire.

Infectious diseases

For infectious diseases not specifically addressed elsewhere in this guide, generally a deferral period of at least 2 weeks after cessation of symptoms should be respected.

If there was contact with an infectious disease, the deferral period should equal the incubation period, or if unknown, the nature of the contact and the deferral period has to be determined by the responsible physician.

Some emerging infectious diseases may represent a threat to the safety of blood transfusion. A risk/benefit analysis should be carried out on a country by country basis. Precautionary measures, which should be proportionate to the risk, should be implemented in a timely fashion in line with the emerging evidence. Donor selection policies to address the risk may include deferral for a suitable period of donors exposed in geographic areas where the disease is occurring. The introduction of appropriate testing strategies may have to be considered.

It is recommended that national authorities develop detailed guidance based on prevailing epidemiology in the populations they serve.

Variant Creutzfeldt-Jakob disease

A new variant of Creutzfeldt-Jakob disease (vCJD) has been described. It is accepted that BSE and vCJD are caused by the same agent, and that vCJD is acquired by eating contaminated beef. Transmission of vCJD by transfusion of blood components has also been documented.
The epidemic of clinical vCJD cases in the UK is presently declining but a “second wave” cannot be excluded and endogenous vCJD cases have been found in other EU countries. Precautionary measures such as donor selection, leucocyte depletion and limiting donor exposure to recipients can be taken. Prion removal filters and prion tests are under development. Prion removal filters need to be thoroughly validated for efficacy and safety. In addition the therapeutic component would need to be unaffected and sufficient in yield. Prion tests need to be thoroughly validated for sensitivity and especially specificity, insufficiency of which could pose a serious threat to blood supply and donor base. It is essential that these tests are accompanied by confirmatory tests and are regulated within the scope of Annex II List A of the Directive 98/79/EC on in vitro diagnostic medical devices. The (cost-) effectiveness of blood safety measures with regard to vCJD differs greatly among EU countries according to prevalence and their implementation should be balanced in relation to sufficient supply of blood and blood components.

**History of malignancy**

Individuals with a malignant disease or a history of such are usually permanently deferred (see Standards). There is however a lack of evidence to support the theoretical concern that cancer is transmitted via blood.

Recent studies have significantly added to the available data on the risk of cancer following allogeneic blood transfusion in general and specifically on the risk of cancer following transfusion from donors with undiagnosed cancer. These large, observational studies provide convincing evidence that the risk of transmitting cancer via blood transfusion is either undetectable or insignificant.

Based on this the following framework is recommended.

Donors with a history of malignancy may be considered using the following criteria:

- Permanent deferral for history of haematological malignancies (e.g. leukaemia, lymphoma, and myeloma).
Permanent deferral for history of malignancies known to be associated with viraemic conditions (except for carcinoma in situ of the cervix, see below).

For other cancers the donor should have fully recovered with no expectation of recurrence (i.e. cured) and following conditions apply:

- for cancers with negligible metastatic potential (e.g. basal cell carcinoma and carcinoma in situ of the cervix) the donor may be accepted immediately following successful removal and cure;
- for all other cancers at least 5 years would have elapsed since completion of active treatment.

No deferral is required for pre-malignant conditions.

**Paragraph 3. Specific considerations for donors of different components**

**Quantity of whole blood donation**

A standard whole blood donation must not be collected from persons weighing less than 50 kg. A standard whole blood donation exclusive of anticoagulants must not exceed 500 mL and usually consists in a donation of 450 mL ± 10 percent (see Standards). In addition 30 to 35 mL of blood is taken for laboratory tests and retention of a donation sample.

Because of the risk of adverse reactions, no more than 15% of the estimated blood volume should be collected as whole blood during one blood donation. The blood volume of the donor can be calculated from the weight, height and gender using a validated formula. It is recommended to calculate the blood volume using the formula developed by the International Council for Standardisation in Haematology (ICSH). The formula is derived from a large study on red cell mass and plasma volume measurements in the European population.11

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

In case of women donating in total > 485 mL and weighing < 65 kg the blood volume should be calculated. The calculated blood volume should exceed the minimum acceptable blood volume for the volume of blood to be collected (Table 1). If the calculated blood volume is less than acceptable a smaller volume should be collected or the donor should be deferred.

When the donation volume may exceed 15 percent of the blood volume of the donor it is recommended that blood establishments use a blood volume table prepared according to the ICSH formula for checking the blood volume of the donor (see examples in Annex page 373).

**Table 1. Calculated minimum blood volume of a female donor donating 485 mL, 510 mL or 535 mL**

<table>
<thead>
<tr>
<th>Volume of blood to be collected</th>
<th>Maximum percentage of blood volume collected</th>
<th>Minimum acceptable blood volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>450 mL + 35 mL</td>
<td>15 %</td>
<td>3,233 mL</td>
</tr>
<tr>
<td>475 mL + 35 mL</td>
<td>15 %</td>
<td>3,400 mL</td>
</tr>
<tr>
<td>500 mL + 35 mL</td>
<td>15 %</td>
<td>3,567 mL</td>
</tr>
</tbody>
</table>

**Frequency of whole blood donation**

It is acknowledged that current practices in some transfusion services in Europe allow up to 6 standard whole blood donations per year from males and 4 per year from females, with a minimum interval between standard donations of 2 months. Routine haemoglobin measurement does not reflect iron stores. It is therefore recommended that an active
donor panel be maintained of sufficient size to allow donors to be bled less often than the maximum annual rates stated (see Standards), with the recommendation that 4 whole blood donations for males and 3 donations for females should ordinarily not be exceeded, thus affording the donors extra protection and giving the system flexibility to deal with large-scale emergency situations.

The maximum donation rates of 6 whole blood donations per year from males and 4 per year from females must never be exceeded and should only be adopted after careful consideration of the dietary habits of the populations 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.

**Laboratory examination before donation**

Abnormally high and low haemoglobin values should be further investigated, as should a fall in haemoglobin concentration of more than 20 g/L between 2 successive donations.

It is recognised that blood donation may result in iron deficiency in repeat blood donors. This problem may arise without being evident through pre-donation haemoglobin measurement. This may be especially important in women in the child-bearing years. Blood establishments should include appropriate measures to minimise this problem, and to protect donor health. Such measures may include the use of tests to assess iron status, the provision of materials for donor education particularly in regard to the importance of an iron rich diet, the tailoring of donation frequency based on iron status and if appropriate the supplementation of a dietary iron through appropriate prophylactic medication. At the same time, blood establishments should recognise that many donors currently deferred because of low haemoglobin are in a satisfactory state of health and, once their iron status is confirmed as satisfactory, they may be re-entered into donation programs. Therefore, managing the problem of iron-deficiency contributes to the maintenance of donor health and the sufficiency of the blood supply.
Apheresis donors

General remarks:

- Specific information on the nature of the procedures involved in the allogeneic or autologous donation process and their respective associated risks must be provided to the prospective donor (see Standards).
- Written informed consent should be obtained before the first apheresis procedure.
- To ensure that the maximum extracorporeal volume (ECV) is not exceeded (see Standards), for donors with a weight between 50 and 65 kg the total blood volume should be estimated using the approach described in Principles, Chapter 2, Paragraph 3.
- The Standards identify the maximum annual donation frequency and the minimum inter-donation intervals and the maximum volumes of components collected by apheresis. An incomplete apheresis procedure must be taken into account when determining the timing of the next donation. This should include consideration of non-reinfusion of red cells and the amount of primary component already collected.

Special attention should be given to the following conditions:

- abnormal bleeding episodes;
- a history suggestive of fluid retention (of special interest if steroids and/or plasma expanders are to be used);
- the intake of drugs containing acetylsalicylic acid or other platelet inhibitory components within five days prior to platelet apheresis;
- a history of gastric symptoms (if steroids are to be used);
- adverse reactions to previous donations.

Frequency of donation and maximal amounts of the removal of plasma

Current recommendations are made in the absence of conclusive studies of outcomes from different regimes of volumes and frequencies.
of plasmapheresis. Limited data is however available from small studies with several years follow-up which indicated that the approach mentioned in the Standards is acceptable.

The collection volume (excluding anticoagulant) for each plasmapheresis procedure must not exceed 16% of the estimated total blood volume. The total blood volume must be calculated on the basis of gender, height and weight. Alternatively a collection volume based on 10 mL per kg of body weight will equate broadly to 16% of estimated total blood volume (see Standards).

The Standards identify additional requirements for donors undergoing plasmapheresis. In addition special attention should be given to any significant fall in the results of testing even when they still fall within the accepted normal limits.

**Additional requirements for platelet apheresis**

The calculated minimum pre-donation platelet count must not be less than $150 \times 10^9/L$ (see Standards). In addition when undertaking high dose platelet collection ($> 5 \times 10^9$ platelets per unit) care should be taken to ensure that the post-donation count does not fall below $100 \times 10^9/L$.

**Additional requirements for granulocytapheresis**

Clinical efficacy, indications and dosage of granulocyte transfusion have not been established. Prior to the collection the potential donor of granulocytes needs to receive medication and sedimenting agents may be needed during the apheresis procedure. Both of these have potentially severe side effects which are described below. Thus, it is essential to gain the informed consent of the donor. In addition to the recognized complications of routine donor apheresis, the following side effects may occur:

- Hydroxyethyl starch (HES): acts as a volume expander, and donors who have received HES may experience headaches or peripheral edema because of expanded circulatory volume, HES may cumulate, which can result in pruritus, and allergic reactions are possible.
• Corticosteroids: may cause, for example hypertension, diabetes, cataracts, and peptic ulcer.

• 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 over Acute Myeloid Leukemia (AML)/Myelodysplasia (MDS) development following G-CSF administration are based primarily on reports of increased rates of AML/MDS among women with breast cancer who received chemotherapy or patients with Severe Chronic Neutropenia (SCN) who received G-CSF support.

To date registry data from Europe and the United States have not identified any increased risk of AML/MDS including data of over 100,000 healthy individuals who donated PBSCs and received G-CSF as pre-treatment, but the median follow-up of these studies is less than 5 years.

When G-CSF is given to the donor a follow up protocol should be in place for instance as advised by JACIE for G-CSF stimulated donors.\textsuperscript{12}

\textbf{Additional requirements for 1 unit red cell apheresis (alone or combined with plasma and/or platelets)}

• One unit is equivalent to the red cell amount of a red cell concentrate gained from a whole blood donation.

• Haemoglobin or haematocrit should be examined before donation and should conform to those specified for whole blood donation.

• The total collected volume of the red cell unit should be subtracted from the total volume of plasma that can be collected in combined procedures with platelet and/or plasma collections. The same restrictions apply for the plasma and platelet portion of the procedure as for those procedures without red cell collection.

\textsuperscript{12} JACIE/FACT International Standards for Cellular Therapy Product Collection, Processing and Administration (http://www.jacie.org).
Additional requirements for 2 unit red cell apheresis

- The donor should have an estimated blood volume of > 5 L (a requirement generally met by a non-obese person weighing > 70 kg).

- Haemoglobin should be examined before donation and the minimum value should be > 140 g/L. For the safety of the donor the haemoglobin level should not fall below 110 g/L after donation.

- For autologous 2 unit red cell apheresis lower haemoglobin levels and/or shorter donation intervals can be accepted at the discretion of the physician responsible for collection.

Additional requirements for donors of red cell for anti-RhD immunisation

This section does not consider specific immunisation programmes but red cell donors enrolled for this purpose should at least fulfil the following minimum criteria:

- infectious markers to be tested include HBs antigen and antibodies to HIV-1/2, HCV, HTLV-I/II, Anti-HBc, and NAT test for proviral HIV-DNA and HCV-RNA. HBV-DNA, Parvovirus B19-DNA or Parvovirus B19-Antibodies, and Hepatitis A-DNA should be considered;

- an 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 above stated infectious markers should be found negative on a new donor sample before release of the stored red cells for immunization;

- to address changes in donor selection criteria and infectious marker testing for regular whole blood donations that may occur over time, immunisation programs should:
  a. maintain retention samples from each RBC donation suitable for future testing;
b. requalify past donations by current screening and testing of the donor whenever feasible or, testing of retention samples when current donor screening and testing is unfeasible or insufficient to exclude a prior risk;

c. exempt prior collections of RBCs from current standards only after careful considerations of the risks to the immunised donors and ultimate plasma product recipients.

**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 donations are those intended for named patients based on medical indications. These donations may include family members, but clinical benefits for the patient are weighed against the risk by the physician. Circumstances where this may occur are:

1. for patients with rare blood types, where no compatible anonymous donations are available;

2. in case donor-specific transfusions are indicated for immune modulation or immunotherapy, for instance in the preparation procedure for kidney transplant or for lymphocyte transfusions aimed at a graft-versus-leukaemia effect;

3. in certain cases of alloimmune neonatal thrombocytopenia, for instance, when HPA typed platelets are not available and IVIG therapy is insufficient.

The practice of transfusing parental blood to infants is not without risk. Mothers may have antibodies to antigens which are present on the infant’s red blood cells, platelets or white blood cells, therefore maternal plasma should not be transfused. Fathers should not serve as cell donors to neonates, because maternal antibodies to antigens inherited from the father may have been transmitted through the placenta to the foetus. In addition due to partial histocompatibility,
transfusions of cells from parental or family donors carry an increased risk of GVHD, even in the immunocompetent.

**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 directed donations to be safer than anonymous voluntary non-remunerated donations, but this is not the case: even if directed donations are screened and tested in the same manner as voluntary non-remunerated donors, infectious disease marker rates are in general higher among directed donors.

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

**Paragraph 4. Example of a donor screening questionnaire**

The main issues to be covered either by the questionnaire or by direct questions are included in an example questionnaire:

**General questions**

- Are you in good health?
- For women: Have you had a pregnancy in the past year?
- Do you have a hazardous occupation or hobby?
- Have you previously been told not to give blood?
- Have you experienced any unexplained fever?
- Are you currently on any medication, including aspirin?
- Have you had any recent vaccinations or dental treatment?
- Have you ever had medication with isotretinoin (e.g. Accutane R), etretinate (e.g. Tegison R), acitretin (e.g. Neotigason R) finasteride (e.g. Proscar R, Propecia R), dutasteride (e.g. Avodart R)?
• Have you ever suffered from any serious illness such as:
  • jaundice, malaria, tuberculosis, rheumatic fever?
  • heart disease, high or low blood pressure?
  • severe allergy, asthma?
  • convulsions or diseases of the nervous system?
  • chronic diseases such as diabetes or malignancies?

Questions related to HIV or hepatitis transmission risk

• Have you read and understood the information on AIDS (HIV infection) and hepatitis?
• Have you ever injected any drugs?
• Have you ever accepted payment for sex in money or drugs?
• For men: have you ever had sex with another man?
• For women: to the best of your knowledge has any man with whom you have had sex in the past 12 months had sex with a man?
• During the past 12 months have you had sexual contact with someone who:
  • is HIV positive or has hepatitis?
  • has injected drugs?
  • receives or has received payment for sex in money or drugs?
• Have you had a sexually transmitted disease?
• Have you been exposed to hepatitis? (family or job)?
• Since your last donation or in the previous 12 months have you had:
  • an operation or medical investigations?
  • any body piercing and/or tattoo?
  • acupuncture treatment by anyone other than a registered practitioner?
  • a transfusion?
  • an accidental injury involving a needle and/or mucous membrane exposure to blood?
Questions related to CJD risk

- Have you been told of a family history of Creutzfeldt-Jakob Disease (CJD)?
- Have you had a corneal graft?
- Have you ever had a dura mater graft?
- Have you ever had treatment with human pituitary extracts?

Questions related to travel risk

- Were you born or have you lived and/or travelled abroad? Where?
Chapter 3

Principles of blood collection

Paragraph 1. Overview

Records should be kept for each activity associated with the donation. The record should reflect also any unsuccessful donation, the rejection of a donor, adverse reactions or unexpected events. An authorised interviewer should sign the donor selection records and final assessment.

The sterile collection systems should be used in accordance with the instructions of the manufacturer. A check should be made before use, to ensure that the collection system used is not damaged or contaminated, and that it is appropriate for the intended collection. Defects in blood bags should be reported to the supplier and subject to trend analysis.

The donor identification, donor selection interview and donor assessment should take place before each donation. The donor should be re-identified immediately prior to venepuncture.

Paragraph 2. Premises for donor sessions

When the venue of the donor session is permanent and under the control of the transfusion centre, provision should additionally be made for proper cleaning by, for example, the use of non slip, washable floor material installed without inaccessible corners, avoidance of internal window ledges, etc. Where possible, ventilation should be by an air conditioning unit to avoid the need for open windows. Air changes, together with temperature and humidity control, should be
adequate to cope with the maximum number of people likely to be in the room, and with the heat output from any equipment used.

When sessions are performed by mobile teams, a realistic attitude towards environmental standards may be taken. Points to check should include adequate heating, lighting and ventilation, general cleanliness, provision of a secure supply of water and electricity, adequate sanitation, compliance with fire regulations, satisfactory access for unloading and loading of equipment by the mobile team, adequate space to allow free access to the bleed, and rest beds.

**Paragraph 3. Equipment used at blood donation sessions**

It is recommended that the manufacturer’s identity and container information (catalogue number and the container number of the set) as well as the manufacturer’s lot number should be given in eye and machine readable codes.

**Paragraph 4. Pre-donation checks and labelling**

- Defects may be hidden behind the label pasted on the container. Abnormal moisture or discolouration on the surface of the bag or label after unpacking suggests leakage through a defect.
- The unique identity number may consist of a code for the responsible blood collection organisation, the year of donation and a serial number.

**Paragraph 5. Venepuncture**

**Preparation of the venepuncture site**

The venepuncture site should be prepared using a defined and validated disinfection procedure. The effectiveness of the disinfection procedure should be monitored and corrective action taken where indicated.

Although it is impossible to guarantee 100% sterility of the skin surface for phlebotomy, a strict, standardised procedure for the preparation of the phlebotomy area must exist (see Standards). Of
particular importance is that the antiseptic solution used be allowed to dry completely before venepuncture. The time taken will vary with the product used but should be subject to an absolute minimum of 30 seconds.

The prepared area must not be touched with fingers before the needle has been inserted (see Standards).

**Successful venepuncture and proper mixing**

Where an anticoagulant solution is used in the collection, the collection bag should be mixed gently immediately after start of collection and at regular intervals thereafter during the whole collection period. 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.

Proper mixing of the blood with the anti-coagulant is essential at all phases of the bleeding.

Attention should be paid to the following:

- as the blood begins to flow into the collection bag, it must immediately come into contact with the anticoagulant and be properly mixed;
- the flow of the blood must be sufficient and uninterrupted;
- donation of a whole blood unit should ideally not last more than 10 minutes. If duration of the bleeding is longer than 12 minutes, the blood should not be used for the preparation of platelets. If the duration of the bleeding is longer than 15 minutes, the plasma should not be used for direct transfusion or the preparation of coagulation factors;
- in the case of apheresis, any unintended interruption of the flow occurring during the procedure should be evaluated for possible exclusion of that blood component.
Handling of filled containers and samples

At completion of the donation, the donation number issued should be checked on all records, blood bags and laboratory samples. Donation number labels that have not been used should be destroyed via a controlled procedure. Routines to prevent misidentification should be in place.

If integral blood bag collection tubing is to be used to prepare segments for testing, it should be sealed off at the end and then filled with anticoagulated blood as soon as possible after blood collection.

After blood collection, the blood bags should be handled, transported and placed into storage according to defined procedures.

Immediately after sealing of the collection bag, the contents of the bag line should be completely discharged into the bag.

The organisation should be such as to minimise the possibility of errors in labelling of blood containers and blood samples. In this respect, it is recommended that each bed should have its individual facilities for the handling of samples during donation and labelling.

Laboratory test samples should be taken at the time of donation. Procedures should be designed to minimise the risk of bacterial contamination of the collected blood or deterioration of the sample, and to prevent potential misidentification.

The test samples should be taken directly from the bleed line or from a sample pouch (deviation bag) of the collection system.

If samples are taken at the end of donation, this must be done immediately.

The blood bag and corresponding samples must not be removed from the donor’s bedside until correct labelling has been checked.

After collection, blood bags should be promptly placed into controlled temperature storage and transported to the processing site under temperature conditions appropriate for the component that will
be prepared. There should be validation data to demonstrate that the storage and transport conditions used after collection ensure maintenance of the blood within the specified temperature range.

**Paragraph 6. Apheresis**

**Premedication and apheresis**

Routine premedication of donors for the purpose of increasing component yield is not recommended.

Caution is recommended regarding pre-treatment of donors with corticosteroids and G-CSF.

**Manual apheresis**

Manual apheresis is no longer recommended.

**Paragraph 7. Repository of archive samples**

The retention of donor samples for a period of time may provide useful information. The provision of such systems is contingent on the availability of adequate human and financial resources.

If archive samples from the donations are kept, then procedures must be in place prescribing the use and final disposal thereof (see Standards).

**Paragraph 8. Management of adverse reactions in donors**

Special attention should be given to all donors, in whom an adverse reaction in relation to blood donation is identified.

In the case of an adverse reaction the donor should be referred as soon as possible to the responsible health care worker/physician in charge.

The source of the adverse reaction should be identified and corrective and preventive measures considered.
All situations, including treatment and preventive actions taken, should be documented in donor’s and quality systems records.

Severe adverse reactions in donors should be reported to the system established on national level (see Chapter 11 Principles on hemovigilance and Chapter 11 Standards on hemovigilance).

Examples of adverse reactions related to blood collection

**Local reactions related to needle insertion**

<table>
<thead>
<tr>
<th>Vessel injuries</th>
<th>Hematomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial puncture</td>
</tr>
<tr>
<td></td>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td>Nerve injuries</td>
<td>Injury of nerve</td>
</tr>
<tr>
<td></td>
<td>Injury of nerve by haematoma</td>
</tr>
<tr>
<td>Other complications</td>
<td>Tendon injury</td>
</tr>
<tr>
<td></td>
<td>Allergic reaction (local)</td>
</tr>
<tr>
<td></td>
<td>Infection (local)</td>
</tr>
</tbody>
</table>

**General reactions**

Vasovagal reaction  
Immediate type  
Delayed type

**Rare, important complications**

Related to vessel injury  
Brachial artery pseudoaneurysm  
Arteriovenous fistula  
Compartment syndrome  
Axillary vein thrombosis

Accidents  
Accidents or injuries related to vasovagal syncope  
Other kinds of accidents
Cardiovascular reactions
- Angina pectoris
- Myocardial infarct
- Cerebral ischemia

Related to apheresis procedures
- Citrate toxicity
- Systemic allergic reaction
- Anaphylaxis
- Haemolysis
- Air embolism

Prevention of adverse reactions in donors
Prospective donors are informed of the possible adverse reactions of blood donation and their prevention.

Training of the personnel collecting blood should include preventing, and recognising the (early) signs of adverse reactions and treatment.

A physician in charge is responsible for medical supervision of blood collection and each session must be staffed with a qualified health professional.

Treatment of adverse reactions in donors
The treatment of adverse reactions related to blood donation is described in standard operation procedures.

The staff is properly and regularly trained to be attentive for early signs of an adverse reaction and is able to respond immediately with the appropriate action.

In each collection facility, a specific space is reserved for dealing with donors who have an adverse reaction.

The donor is observed until full recovery and in the event of a serious adverse reaction that the blood establishment stays in contact with the donor until the complication has disappeared or the donor is in stable conditions.
Documentation of adverse reactions in donors

The treatment and outcome of all adverse reactions related to blood donation, at any stage of the procedure, are fully documented.

The medical supervisor is informed about serious adverse reactions.

Data should be collected and analysed in order to initiate corrective actions, which could prevent or reduce the frequency or minimise the severity of adverse reactions in the future.

Serious adverse reactions are reported to the appropriate authority.

Information for the donor with adverse reactions

When an adverse reaction occurs, the donor is informed about the reaction, its treatment and expected outcome. The donor should be given the opportunity to contact the physician on call at any time.

The collection staff should instruct the donor in post collection care and keep the donor under observation until release.

In particular, a donor who has experienced vasovagal reactions should be informed about the risk of delayed fainting. The donor should not drive a vehicle or resume work or any hazardous occupation or hobby in the ensuing 12 hours if delayed fainting could put the donor or other persons at risk.

Paragraph 9. Donor clinic documentation

Full records should be maintained at blood donation sessions, to cover the following parameters:

- the blood component(s) collected, the date, donation number, identity, and medical history of the donor;
- the date, donation number, identity, and medical history of the donor for each unsuccessful donation, with reasons for the failure of the donation;
- list of rejected donors with the reasons for their rejection;
• full details of any adverse reactions in a donor at any stage of the procedure;
• in the case of apheresis: volume of collection, volume of blood processed, volume of replacement solution and volume of anticoagulant.

As far as possible the records of blood donation sessions should allow identification by blood transfusion staff of each important phase associated with the donation. These records should be used for the regular compilation of statistics which should be studied by the individual with ultimate responsibility for the blood donation session, who will take such action on them as deemed necessary.
Chapter 4

Principles of blood component preparation

Paragraph 1. Overview

Transfusion therapy in the past was largely dependent on the use of whole blood. While whole blood may still be used in certain limited circumstances, the thrust of modern transfusion therapy is to use the specific component that is clinically indicated. Components are those therapeutic constituents of blood that can be prepared by centrifugation, filtration and freezing using conventional blood bank methodology.

Transfusions are used mainly for the following purposes:

- to maintain oxygen/carbon dioxide transport;
- to correct or avoid bleeding and coagulation disorders.

It is evident that one single product, whole blood, is not necessarily suitable for all these purposes unless the patient requiring treatment has multiple deficiencies. Even then, the storage defects of whole blood make it unsuitable for such replacement. Patients should be given the component needed to correct their specific deficiency. This will avoid unnecessary and possibly harmful infusion of surplus constituents. The change from collection of blood in glass bottles to multiple plastic bag systems has greatly facilitated the preparation of high quality
components. Storage considerations are a major reason for promoting the use of components. Optimal conditions and consequently shelf life vary for different components. Red cells maintain functional capability best when refrigerated. The quality of plasma constituents is best maintained in the frozen state while platelet storage is at room temperature with continuous agitation. Thus it is only the red cells whose storage requirement is fulfilled when whole blood is stored refrigerated, with consequent loss of therapeutic effectiveness of most of the other constituents.

Component therapy also offers logistic, ethical and economic advantages. The majority of patients requiring transfusion do not need the plasma in the whole unit and certainly not at a 1 to 1 ratio. Production of plasma derived products can thus be facilitated by the use of red cells rather than whole blood. Leucocyte depletion may further improve the quality of blood components.

**Paragraph 2. Preparation procedures**

The procedures should detail the specifications for materials which 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 material, additive solutions, primary package material (bags) and equipment.

The premises used for the processing of blood components should be kept in a clean and hygienic condition and the bacterial contamination load on critical equipment, surfaces and the environment of the processing areas should be monitored.

Sterile connecting devices should be used in accordance with a validated procedure. The resulting weld should be checked for satisfactory alignment and the integrity validated. If validated and used properly, connection done using sterile connecting devices can be regarded as closed system processing.
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.

Blood components may be prepared during collection using apheresis technology. Plasma, leucocytes, platelets and red cell concentrates may be obtained thus. Alternatively, whole blood may be collected in the traditional manner with the components being made available by the post donation processing of whole blood.

Time limits should be defined for the processing of blood components.

Due to the potential deterioration of activity and function of labile blood components, conditions of storage and time prior to processing are vital to the preparation of components. Delays in preparation or unsuitable conditions of storage may adversely affect quality of the final components.

**Paragraph 3. Choice of anticoagulant and bag system**

Whole blood is collected into a bag containing an anticoagulant solution. The solution contains citrate and cell nutrients such as glucose and adenine. The first centrifugation steps will remove more than half of these nutrients from the residual red cells. Thus it may be more logical to provide the proper nutrients for the cells using a resuspension medium instead of incorporating them in the initial anticoagulant solution.

Plastic ware used for blood collection, apheresis and component preparation should comply with the requirements of the relevant supplement of the European Pharmacopoeia with regard to haemocompatibility in addition to its suitability for achieving the respective technological goal. Polyvinyl chloride (PVC) has been found satisfactory for red blood cell storage. The biocompatibility of any plasticisers used must be assured. Storage of platelets at +20 °C to +24 °C requires a plastic with increased oxygen permeability.
This has been achieved by plastic materials of alternative physical and/or chemical characteristics. Leaching of plasticisers into blood or a component should not pose any undue risk to the recipient. Any possible leaching of adhesives from labels or other device components should be kept within acceptable safety limits. Care should be taken to minimise levels of residual toxic substances after sterilisation, for example ethylene oxide.

Whenever new plastics are to be introduced an adequate study of component preparation and/or storage should be conducted. The following parameters could be useful:

- red blood cells: glucose, pH, haematocrit, haemolysis, ATP, lactate, extracellular potassium and 2,3-bisphosphoglycerate;
- platelets: pH, pO\textsubscript{2}, pCO\textsubscript{2}, bicarbonate ion, glucose, lactate accumulation, ATP, P-selectin, LDH release, beta thromboglobulin release, response from hypotonic shock and swirling phenomenon; morphology score and extent of shape change;
- plasma: Factor VIII and signs of coagulation activation, for example thrombin–antithrombin complexes.

These studies would normally be carried out by the manufacturer before introduction of the new plastics and the results be made available to the transfusion services.

The evaluation of new plastics can be completed by the evaluation of 24 hours post transfusion \textit{in vivo} recovery and survival of autologous red cells and by the assessment of platelet recovery, survival and corrected count increments (CCI).

In order to maintain a closed system throughout the separation procedure, a multiple bag configuration, either ready made or sterile-docked, should be used. The design and arrangement of the pack system should be such as to permit the required sterile preparation of the desired component.
Although use of closed systems is recommended for all steps in component processing, open systems may sometimes be necessary due to local constraints in an environment specifically designed to minimise the risk of bacterial contamination. When open systems are employed, careful attention should be given to use of aseptic procedures. The red cells so prepared should be transfused within 24 hours of processing. The platelets so prepared should be transfused within 6 hours of processing.

**Paragraph 4. Centrifugation of blood components**

The sedimentation behaviour of blood cells is determined by their size as well as the difference of their density from that of the surrounding fluid (see Table below). Other factors are viscosity of the medium and flexibility of the cells which are temperature dependent. The optimal temperature with respect to these factors is +20 °C or higher.

**Volume and density of principal blood constituents**

<table>
<thead>
<tr>
<th></th>
<th>Mean Density (g/mL)</th>
<th>Mean Volume (10^-6 litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td>1.026</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>1.058</td>
<td>9</td>
</tr>
<tr>
<td><strong>Monocytes</strong></td>
<td>1.062</td>
<td>470</td>
</tr>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>1.070</td>
<td>230</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>1.082</td>
<td>450</td>
</tr>
<tr>
<td><strong>Red Cells</strong></td>
<td>1.100</td>
<td>87</td>
</tr>
</tbody>
</table>

In the first phase of centrifugation, the surrounding fluid is a mixture of plasma and anticoagulant solution. Leucocytes and red cells now sediment more rapidly than platelets as they both have a bigger volume than platelets. In a later phase, depending on the time and speed of centrifugation, most of the leucocytes and red cells therefore settle in the
lower half of the bag and the upper half contains platelet rich plasma. More prolonged centrifugation results in platelet sedimentation driven by a force proportional to the square of the number of rotations per minute and the distance of each cell to the centre of the rotor, whereas the leucocytes being now surrounded by a fluid of higher density (the red cell mass), move upwards. At the end of centrifugation, cell-free plasma is in the upper part of the bag and red cells at the bottom.

Platelets accumulate on top of the red cell layer, while the majority of leucocytes are to be found immediately below in the top 10 mL of red cell mass. Haematopoietic progenitor cells have similar characteristics to normal mononuclear blood cells. However, their contaminants may be immature or malignant cells from different haematopoietic lineages which commonly have larger sizes and lower densities than their mature counterparts.

The choice to be made is the conditions of centrifugation, such as g-force, acceleration, time, deceleration, etc. which will determine the composition of the desired component, i.e. if platelet-rich plasma is desired, centrifugation should stop prior to the phase where platelet sedimentation commences. A low centrifugation speed will allow for some variation in centrifugation time. If cell-free plasma is required, fast centrifugation for an adequate time will allow separation to cell-poor plasma and densely packed cells. It is important that the optimal conditions for a good separation be carefully standardised for each centrifuge. A number of choices exist for the selection of a procedure for centrifugation for component preparation from whole blood.

The next Table outlines five different methods of performing the first step in the separation of whole blood as well as the approximate composition of the resulting initial components. The choice of the initial separation step strongly influences the methods of further processing of the initial fractions. This leads to a system of interdependent preparation of a blood component and reference should always be made to the initial separation step.
Paragraph 5. Component Separation

Separation after the initial centrifugation

After centrifugation, the bag system is carefully removed from the centrifuge. The primary bag is placed into a plasma extraction system and the layers are transferred, one by one, into satellite packs within the closed system.

The choice to be made is whether or not the buffy coat is to be separated from the packed cells. The advantage of this is that the red cells are leucocyte poor and will remain aggregate poor during storage. Moreover the red cells can be resuspended into a solution designed to offer optimal conditions for red cell storage, e.g. saline-adenine-glucose-mannitol (SAGM). The resuspension may still be done within the closed system. Plasma can now be frozen and be stored as fresh frozen plasma to be used as such or as a starting material for further products.

The next Table provides an estimation of the results that can be obtained using initial centrifugation (4 options) or filtration (1 option).

Depending on the choice of technique for component preparation:

- methods I and II will be followed by recentrifugation of the platelet rich plasma for the preparation of cell free plasma and platelet concentrate;
- method III will be followed by preparation of platelet concentrate from buffy coats.

Separation after initial filtration

Whole blood may be filtered for leucocyte depletion prior to high speed centrifugation. This procedure enables a separation into almost cell-free plasma and leucocyte-depleted (and platelet depleted) red cells.
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Five different methods of initial separation of whole blood and the approximate composition of the fractions obtained (figures refer to a standard donation of 450 mL ± 10% taken into 60-70 mL of anticoagulant)

<table>
<thead>
<tr>
<th>Method</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial filtration</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Centrifugation speed</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Separation into</td>
<td>plasma + buffy coat + red cells</td>
<td>plasma + red cells</td>
<td>plasma + buffy coat + red cells</td>
<td>plasma + red cells</td>
<td>plasma + red cells leucocyte depleted</td>
</tr>
</tbody>
</table>

Resulting crude fractions:

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma, volume</td>
<td>200-280 mL</td>
<td>200-280 mL</td>
<td>270-320 mL</td>
<td>270-330 mL</td>
<td>240-290 mL</td>
</tr>
<tr>
<td>Platelets</td>
<td>70-80%</td>
<td>70-80%</td>
<td>10-20%</td>
<td>10-20%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>5-10%</td>
<td>5-10%</td>
<td>2-5%</td>
<td>2-5%</td>
<td>&lt; 0.01%</td>
</tr>
</tbody>
</table>

Red cells:

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>0.75-0.80</td>
<td>0.65-0.75</td>
<td>0.85-0.90</td>
<td>0.80-0.90</td>
<td>0.80-0.90</td>
</tr>
<tr>
<td>Platelets</td>
<td>5-15%</td>
<td>20-30%</td>
<td>10-20%</td>
<td>80-90%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>25-45%</td>
<td>90-95%</td>
<td>25-45%</td>
<td>95-98%</td>
<td>&lt; 0.01%</td>
</tr>
</tbody>
</table>

Buffy coat:

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>50-70%</td>
<td>40-60%</td>
</tr>
<tr>
<td>Red cells</td>
<td>10-15%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Platelets</td>
<td>10-25%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>60-70%</td>
<td>50-70%</td>
</tr>
</tbody>
</table>
Other separation principles

Zonal centrifugation

Sedimentation of blood cells can be achieved when a centrifugal force is exerted on flowing blood more or less perpendicular to the direction of the flow. The efficiency of the separation depends on the ratio between the centrifugal force and the flow velocity. At a high ratio the plasma obtained is platelet poor, and at a lower ratio platelet rich plasma can be obtained.

A number of apheresis devices are available in which this principle is applied for the production of cell poor plasma or platelet rich plasma.

A further application of zonal centrifugation is the removal of plasma protein from a blood cell suspension. A unit of blood cells is introduced into the centrifuge bowl and a flow of washing fluid is then maintained until the protein concentration in the effluent is sufficiently reduced. Centrifugation is discontinued and the “washed” blood cell suspension is harvested.

The same principle is also used for both the addition and the removal of cryoprotectant before freezing and after thawing of blood cell suspensions in cryopreservation.

Buoyant density centrifugation

Buoyant density centrifugation of blood, bone marrow or buffy coat cells on top of a layer with a density of 1.077 g/mL leads to a layer of mononuclear cells floating on the interface and a pellet of red cells and granulocytes which have penetrated through the separating medium according to the density of the cells involved.

Buoyant density separation is generally applicable for separations based on density differences between cells e.g. also for the separation of cells complexed with red cells to rosettes from the non-rosetted cells.
Counter current centrifugation (elutriation)

Cells that are subjected simultaneously to a liquid flow and a centrifugal force in opposite directions tend to be separated according to their size. This property has been applied in cell separators to collect apheresis platelet concentrates with a reduced leucocyte content, which, for some devices, may reach the specification of leucocyte depletion, i.e. \(< 1 \times 10^6\) leucocytes per unit.

Using specific centrifuges, counter current centrifugation is also used to separate subpopulations of mononuclear cells obtained from blood or bone marrow.

Filtration

At present, two major types of filtration are available for blood component preparation:

- the separation of plasma from blood by cross-flow filtration;
- the removal of leucocytes from cell suspensions by depth-filtration or surface filtration.

Cross-flow filtration

When blood flows along a membrane with a pore size allowing free passage of plasma proteins but not of blood cells, cell-free plasma may be obtained by filtration.

Plasmapheresis devices have been developed in which a pumping system takes blood from the donor's vein, mixes it at a constant ratio with anti-coagulant solution and then leads it along a plasma-permeable membrane (flat membrane or hollow fibre system). Two pressures are exerted on the blood: one parallel to the membrane, keeping the blood flowing along the membrane, and the other perpendicular to the membrane, the actual filtration pressure. This system prevents accumulation of cells on the membrane while plasma is removed from the blood (the haematocrit in the system may increase from 0.40 to 0.75). In some devices, velocity of the flow parallel to the membrane is increased by an additional vortex action or by movement of the membrane.
When a specified extra-corporeal cell volume has been reached, the cells are reinfused to the donor, and the next cycle starts until the required volume of cell-free plasma has been obtained.

*Depth and surface filtration*

Owing to the specific properties of platelets and granulocytes as well as the low flexibility of lymphocytes, these cells are more easily trapped in a filter bed of fibres than red cells. Four mechanisms of trapping have been recognised in filters used for leucocyte depletion of red cell concentrates:

- a. the activation of platelets leading to the attachment of these cells to the fibres in the top of the filter, followed by the interaction of the attached platelets and granulocytes;
- b. the activation of granulocytes by another type of fibre leading to attachment of these cells in the middle part of the filter;
- c. the obstruction of the lymphocytes in the pores and fork junctions of the finest fibre material in the bottom layers of the filter. Blow-moulded mats of fibre material with different pore sizes and fibre thicknesses are now used to produce leucocyte depletion filters for red cell concentrates;
- d. surface treatment of the filter material allows the production of filters which reduce the contaminating leucocytes from platelet concentrates by sieving and may prevent activation of platelets.

Filters used for leucocyte removal from red cells or platelets show considerable variations in efficacy and capacity. Besides filter properties, the final result of filtration is influenced by several process parameters (e.g. flow rate, temperature, priming and rinsing) and properties of the component to be filtered (e.g. storage history of the component, number of leucocytes and number of platelets). When a standardised filtration procedure is established, limits must therefore be set for all the variables affecting the efficacy of filtration and the Standard Operating Procedures (SOPs) should be fully validated under the condition to be used.
Washing of cellular components
This technique is occasionally used when there is requirement for cellular blood components with a very low level of plasma protein.

**Paragraph 6. Leucocyte-depletion**

The introduction of any leucocyte depletion process either by filtration or special centrifugation technique needs careful validation. An appropriate method should be used for leucocyte counting after leucocyte depletion. This method should be validated.

The validation should be carried out by the blood establishment using the manufacturer’s instructions against the requirements for leucocyte depletion and other quality aspects of the components including plasma for fractionation.

To enable comparison of filters aimed at leucocyte depletion and to allow selection between them, the manufacturers should report data on their system performance under defined conditions. Manufacturers should also provide performance data to the blood establishment on variations between different modifications to a given filter type and between batches.

Mathematical models have been developed to calculate the sample size necessary to validate and control the leucocyte depletion process (Chapter 1 *Principles of a quality system for blood establishments*).

After full validation of the process, tools such as statistical process control could be used in ongoing process control to detect any change in the process and/or the procedures.

Particular problems may arise with donations from donors with red cell abnormalities (e.g. sickle-cell trait) where adequate leucocyte depletion may not be achieved and more detailed quality control procedures are necessary (e.g. leucocyte counting of every donation). The quality of the red cells following filtration processes needs further investigation.
Paragraph 7. Freezing and thawing of plasma

Rationale

Freezing is a critical step in the conservation of plasma Factor VIII. During freezing, pure ice is formed and the plasma solutes are concentrated in the remaining water. When the solubility of the solutes is exceeded, each solute forms crystals but may be influenced by the anticoagulants used. Further studies on this aspect are ongoing.

The ice formation depends on the rate of heat extraction, whereas the diffusion rates of the solutes determine their displacement. At slow freezing rates, the diffusion of solutes copes with the rate of ice formation; solutes are increasingly concentrated in the middle of a plasma unit.

Since all solutes are displaced simultaneously, the Factor VIII molecules are exposed to a high concentration of salts for a prolonged time and thus inactivated. At a high freezing rate, the ice formation overtakes the solute displacement and small clusters of solidified solute are homogeneously trapped in the ice without prolonged contact between highly concentrated salts and Factor VIII.

To achieve the highest yield of Factor VIII, plasma should be frozen to −30 °C or below.

Decrease of Factor VIII during freezing occurs when the solidification of plasma takes more than one hour. This can be monitored by measuring the total protein content of a core sample of the frozen plasma; this protein concentration should be identical with the total protein content of plasma before freezing. An optimal freezing rate is obtainable when a heat extraction of 38 kcal per hour per unit of plasma is achieved, and can be monitored by the use of thermocouples.

In order to effectively incorporate these techniques into a coherent daily routine, the blood bank staff has to be familiar with the thinking behind the technique as well as its potential limitations and pitfalls.
Methods of freezing

When freezing plasma, the rate of cooling should be as rapid as possible and optimally should bring the core temperature down to \(-30\,{\text{C}}\) or below within 60 minutes.

Experience has shown that without the use of a snap-freezer it takes several hours to reach this temperature. The time can be reduced, for example by the following means:

- plasma should be presented in a regular configuration to maximise exposure to the freezing process (e.g. bags laid flat or in formers if vertical), immersion in an environment at very low temperature;
- if a liquid environment is used, it should have been shown that the container cannot be penetrated by the solvent.

As for the required storage conditions, reference is made to Paragraph 14 in this Chapter, and the individual monographs.

Methods of thawing

Frozen units should be handled with care since the bags may be brittle. The integrity of the pack should be verified before and after thawing to exclude any defects and leakages. Containers which leak must be discarded. The product should be thawed immediately after removal from storage in a properly controlled environment at \(+37\,\text{C}\) according to a validated procedure. After thawing of frozen plasma, the content should be inspected to ensure that no insoluble cryoprecipitate is visible on completion of the thaw procedure.

The product should not be used if insoluble material is present. In order to preserve labile factors, plasma should be used immediately following thawing. It should not be refrozen.

Thawing of the plasma is an inevitable part of some of the current viral inactivation processes after which the products may be refrozen. In order to preserve liable component, the final component should be used immediately following thawing for clinical use and not further refrozen.
Cryoprecipitation

The isolation of some plasma proteins, most importantly Factor VIII, vWF, fibronectin and fibrinogen, can be achieved by making use of their reduced solubility at low temperature. In practice, this is done by freezing units of plasma, thawing and centrifugation at low temperature.

Details regarding the freezing, thawing, and centrifugation conditions required for cryoprecipitate production, are provided under Standards, Chapter 5, Part D, Paragraph 3 Cryoprecipitate.

Paragraph 8. Open and Closed systems and sterile connection devices

It is suggested that any new development in component preparation involving an open system should be subjected to intensive testing during the developmental phase for maintenance of sterility.

Blood components prepared by an open system should be used as quickly as possible.

Components prepared in systems using fully validated sterile connecting devices may be stored as if prepared in a closed system. Monitoring should be carried out by pressure testing of all connections and regular traction tests.

Paragraph 9. Ionising irradiation of blood components

Viable lymphocytes in blood components can cause fatal graft versus host reaction in severely immunocompromised patients, e.g. patients receiving immunosuppressive therapy, children with severe immunodeficiency syndromes and low birth-weight neonates. Other categories of patients are also at risk of this rare complication e.g. following intrauterine transfusion, transfusion between family members and transfusion of HLA-matched components.

Lymphocytes can be rendered non-viable by exposure to ionising radiation. This treatment does not cause significant harm to other
blood components and an irradiated component can therefore safely be given to all patients.

Irradiated platelets can be used up to their original expiry date.

The use of radiation-sensitive labels to demonstrate that the component has been irradiated is recommended.

**Paragraph 10. Prevention of CMV transmission**

Cytomegalovirus (CMV) is a common infectious agent that can be transmitted by transfusion of blood components. The risk of disease transmission is highest with fresh components containing mono and polymorphonuclear leucocytes. CMV infection is often asymptomatic in healthy persons. Antibodies usually appear 4 to 8 weeks after infection and can be demonstrated in standard screening tests. Since the infection is common, the test has to be repeated on each donation from a previously sero negative donor.

Infection caused by this virus is usually not clinically significant in immuno-competent recipients, but can cause severe, even fatal, disease in certain patients not previously exposed to the virus:

- transplant recipients;
- patients with severe immuno-deficiency;
- foetus (intra-uterine transfusion);
- anti-CMV negative pregnant women;
- low weight premature infants and neonates.

These patients should receive components selected or processed to minimise risk of CMV infectivity. Use of components from anti-CMV negative donors or leucocyte depleted components significantly reduces the risk of CMV-transmission and CMV-disease in immuno-compromised patients. However, neither method nor the combination can completely avoid transmission from occasional case of CMV-viremia 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. While some services, especially in areas that have a high seroprevalence of CMV have ceased antibody screening, others believe that the combination of antibody screening and leucocyte depletion may confer some additional safety.

**Paragraph 11. Pathogen reduction**

Systems exist that will remove or reduce the infectivity of a wide range of microbiological pathogens in blood components. These procedures are currently available for platelets and plasma, but are still in development for red blood cells. National transfusion services should decide individually about the value for implementation of these systems in the given context taking into account the available epidemiological and haemovigilance data, and the new possibility of a proactive attitude towards emerging pathogens.

**Paragraph 12. Purity of components**

Since blood components are used to correct a known deficit, each preparation must be subjected to strict quality control. The aim is to produce “pure” components, but a very high degree of purity can be difficult and expensive to obtain and might not even be necessary in all instances. However, it is absolutely necessary to declare the quality and to be able to make different types of preparations in order to give the clinicians a reasonable choice for patients with different transfusion demands.

For example, a red cell concentrate can be produced with varying concentrations of contaminating leucocytes and platelets. A buffy coat depleted preparation where the majority of the leucocytes and the platelets have been removed is useful to the majority of recipients since microaggregate formation during storage will be inhibited. If the patient has antibodies against leucocyte antigens or if it can be foreseen that he/she will need a very large number of transfusions, leucocyte depletion must be much more efficient.
In order to institute an adequate scheme of component therapy, all components must be carefully defined and minimum requirements set. Clinical users should be informed of the properties of all components.

**Paragraph 13. Bacterial safety of blood components**

**Overview**

Although blood collection and processing procedures are intended to produce non-infectious blood components, bacterial contamination still may occur. Bacterial quality control testing in all blood components may be appropriate. However, for whole blood collection, bacterial cultures of platelets provide the best indication of the overall rate of contamination, provided that the sample for culture is obtained on a suitable sample volume and at a suitable time post-collection. Surveillance studies have found rates of contamination as high as 0.4% in single donor platelets, although rates at or below 0.2% more often have been reported. The causes include occult bacteraemia in the donor, inadequate or contaminated skin preparation at the phlebotomy site, coring of a skin plug by the phlebotomy needle, and breaches of the closed system from equipment defects or mishandling. Platelet components are more likely than other blood components to be associated with sepsis due to their storage at room temperature, which is permissive of bacterial growth.

A variety of procedures may be used to obtain a valid platelet sample for bacterial culture. Aseptic techniques are required in order to minimise the risk of false positive cultures due to contamination at the time of sampling or upon inoculation in culture. Additionally, it is prudent to retain a sample that can be used for repeat culture to validate a positive result. Large volume samples removed from a several unit platelet pool or single donor apheresis unit can be cultured any time post collection. However small volume samples (e.g. 2-5 mL removed from a single whole blood unit) should be taken for culture after a 48 hour delay post-collection. The delayed sampling of a small volume permits bacterial growth to a level that subsequent assays will reliably detect, thereby overcoming sampling errors at low contamination levels.
Quality control for aseptic collection and processing of blood components

The goal of quality control testing for bacterial contamination should be to assure that blood collection and processing procedures conform to current standards. Statistically defined sampling of platelets for culture (or nucleic acid testing) by a validated method will provide a reliable indication of the rate of contamination for all the blood components. Quality control testing may be of value in long term process control, if validated and conducted according to an appropriate statistical plan.

Based on these considerations one possible approach for monitoring sterility is as follows:

a. As a quality control for aseptic collection of blood components, blood collection centres should determine the rate of bacterial contamination in platelets at least yearly by culturing 1500 or more units (about 30 units per week or 5% of units released after 48 hours of collection, whichever is larger). Standard statistical methods should be used to identify significant deviations from a baseline contamination rate not to exceed 0.2%. The chosen method should be based on a predetermined level of confidence to exclude a maximum tolerated rate of contamination, and an action limit should be established.

b. All instances of a positive culture should be investigated promptly to identify a correctable cause.

c. Whenever the observed rate of bacterial contamination exceeds the defined action limit, a comprehensive investigation into potential causes of contamination should be undertaken and all collection and processing procedures should be revalidated.

Example

A blood centre wishes to establish surveillance to detect bacterial contamination rates significantly in excess of 0.2%. The following chart is derived from binomial statistics:
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<table>
<thead>
<tr>
<th>Candidate action limit</th>
<th>Confidence in positive result</th>
<th>Power to detect actual contamination rate at</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. positive units/ no. sampled units</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>≥ 3 per 400</td>
<td>95.3%</td>
<td>22%</td>
</tr>
<tr>
<td>≥ 5 per 800</td>
<td>97.6%</td>
<td>22%</td>
</tr>
<tr>
<td>≥ 7 per 1600</td>
<td>95.5%</td>
<td>46%</td>
</tr>
</tbody>
</table>

The blood centre collects 12 units of platelets per day, five days per week. Cultures of units released after 48 hours, plus outdated units, number 30 units per week that are processed as 6 weekly cultures of five unit pools. An action limit is set to revalidate the collection procedures if the observed contamination rate exceeds 0.42% for yearly samples of 1560 units. The action limit was established based on an expected contamination rate of 0.2%, a sample size of 1560, and a cut-off determined as baseline plus 2-sigma variation. For this scheme, the likelihood of rejecting a conforming process is 4.5% (once every 22 years). The confidence levels (i.e. power) to exclude actual contamination rates of 1%, 0.8% and 0.6% are 99.6%, 97% and 84% respectively.

Over a one-year period, 7 positive platelet pools are identified, traceable to 7 individual units. The individual cases were investigated, but no attributable cause was identified. The observed contamination rate of $7/1560 = 0.45\%$ exceeds the action level. Confidence that the actual contamination rate exceeds 0.2% is greater than 95%. An intensive review is conducted, and all collection and processing procedures are revalidated.

**Release as culture-negative to date**

Routine pre-release bacteriological testing of all platelets to establish a criterion for issue of platelets as “culture-negative to date” obviates recommendations in “Quality control of aseptic collection and processing of blood components”. Sampling of platelets for the purpose of establishing a release criterion based on a negative result of bacterial
cultures requires that the integrity of the closed system should be maintained. This is because platelets may continue to be stored for a variable period after sampling and before use. Suitable methods of sampling in this case would include the use of integral satellite containers, or stripping, refilling, and then pinching off duplicate pigtails. Sampling also may be done into collection containers via the use of sterile connecting devices.

**Paragraph 14. Storage of blood components**

Storage conditions for blood components are designed to preserve optimal viability and function during the whole storage period. The risk of bacterial contamination decreases substantially if only closed separation and storage systems are used.

**Equipment**

Blood components are stored at +20 °C to +24 °C, at +2 °C to +6 °C or at different temperatures below 0 °C. Whatever type of storage device is chosen, the following points should be considered before purchase:

i. refrigerators and freezers must have surplus capacity. The space should be easy to inspect;

ii. the operation must be reliable and temperature distribution must be uniform within the unit;

iii. the equipment must have temperature recording and alarm devices;

iv. the equipment should be easy to clean and should withstand strong detergents. It should also conform to local safety requirements.

**Storage at +2 °C to +6 °C**

The space for each of the component types should be clearly indicated. The temperature within the unit should be recorded continuously. The sensor of the temperature monitoring device should be placed within a blood bag filled with 10% glycerol solution to a volume of 250 mL or a volume equivalent to the normal volume of the stored component.
This container should be placed in the upper part of the refrigerated space. In large refrigerated rooms, 2 such sensors should be applied.

The alarm system should preferably have both acoustic and optical signals and should be tested regularly.

Refrigerators for blood components should ideally be connected to a reserve power unit as well as the main supply.

**Storage of frozen plasma components**

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

Freezers should ideally be connected to a reserve power source as well as the main supply.

**Storage at +20 °C to +24 °C**

Platelets are stored at +20 °C to +24 °C. A closed device that permits temperature control is recommended. If such a device is unavailable, the space chosen should be capable of maintaining the required constant temperature.

The platelets should be stored in agitators which should:

- enable satisfactory mixing in the bag as well as gas exchange through the wall of the bag;
- avoid folding of the bags;
- have a set speed to avoid foaming.

**Aspects of red cell preservation**

The anticoagulant solutions used in blood collection have been developed to prevent coagulation and to permit storage of red cells for a certain period of time. While originally designed for whole blood storage, they have also been used in blood from which components are prepared. All of the solutions contain sodium citrate, citric acid and glucose, some of them may also contain adenine, guanosine and phosphate.
Citrate binds calcium and prevents clotting of the blood. Glucose is used by the red cell during storage and each glucose molecule gives 2 molecules of adenosine tri phosphate (ATP) which is formed by phosphorylation of adenosine di phosphate (ADP). ATP is an energy-rich molecule which is used to support the energy-demanding functions of the red cell, such as membrane flexibility and certain membrane transport functions. During its action in energy-consuming operations, ATP is transferred back to ADP. Citric acid is added to the anticoagulant in order to obtain a hydrogen ion concentration which is suitably high at the beginning of storage at +4 °C. Without this addition the blood would be too alkaline at storage temperature.

During storage, an increasing acidity occurs which reduces glycolysis. The content of adenosine nucleotides (ATP, ADP, AMP) decreases during storage. By addition of adenine which is a main component in the adenosine nucleotides, the red cells can synthesise new AMP, ADP and ATP and compensate for (or reduce) the losses. When red cell concentrates are prepared, a considerable part of the glucose and adenine is removed with the plasma. If not compensated for in other ways (e.g. larger amount than normal of adenine and glucose in the anticoagulant or by separate addition of a suspension/preservative medium), sufficient viability of the red cells can only be maintained if the cells are not over-concentrated. Normal CPD adenine red cell concentrate should therefore not have an Hct above 0.70 on average. This also keeps the viscosity sufficiently low to permit transfusion of the concentrate without pre administration dilution.

**Additive solutions**

An additive solution should allow maintenance of red cell viability even if more than 90% of the plasma is removed. The use of glucose and adenine is necessary for the maintenance of red blood cell post-transfusion viability, phosphate may be used to enhance glycolysis, and other substances may be used to prevent *in vitro* haemolysis (i.e. mannitol, citrate). Sodium chloride or di-sodium phosphate may be used to give the additive solution a suitable osmotic strength.
**Microaggregates**

Platelets and leucocytes rapidly lose their viability at + 4 °C. They form microaggregates which are present in considerable amounts even after 3 to 4 days’ storage of whole blood and even more so in red cell concentrates. Microaggregates can pass through the filters of ordinary blood transfusion sets. They are considered to be able to cause decreased lung function by blocking the lung capillaries and this may be of clinical importance in massive transfusions. Removal of platelets during component preparation reduces microaggregate formation. Likewise, leucocyte depletion by buffy coat removal will also reduce the frequency of febrile transfusion reactions and will help in obtaining high-grade depletion of leucocytes when leucocyte removal filters are used for this purpose.

**Red cell preparations**

The maximum duration of storage (expiry date) should be noted on each container. This duration may vary with the type of preparation (concentration of cells, formula of anticoagulant, use of additive solution, etc.) and should be determined for each type on the basis of achieving a mean 24 hours post transfusion survival of no less than 75% of the transfused red cells.

Red cells may be stored in the fluid state at a controlled temperature of + 2 °C to + 6 °C. The performance of the storage refrigerator must itself be carefully controlled. The maximum duration of storage (expiry date) must be noted on each container.

Red cells in the frozen state should be prepared and reconstituted according to an approved protocol, be stored at – 60 °C to – 80 °C or below, and produce satisfactory post transfusion survival figures.

**Platelet preparations**

Platelets must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved (see Standards).
Plastic bags intended for platelet storage should be sufficiently permeable to gases to guarantee availability of oxygen to platelets and diffusion of carbon dioxide. The amount of oxygen required is dependent on the number of platelets and the concentration thereof in the component. Lack of oxygen increases anaerobic glycolysis and lactic acid production. The quality of platelets is preserved if the pH stays continuously above 6.4 under storage period used.

Agitation of platelets during storage should be sufficient to guarantee availability of oxygen but as gentle as possible to prevent induction of activation and storage lesion of platelets. Storage temperature should be +20 °C to +24 °C. Below +20 °C platelets undergo membrane phase transition and cold activation and the discoid platelet structure gradually converts to a sphere.

**Granulocyte preparations**

Ordinarily, granulocyte suspensions are prepared for a specific patient and administered immediately.

**Plasma components**

Recommended storage conditions for fresh frozen plasma and cryoprecipitate and for cryoprecipitate depleted plasma are given in the Table below.

<table>
<thead>
<tr>
<th>Product</th>
<th>Length of storage and temperature</th>
</tr>
</thead>
</table>
| Fresh frozen plasma, cryoprecipitate and cryoprecipitate-depleted plasma | 36 months at or below – 25 °C  
3 months at –18 °C to –25 °C |

1 For plasma intended for fractionation refer to the appropriate Ph. Eur. monograph.  
2 The recommended temperature ranges are based upon practical refrigeration conditions.
Paragraph 15. Transportation of blood components

Blood components should be transported by a system which has been validated to maintain the recommended storage temperature of the component over the proposed maximum time and extremes of ambient temperature of transport. It is recommended that some form of temperature indicator be used to monitor the in transit temperature. Also the temperature on receipt can be monitored as follows: take 2 bags from the container, place a thermometer between the bags and fix them together with rubber bands. Quickly replace them into the container and close the lid. Read the temperature after 5 minutes. Alternatively an electronic sensing device may be used to take immediate measurements from the surface of a pack.

On receipt, if not intended for immediate transfusion, the product should be transferred to storage under recommended conditions.

Transport of red cell components

Red cell components should be kept between +2 °C and +6 °C. The temperature of red cell bags should not go below +1 °C nor exceed +10 °C. Validated transport systems are to ensure that at the end of a maximum transit time of 24 hours the temperature has not exceeded +10 °C.

Transport of platelet components

During transport platelets components cannot be agitated and therefore oxygen delivery to platelets is reduced. The agitation of platelets can be interrupted (simulated shipping conditions) for up to 30 hours either for one or two to three periods without major effect on the in vitro quality of platelets at the end of storage time of 5 or 7 days. The pH of the platelet components is better preserved when agitation is interrupted for several short periods as compared to one long period.

Platelet components should be transported in an insulated container with temperature stabilising elements which ensure transport temperature as close as possible to recommended storage temperature.
The transport time without agitation should not exceed 24 hours. On receipt, unless intended for immediate therapeutic use, platelet components should be transferred to storage under recommended conditions including further agitation.

The impact of transport conditions on the quality of platelet components should be validated by quality control tests, e.g. swirling tests and pH measurements of components at the end of storage period.

**Transport of frozen plasma components**

Frozen plasma components should be transported in the frozen state as close as possible to the recommended storage temperature.

**Paragraph 16. Component information and principles of labelling**

Before use all containers should be labelled with relevant information of their identity. The type of label to be used as well as the labelling methodology should be established in written procedures. Critical information should where possible be provided in machine readable format to eliminate transcription errors.

The blood establishment responsible for the processing of the blood component should supply the person(s) using the blood component with information on its use, composition, and special conditions that do not appear on the label.

Blood components for autologous use should be labelled as such.

Brief information about the various blood components should be made available to clinicians with regard to composition, indications, storage and transfusion practices.

This would include that the blood must not be used for transfusion if there is abnormal haemolysis or other deterioration and that all blood components must be administered through a 150-200 μm filter, if not otherwise stated. The information should be presented to the clinicians in a booklet and/or in a product information leaflet.
The labelling of blood components should comply with the relevant national legislation and international agreements. Each single blood container must be uniquely identified by the identity number and the component description, preferably in eye and machine readable codes, allowing full traceability to the donor and the collection, testing, processing, storage, release, distribution and transfusion of the blood component.

The label on the component ready for distribution should contain eye readable information necessary for safe transfusion, i.e. the unique identity number (preferably consisting of a code for the responsible blood collection organisation, the year of donation and a serial number), the ABO and RhD blood group, the name of the blood component and essential information about the properties and handling of the blood component, the expiry date.
Chapter 5

Principles of blood component monographs

Monographs with detailed information are given in the Standards Section for typical categories of blood components:

A. Whole blood
B. Red cells
C. Platelets
D. Plasma
E. White cells

The given blood components in the monographs are to be regarded as standard blood components across Europe. However, it can be stated that some components are in use only in few countries. Based on future consensus the number of variant components may be reduced.

The component monographs have a standardized structure, which encompasses:

1. **Definition and properties**
   Here information is given about the component including its origin, the active constituents and contaminating cells if appropriate.

2. **Preparation**
   Here a short description is given about the method of preparation. It differentiates between primary and secondary processing. Primary processing results in different blood components each of which is
described in Chapter 5 of the Standards Section. Secondary processing leads to variant preparations which are very similar to the primary component and do not differ in handling, release and application. More detailed information about the preparation process is available from Chapter 4 of the Principles Section.

3. Requirements and quality control

Typical component specific handling and testing for quality control are given in tables formatted as below.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
</table>

If appropriate, the requirements may be met by performing the test on the donation sample taken as part of the donor screening process, in lieu of individual component testing.

Quality control may be carried out either as a separate quality control procedure for the given component or as a routine part of the issue and transfusion of these components. Detailed information on the preparation processes are given in Chapter 4 Principles of blood component preparation.

4. Storage and transport

Typical mandatory storage and transport conditions for the respective blood components are given. Detailed and descriptive information about the process of storage and transport is given in Chapter 4 Principles of blood component preparation.

5. Labelling

The labelling should comply with the relevant national legislation and international agreements. The given information should be shown on the label or contained in the component information leaflet.

6. Warnings

Typical warnings and side-effects are given that should be communicated to the physician in a written form as in a component information leaflet.
Chapter 6

Principles of blood components for fetal, neonatal and infant use

Paragraph 1. Overview

Specially designed blood components are required for intrauterine and infant transfusions. The following factors must 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 fetal transfusions and for small premature infants. There is a significant risk of GvHD and CMV transmission when the foetus or small infants are transfused.

These patients should receive components selected or processed to minimise the risk of CMV transmission.

There are specific national regulations or guidelines for pretransfusion blood grouping and compatibility testing of neonates.

Components for intrauterine transfusions

All components for intrauterine transfusion (IUT) must be irradiated.

To minimise the effect of potassium load, Red Cells for IUT must be used within five days from donation and within 24 hours of irradiation.
Indications for use:

- Intrauterine Red Cell transfusions are performed to treat severe fetal anaemia.
- Intrauterine platelets are administered for the correction of severe thrombocytopenia which may be due to antenatal HPA alloimmunisation.

**Components for neonatal exchange transfusion**

Exchange transfusion is a special type of massive transfusion. The components used must be fresh enough so that metabolic and haemostatic disturbances can be minimised.

A number of components can be utilised for exchange transfusion, including:

- Whole Blood, LD;
- Whole Blood, LD, Plasma Reduced;
- Red Cells, LD, re-suspended in Fresh Frozen Plasma.

ABO and Rh groups, as well as other red cell antigens to which the mother has become sensitised have to be taken into account when selecting blood for exchange transfusion.

Whole blood and red cell components for exchange transfusion should be irradiated unless compelling clinical circumstances indicate that delay would compromise clinical outcome. Irradiation is essential if the infant has had a previous IUT.

To minimise the effect of potassium load, whole blood and red cells components must be used within five days from donation and within 24 hours of irradiation. For reconstituted components, the shelf-life is 24 hours.

Indications for use:

- Exchange transfusions of neonates.
- These components are also suitable for large volume (massive) transfusion of neonates and small infants.
- If the platelet count of the infant undergoing/following exchange or other massive transfusion is very low, specific platelet transfusion should be given.

**Red cells for neonatal and infant small volume transfusion**

Preterm infants are amongst the most intensively transfused of all hospital patients and have the greatest potential for long-term survival. Minimising the number of donor exposures is therefore a central aim in designing proper components and guiding transfusion practice.

Therefore, it is good practice is to divide a component unit into several sub batches and dedicate all the satellite units from a donation for a single patient. Because fresh blood and red cells are used in intrauterine and exchange transfusions it is often thought that fresh blood is necessary for all neonatal transfusions. There is no scientific or clinical evidence to support this concept in the case of small volume, top-up transfusions, provided that transfusion rates are carefully controlled.

The component may be irradiated where clinically indicated. If the component is irradiated, it should be used within 48 hours.

Indications for use:
- anaemia of prematurity;
- to replace the blood losses of investigative sampling;
- suitable for surgical replacement for infants and other children.

**Fresh Frozen plasma for neonatal and infant use**

In order to reduce donor exposure, a fresh frozen plasma (FFP) unit can be divided into approximately equal volumes into satellite packs, prior to freezing, by using a closed or functionally closed system. Three to four of such bags are dedicated to one patient.

ABO blood group compatible plasma should be used. National requirements may require the use of plasma only from AB RhD-negative and positive donors.
Indications for use:

- Fresh frozen plasma may be used in coagulation defects, particularly in those clinical situations in which a multiple coagulation deficit exists and only where no suitable viral inactivated alternative is available.
- Congenital deficiency of single clotting factors where no virally inactivated concentrate exists.

Contra-indications:

- FFP should not be used simply to correct a volume deficit in babies in the absence of a coagulation defect nor as a source of immunoglobulins.
- FFP should not be used where a suitable virally inactivated clotting factor concentrate is available.
- FFP should not be used in a patient with intolerance to plasma protein.

**Platelets for neonatal and infant use**

When preparing platelets for infants every effort should be made to minimise donor exposure.

Platelets, Apheresis, offers the greatest potential to reduce donor exposure and can be divided into satellite packs by using a closed system as for FFP.

Volume Reduction: the clinical situation of a small child may necessitate the use of volume reduced platelets; volume reduction to around 25 mL causes about 10% loss of platelets. Platelets after volume reduction should be used as soon as possible.

The platelet component must be used within 24 hours of any washing procedure and within 6 hours of any concentration process.

The platelet component should be irradiated where clinically indicated.

Control the rate of transfusion to avoid excessive fluctuations in blood volume.

Indications for use: severe neonatal thrombocytopenia of any cause.
Chapter 7

Principles of autologous predeposit transfusion

Paragraph 1. Overview

Several autologous transfusion techniques may be useful in surgery. They were designed to avoid the risks of alloimmune complications of blood transfusion, and reduce the risk of transfusion-associated infectious complications. This chapter deals with autologous predeposit donations.

Autologous predeposit blood components can be obtained from pre-operative autologous predeposit whole blood donations in the weeks preceding surgery. In selected conditions, red cell or platelet concentrates can be collected using a cell separator: the equivalent of 2 to 3 red cell concentrates, or 4 to 10 standard platelet concentrate can be collected in a single procedure.

Autologous predeposit blood components obtained from pre-operative donations must be collected, prepared and stored in the same conditions as allogeneic donations. For these reasons, autologous predeposit autologous donations must be done in or under the control of blood establishments or in authorised clinical departments which are subject to the same rules and controls of this activity as blood establishments (see Standards).
Acute normovolemic haemodilution is the collection of blood immediately before surgery, with blood volume compensation, leading to a haematocrit below 0.32, with reinfusion during or after surgery.

Red cell salvage during surgery is another means of autologous transfusion. Blood collected from operation site may be given back to the patient either after a simple filtration, or a washing procedure. These techniques do not allow the storage of the collected blood. They are usually performed under the responsibility of anaesthesiologists and/or surgeons.

**Paragraph 2. Selection of patients for autologous predeposit transfusion**

**Role of the physician in charge of the patient**

In elective surgery situations where a blood transfusion is expected, the physician in charge of the patient, usually the anaesthesiologist or the surgeon, may prescribe pre-operative donations.

The prescription should indicate:

- the diagnosis;
- the type and number of components required;
- the date and location of the scheduled surgery.

The patient should be informed of the respective risks and constraints of autologous and allogeneic transfusion, and that allogeneic transfusion may also have to be used if necessary.

In case of contra-indication, the physician in charge of blood collection informs the patient and the physician in charge of the patient.

**Contra-indications of autologous predeposit donations**

Autologous predeposit donation 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.
Children under 10 kg should not be included in an autologous predeposit donation programme. For children between 10 and 20 kg, the use of volume compensation solutions is usually needed.

Autologous predeposit donation should not be done in patients with haemoglobin concentration below 100 g/L.

In patients with haemoglobin concentration between 100 and 110 g/L, autologous predeposit donation may be discussed according to the number of scheduled donations and the aetiology of the anaemia.

It is recommended that patients positive for the following virological markers should not be included in an autologous predeposit donation programme HBV, HCV, HIV and (when required) HTLV.

The presence of a cardiac disease is not an absolute contra-indication, and autologous predeposit donation may be done, subject to the assessment of a cardiologist, if needed. However patients with certain unstable clinical conditions such as unstable angina, severe aortic stenosis, or uncontrolled hypertension must not normally be included in an autologous predeposit donation programme.

**Medications**

Oral iron may be given to patients before the first donation and until surgery.

Any use of erythropoietin should comply with the product marketing authorisation.

**Records**

The following records should be maintained (see also the standards):

- the concurrent use of peri-operative autologous transfusion techniques;
- the technique and the volume of autologous blood reinjected;
- the use of allogeneic blood components.
Paragraph 3. Autologous predeposit components preparation, storage and distribution

Autologous predeposit blood components are prepared, stored and distributed according to the same regulations as homologous blood components.

Labeling

The labeling should comply with the relevant national legislation and international agreements.

Storage

Autologous predeposit plasma may be used as a volume expander until 72 hours after thawing, provided that it is stored in controlled conditions between +2 °C and +6 °C. Otherwise autologous predeposit components must be stored under the same conditions as their allogeneic counterparts but clearly separated from them.

Records

Blood establishments and hospitals should both maintain the following records for every patient included in a autologous predeposit transfusion programme:

- the date and type of surgery;
- the name of the anaesthesiologist or the surgeon;
- the time of transfusion, specifying whether used during surgery or post-operative;
- the actual use of the prepared pre-operative autologous blood components;
- the concurrent use of peri-operative autologous transfusion techniques;
- the technique and the volume of autologous blood reinjected;
- the use of allogeneic blood components;
- the occurrence of any adverse reaction related.
Chapter 8

Principles of blood group serology

Paragraph 1. Overview

The aim of any blood transfusion laboratory is to perform the right test, on the right sample and obtain the right results ensuring that the right blood component is issued to the right patient. It is essential to obtain accurate results for tests such as ABO/RhD grouping on the donor and patient, antibody screening and compatibility testing.

Errors at any stage of performing such tests can lead to incompatible or inappropriate blood being transfused with significant adverse health affects on patients. These errors can be due to either technical failure in serological testing or inadequate procedures leading to misidentification of patient or donor samples, transcription errors or misinterpretation of results. Haemovigilance data indicate that in some cases, a combination of factors contribute to error, with the original error being perpetuated or compounded by the lack of adequate checking procedures within the laboratory or at the bedside.

The implementation of a quality management system will help to reduce the number of technical and more often procedural errors made in the laboratory. These include quality assurance measures such as 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 the analytical procedure.
Paragraph 2. Validation and quality assurance

Only tests that have been licensed or evaluated and considered suitable by the responsible Health Authorities can be used.

In the EU, blood group reagents are considered as in vitro diagnostic devices and must be CE marked. EU Directive 98/79/EC classified the ABO RhD, Kell test serum and A and B cells in list A. The manufacturer must have a full Quality System certified by an authorised body and submit an application containing all the control results for each lot.

The Council of Europe has issued requirements for blood grouping, and antiglobulin reagents (European Agreement on the exchange of blood grouping reagents, European Treaty Series, No. 39). Summarised requirements are included in the tables of this chapter.

Validation of reagents

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>REAGENT RED CELLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>No haemolysis or turbidity in the supernatant by visual inspection</td>
<td>Each lot</td>
</tr>
<tr>
<td>Reactivity and specificity</td>
<td>Clear-cut reactions with selected reagents against declared RBC antigens</td>
<td>Each lot</td>
</tr>
<tr>
<td>ABO-TYPING REAGENTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>No precipitate, particles or gel-formation by visual inspection</td>
<td>Each new lot</td>
</tr>
<tr>
<td>Reactivity and specificity</td>
<td>No immune haemolysis, rouleaux formation or prozone phenomenon. Clear-cut reactions with RBC bearing the weakened expression of the corresponding antigen(s), no false reactions. (see also quality control of ABO- and Rh-typing)</td>
<td>Each new lot</td>
</tr>
<tr>
<td></td>
<td><strong>Potency</strong></td>
<td>Each new lot</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Principles. Chapter 8</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>Undiluted reagent should give a 3 to 4 plus reaction in saline tube test using a 3% RBC suspension at room temperature. For polyclonal reagents, titres should be of 128 for anti-A, anti-B and anti-AB with A₁ and B cells; 64 with A₂ and A₂B cells</td>
<td>Each new lot</td>
</tr>
<tr>
<td><strong>Rh-TYPING REAGENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>No precipitate, particles or gel-formation by visual inspection</td>
<td>Each lot</td>
</tr>
<tr>
<td><strong>Reactivity and specificity</strong></td>
<td>As for ABO- typing reagents</td>
<td>Each new lot</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>Undiluted serum to give a 3 to 4 plus reaction in the designated test for each serum and a titre of 32 for anti-RhD and of 16 for anti-C, anti-E, anti-c, anti-e and anti-CDE using appropriate heterozygous red blood cells</td>
<td>Each new lot</td>
</tr>
<tr>
<td><strong>ANTIGLOBULIN SERUM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Appearance</strong></td>
<td>No precipitate, particles or gel-formation by visual inspection</td>
<td>Each lot</td>
</tr>
<tr>
<td><strong>Reactivity and specificity</strong></td>
<td>a. No haemolytic activity; no agglutination of RBC of any ABO group after incubation with compatible serum</td>
<td>Each lot</td>
</tr>
<tr>
<td></td>
<td>b. Agglutination of RBC sensitised with anti-RhD serum containing not more than 10-nanograms/mL antibody activity (0.05 IU/mL antibody activity)</td>
<td>Each lot</td>
</tr>
</tbody>
</table>
| | c. Agglutination of RBC sensitised with a complement-binding alloantibody (e.g. anti-JKc⁺) to a higher titre in the presence than in the absence of complement or agglutination of RBC coated with C₃b and C₃d | Each new lotführungs
### ALBUMIN

<table>
<thead>
<tr>
<th>Appearance</th>
<th>No precipitate, particles or gel-formation by visual inspection</th>
<th>Each lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivity</td>
<td>No agglutination of unsensitised RBC; no haemolytic activity; no prozone or “tailing” phenomena</td>
<td>Each lot</td>
</tr>
</tbody>
</table>

### PROTEASE

<table>
<thead>
<tr>
<th>Appearance</th>
<th>No precipitate, particles or gel-formation by visual inspection</th>
<th>Each lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivity</td>
<td>No agglutination or haemolysis using compatible AB-serum; Agglutination of RBC sensitised with a weak IgG anti-RhD</td>
<td>Each lot</td>
</tr>
<tr>
<td></td>
<td>No agglutination of unsensitised RBC; no haemolytic activity</td>
<td>Each new lot</td>
</tr>
</tbody>
</table>

### SALINE

<table>
<thead>
<tr>
<th>Appearance</th>
<th>No precipitate, particles or gel-formation by visual inspection</th>
<th>Each day</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl content</td>
<td>0.154 mol/L (≈ 9 g/L)</td>
<td>Each new lot</td>
</tr>
<tr>
<td>pH</td>
<td>pH 6.6-7.6</td>
<td>Each new lot for buffered saline</td>
</tr>
</tbody>
</table>

### LOW IONIC STRENGTH SOLUTION (LISS)

<table>
<thead>
<tr>
<th>Appearance</th>
<th>No turbidity or particles on visual inspection</th>
<th>Each lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.7 (range 6.5-7.0)</td>
<td>Each new lot</td>
</tr>
</tbody>
</table>
Quality control

The quality control procedures in blood group serology can be divided into controls for equipment, reagents and techniques. This classification is considered to provide clarity, in spite of partial overlapping, especially between controls for reagents and techniques.

Quality control of equipment

Equipment used in transfusion serology, in particular centrifuges, and automatic cell washers, water baths, incubators, refrigerators and freezers should undergo regular quality controls. Equipment for automated blood grouping should also be controlled systematically, according to the manufacturer’s instructions.

Quality control of reagents

Quality control procedures recommended in this section may basically be applied to reagents used for manual and for automated techniques. However, reagents for blood grouping machines may have special quality requirements and more detailed controls; the manufacturers of the equipment usually supply these.

Quality control of techniques

Provided that the quality of equipment and reagents fulfil the requirements, false results are due to the technique itself, either because of inadequacy of the method or, more often, because of operational errors as a consequence of inaccurate performance or incorrect interpretation.

Internal quality control

The quality control procedures recommended in this section are focused on the techniques but they will of course also disclose poor quality of equipment and/or reagents.
<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Minimal requirements for testing</th>
<th>Control samples</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ABO-grouping</td>
<td>Test twice in using 2 different reagents. Use of 2 different reagents: monoclonal anti-A and anti-B from different clones; human antisera anti-A, anti-B and anti-A,B from different batches.</td>
<td>One blood sample of each of the following types: O, A, B</td>
<td>Each test series or at least once a day provided the same reagents are used throughout.</td>
</tr>
<tr>
<td>2. ABO reverse-grouping</td>
<td>Use of A and B cells.</td>
<td></td>
<td>Each test series or at least once a day provided the same reagents are used throughout.</td>
</tr>
<tr>
<td>3. RhD-grouping</td>
<td>Testing twice in using 2 anti-RhD reagents from different clones or batches; use of the indirect anti-globulin test for weak D Confirmation in donors, where required. It must be ascertained that the system recognises the most important D variants (notably D variants category VI) as RhD positive.</td>
<td>One RhD-pos, one RhD-neg sample</td>
<td>Each test series or at least once a day provided the same reagents are used throughout.</td>
</tr>
<tr>
<td>4. Rh and other blood group systems phenotyping</td>
<td>Use specific reagents.</td>
<td>Positive control: RBC with tested antigen in single dose. Negative control: RBC without tested antigen.</td>
<td>Monoclonal antibodies and human antisera once a day</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>5. Antiglobulin testing tube technique</td>
<td>Washing the cells at least 3 times before antiglobulin is added.</td>
<td>Addition of sensitised blood cells to negative test</td>
<td>Each negative test</td>
</tr>
<tr>
<td>6. Testing for high-titre anti-A and anti-B (in donors)</td>
<td>Use of A₁ – and B – RBC, Titration in saline or in antiglobulin test with plasma (serum) diluted 1:50.</td>
<td>Serum samples with an amount of immune anti-A and immune anti-B respectively above and below the accepted saline agglutination titre of anti-A and/or anti-B(16). Using antiglobulin test one control sample should give positive result and the other negative result.</td>
<td>Each test series</td>
</tr>
<tr>
<td>7. Testing for irregular allo-antibodies (in donors)</td>
<td>Use of antiglobulin test or other tests with the same sensitivity.</td>
<td>Serum samples with known RBC-alloantibodies</td>
<td>Occasional input by the supervisor of the laboratory and participation in external proficiency testing exercises</td>
</tr>
<tr>
<td>8. Testing for irregular alloantibodies (in patients)</td>
<td>Use of at least the indirect antiglobulin test or manual or automated testing with equivalent sensitivity and homozygous RBC for the main clinically important antigens.</td>
<td>As for 7</td>
<td>As for 7</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>9. Compatibility testing (including ABO and D-typing in donor and recipient RBC and test for irregular antibodies in patient serum)</td>
<td>Use of at least the indirect antiglobulin test manual or automated testing with equivalent sensitivity.</td>
<td>As for 7</td>
<td>As for 7</td>
</tr>
<tr>
<td>10. Type and screen</td>
<td>Typing – as 1, 2, 3 and 4 with at least antiglobulin test, against a panel of cells chosen to provide homozygosity for important antigens.</td>
<td>As for 7</td>
<td>Each test series but at least daily</td>
</tr>
</tbody>
</table>

1 When reverse grouping is undertaken, the two tests may be performed using the same reagents.
2 If ABO and RhD blood group is already known, a single test is sufficient.
External quality assurance
In external quality assurance, proficiency tests coded “normal” and “problem” blood samples are distributed from a national or regional reference laboratory to the participants, at least twice a year. The exercise can be limited to compatibility testing, since ABO-grouping, Rh-typing and -phenotyping as well as alloantibody detection will be automatically included. The proficiency test panel may consist of four to six blood samples, the participants being asked to test each RBC against each serum (or plasma) for compatibility. The panel should be composed in such a way that compatible as well as incompatible combinations occur. Asking for titration of 1 or 2 of the detected antibodies may complete the proficiency test.

In the reference centre the results are collated and accuracy scores determined. The results should be communicated to all participating laboratories (in coded or uncoded form, according to local agreement) in order to enable each laboratory to compare its own quality standard with that of a large number of other laboratories including the reference centre.

If no proficiency programme is available in a particular geographical area, the laboratory should arrange mutual proficiency testing with another laboratory. Although such an external quality control will not be as informative as participation in a comprehensive proficiency-testing programme, it will be a valuable addition to the internal quality control procedure.

Quality control of antibody quantitation
For practical purposes, RBC antibody quantitation is confined to the quantitation of anti-RhD. It is recommended that this be carried out by automated techniques rather than by manual titration, the test serum being assigned an anti-RhD value expressed in international units per millilitre after comparison with a curve derived from standard sera. All sera should be tested in duplicate as a minimum, and all national and in-house standards calibrated against the international standard for anti-RhD. Records should be kept of the data derived from processing the standard sera; these figures should show no more variance than 2 standard deviations. If automated technique is not available, manual titration by antiglobulin test is recommended.
Chapter 9

Principles of screening for markers of infection

Paragraph 1. Overview (general comments for all mandatory tests)

The quality assurance of screening of donations for infectious markers is particularly important and implies both general and specific approaches.

Only tests that have been licensed or evaluated and considered suitable by the responsible Health Authorities can be used. In the EU, these reagents are considered as \textit{in vitro} diagnostic devices and must be CE marked. EU Directive 98/79/EC classifies the HIV, HTLV, hepatitis B, C screening tests in list A, Appendix II. The manufacturer must have a full Quality System certified by an authorised body and submit an application containing all the control results for each lot.

In addition proper validation demonstrates control, generates useful knowledge of the test and establishes future requirements for e.g. internal quality control, external quality assurance, calibration and maintenance of equipment and training of personnel.

There must be special emphasis on training of staff, assessment of staff competency, maintenance and calibration of equipment, monitoring of storage conditions of test materials and reagents, with documentation of all these actions.

Current tests for the screening of donations are based on the detection of relevant antigen and/or antibody and gene sequences.
It is further recommended that the tests include an external weak positive control in order to allow for statistical process control.

Ideally confirmatory tests should be as sensitive as and more specific than those used for screening. However, some screening tests are more sensitive than the available confirmatory tests. It is recommended that national algorithms be developed to enable consistent resolution of problems associated with discordant or unconfirmed results.

**Paragraph 2. Algorithm for infectious markers screening and confirmatory testing**

The following is an example of a widely used algorithm:
1. E.g. a repeatedly reactive serological screening test or a positive NAT on a single donation.

Confirmatory testing is performed in a certified or accredited medical microbiology reference laboratory, which is responsible for results, and may use tests at its discretion. The confirmatory lab should be kept informed about the type of screening test used by the blood establishment, and is contracted to use tests at least as sensitive as screening test and if feasible based on other principles.

2. The confirmatory laboratory is contracted to provide overall confirmatory test results or interpretation as follows: “positive,” which means infected, “negative” which means not infected, or “indeterminate,” which means a diagnosis cannot be established, the latter may include a demand for follow-up testing. In the situation where a confirmatory test(s) is less sensitive than the screening assay, the conclusion of confirmatory testing should read: "uncertain" (unless positive).

3. The establishment keeps a donor record allowing longitudinal recording of confirmatory laboratory test results as: screening test positive, confirmatory lab positive, negative or indeterminate.

4. The confirmatory laboratory is contracted to keep longitudinal records of unique donor ID linked to lab test results.

5. Refer donor to a medical doctor (general practitioner or specialist). Inform plasma fractionation centre(s) if plasma from earlier donation(s) has been issued. Inform hospital(s) to allow look back if component(s) from earlier donation(s) have been issued.

The specific approach to quality of the screening must rely on the following categories of measures:

a. Internal day-to-day quality control covering both reagents and techniques. Batch pre-acceptance testing (BPAT) of new batches of kits should be performed as an additional quality assurance measure;

b. External quality checks, in particular confirmation of positive findings should be carried out by an appropriate laboratory;

c. Occasional internal exercises, using a panel of sera which have been built up by comparison with standards available;

d. External proficiency exercises, involving the testing of a panel of sera circulated to laboratories by an approved reference institution;

e. Collection of representative data may be useful to monitor test performance.
It is recommended that repeatedly reactive rates and confirmed positive results of screening for infectious markers and epidemiological data be collected and monitored at least on a national level as part of a haemovigilance system. This will allow international comparisons to be made.

It should be noted that following hepatitis B immunisation, a transient positive HBsAg result may be obtained.

**Paragraph 3. Confirmatory testing**

**Anti-HIV-1/2, anti-HCV and HBsAg testing**

The approaches currently used to confirm HIV or HCV infection consist of the use of a nationally established algorithm, which may include alternative Enzyme-linked immunosorbent assay (ELISA), Western blot or recombinant immunoblots. Tests for antigens and the use of the Nucleic acid amplification techniques (NAT) may be of value in the interpretation of uncertain antibody test results. The positive confirmatory test should be repeated on a further sample taken between 2 and 4 weeks after the first.

Confirmation of HBsAg reactivity should include specific neutralisation. The stage of infection of the donor may be determined by anti-HBc (total and IgM specific) and HBe antigen/antibody (HBeAg/anti-HBe).

**Anti-HBc testing**

Selected donors may be tested by an approved test that will detect antibody to hepatitis B core antigen (anti-HBc). The approach to confirmation should be dependent on a nationally established algorithm. Supplemental testing, such as anti-HBs and NAT, may influence local decisions about the acceptability of donors.

**Syphilis testing**

There is a continuing discussion over the need to test blood donors for syphilis, but the test may be used as an indicator of risk behaviours for sexually transmitted diseases and is still required by most countries. Most centres use either a cardiolipin test employing a lecithin-based
antigen either manually or on blood grouping machines, or a test employing a variant of the *Treponema pallidum* haemagglutination assay (TPHA). An ELISA test is occasionally used. Positive syphilis screening results must ideally be confirmed by TPHA, fluorescent Treponemal antibody test (FTA), or an immunoblot test.

**Anti-HTLV testing**

The approach to confirmation is similar to HIV and includes nationally established algorithms as well as specific assays including immunoblotting and NAT. Sensitive tests for genome detection including typing may be helpful in defining the infection status of the donor.

**Chagas testing**

The blood of persons who were born or have been transfused in areas where the disease is endemic can be selected to be tested for *T. cruzi* antibodies. Plasma for fractionation is exempt from such a test procedure.

**Paragraph 4. Nucleic acid screening (HCV- and HIV-NAT) in mini-pools**

The Committee for Medicinal Products for Human Use (CHMP) recommended for HCV a strategy of pretesting by manufacturers of mini-pools (of donations or of samples representative of donations) in order to avoid the loss of a complete manufacturing pool and to facilitate tracing back to the donor in the event of a positive test result.

In order to achieve a sensitivity which will detect 5000 IU/mL of HCV RNA for donations which are tested in mini-pools of say 100; 50 IU/mL should be detected with 95% confidence by the NAT assay. Each assay run should include an external run control (usually at 3 times the 95% detection limit). This reagent must be reactive in every run. The external run control may be omitted if the test is licensed (CE marked) with other procedures to warrant robustness.
Paragraph 5. Additional serological testing

CMV testing

Testing for CMV antibody is most commonly performed using ELISA and Latex particle agglutination test. The screening of donations for anti-CMV negativity will enable the formation of a panel of anti-CMV negative donations for use in highly susceptible patients.

Malaria testing

At present, only a few reliable and robust malaria antibody tests are commercially available. Any malarial antibody testing requirement requires integration within local approaches to donor history taking. If malaria antibody testing is used to determine donor acceptance or rejection, the test employed should be shown to detect antibodies to the malaria types that are likely to pose a risk through transmission by transfusion. NAT for malaria cannot at present be recommended for use in blood donor selection, as it may fail to detect a small number of parasites in a blood donation that is nevertheless sufficient to infect a transfusion recipient. Confirmation of reactivity in malaria antibody tests should be performed by a competent and certified reference laboratory able to define the infectious state of the donor. Users need to be aware that assays may depend on the detection of heterotypic antibodies. Users must ensure that the assay detects antibody to the *Plasmodium* species prevalent in their donor panel.
Chapter 10

Principles of pre-transfusion and transfusion measures

Paragraph 1. Blood group serological investigations

These include blood typing, antibody screening and compatibility testing before transfusion of red cell components.

Blood typing

It is further recommended that antibody screening for the detection of irregular red cell antibodies be carried out in conjunction with patient blood typing.

The normal procedure is to make the investigations in due time before expected transfusions, e.g. in elective surgery. However in emergency situations bloodtyping may be carried out in parallel with transfusion of the blood components.

Compatibility testing

The basis for compatibility is a correctly determined ABO and RhD blood type in donor and recipient.

It is recommended as a routine procedure even when no antibodies have been found but may be omitted if other measures (e.g. type and screen, see below) are taken to guarantee safety. The compatibility testing shall include a sufficiently reliable and validated technique to guarantee detection of irregular red cell antibodies, such as the indirect antiglobulin technique.
Type and screen

A type and screen procedure, where used as a replacement for compatibility testing, must include:

- a reliable and validated, preferably by computer, checking procedure when the blood units are delivered;
- reagent red cells which cover all antigens, preferably homozygous, corresponding to the vast majority of clinically important antibodies;
- sufficiently sensitive techniques for the detection of red cell antibodies;
- laboratory records of tests performed and of the disposition of all units handled (including patient identification).

Paragraph 2. Pre-transfusion measures

Identification of patient at blood sampling

Patient identification should be indicated on the tube label at the time of sampling. Family name and given name and date of birth are minimal requirements for identification but should be supplemented by a unique, medical identification. In newborn infants, the gender and the number on the identification wrist band is noted in addition. If it is not possible to establish a patients’ identity, a unique series of numbers may be used on wrist bands and attached to the patient according to specified rules.

The identification system should link the patient identification, the operator, the blood sample through processing and the blood component and should confirm the original patient identification at the time of blood administration. Emphasis must be placed on error recognition.

At the time of sampling, the data on the tube label must be checked either by asking the patient to state his/her name and date of birth, and/or by reading these or other data on a wrist band securely attached to the patient. This identity control shall be done even if the patient is known to the venipuncturist.
Blood samples which are inappropriately labelled should always be refused for blood typing and/or compatibility testing.

The time when transfusion is started, interrupted and stopped, must be clearly marked in patient records as well as vital signs or any others symptoms suspected from transfusion reaction.

**Paragraph 3. Transfusion**

**Safety measures**

Verification of identity should be carried out both by asking the patient to tell his/her name and date of birth and by reading these or other identification details on a wrist-band which has been attached to the patient according to well-specified rules.

Verification that the relevant infusion equipment is being used according to manufacturer’s recommendations shall be carried out by a medical officer before attaching the blood components unit. It is recommended that no transfusion sets are used for more than 6 hours. Verification that there is no visible deterioration of the blood components shall be carried out with particular emphasis on discolouration.

Verification of compatibility between patient and blood unit shall be carried out by:

- comparing the identity information received from the patient with data on the laboratory's certificate of compatibility testing (if appropriate);
- checking the certificate of the patient’s blood group against the blood group denoted on the blood components label; (bed side testing can be done to confirm blood groups of the donor and patient);
- checking the identification number of blood units on the laboratory's certificate matches with the identification number on the blood unit labels;
- checking that the expiry date of the blood unit has not been passed;
- recording the identity of the patient.
Clinical surveillance

Observation of the transfused patient is essential. Vital signs such as blood pressure, pulse and temperature should be measured before starting the transfusion, and ideally at intervals 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.

The time when transfusion is started, interrupted and stopped, should be clearly marked in patient records as well as vital signs or any others symptoms that could indicate transfusion reaction.

It is also important to determine the efficacy of the transfusion of the specific component by recording appropriate pre- and post transfusion parameters.

Confirmation of transfusion should be sent back to the hospital blood bank.

Surveillance procedures should be described in SOPs and personnel should be trained.

Paragraph 4. Handling and storage of blood in the hospital

Before transfusion the quality and the safety of blood components have to be maintained in the hospital or clinic by handling and storage according to the recommendations of the blood establishment that distributed the product(s). To avoid compromising clinical effectiveness and safety, blood components should be transfused within the time limits required by local procedures.

Relevant staff should be properly trained in the principles and practice of handling different types of blood components and written SOPs should be readily available for use.
Warming of blood

Hypothermia induced by rapid/massive transfusion (more than 50 mL/kg/h in adults and 15 mL/kg/h in children) increases the risks such as organ failure and coagulopathy.

Handling of frozen units

Frozen units have to be handled with great care since the containers may be brittle and may easily crack at low temperatures.

Air embolism

During blood transfusion, air embolism is possible under some circumstances if the operator is not sufficiently careful and skilful.

Paragraph 5. Transfusion complications

Transfusion complications include adverse reactions and also failure of expected therapeutic response (for definitions see Chapter 11 Principles of haemovigilance).

As each transfusion of blood components is a separate biological event, careful recording and reporting of any observed reaction is the responsibility of the attending physician.

Adverse reactions may occur, either in direct relation to the transfusion or with a delay of hours, days or months.

In the case of an immediate adverse reaction, the transfusion bags should not be discarded. A new sample should be taken from the patient and sent to the hospital blood bank together with the transfusion bags and the transfusion reaction report for further investigations.

When a serious adverse reaction after transfusion of red cell preparations has occurred and the patient shows chills, fever, breathing difficulties, shock, or hypotension, back pain (which cannot be
related to the patient's underlying disease) the following should be investigated:

- check all identification of recipient and blood component.
- check that the ABO and RhD blood group of the blood unit label is compatible with the patient's blood group certificate. If irregular antibodies outside the ABO and RhD systems are present, check if blood of compatible blood type has been used.
- a blood sample taken before the transfusion (may be available at the compatibility testing laboratory); a blood sample taken after the transfusion, the blood unit with the transfusion set maintained in site, and the pilot tube or a segment should be sent for investigation.
- it is recommended that this include a direct smear and a bacterial culture test of the content of the blood unit, a serological investigation for blood group incompatibility, and inspection of the blood unit for any damage.

Mild reactions are managed according to the judgment of the responsible physician.

In the case of repeated, febrile non haemolytic transfusion reactions, the use of leucocyte or buffy coat-depleted blood for subsequent transfusions is recommended.

Long term adverse reactions may occur. These include alloimmunisation and infectious disease transmission.

There should be co-operation between the physician and the hospital blood banks to facilitate investigations of possible transfusion transmitted infections and to provide medical follow up of recipient in cases where a donor is subsequently found to have seroconverted.

Appropriate follow up and patient counselling is also necessary when significant alloimmunisation against transfused cells may have taken place (see Chapter 11 Standards of hemovigilance).
Paragraph 6. Hospital transfusion committees

Establishment of hospital transfusion committees is to be encouraged.

A hospital blood transfusion committee should include representatives of the blood establishment and the main clinical units with a significant transfusion activity. It is recommended that physicians, nurses and administrative personnel be represented.

The main goals of a hospital blood transfusion committee are:

- to define blood transfusion policies adapted to the local clinical activities;
- to conduct regular evaluation of blood transfusion practices;
- to analyse any adverse reaction and event due to blood transfusion;
- to take any corrective measures if necessary;
- to ensure that all staff involved in transfusion practice receive adequate training.

Similarly, systems of audit of the clinical use of components will further enhance the efficacy of transfusion practice.
Chapter 11

Principles of haemovigilance

Paragraph 1. Overview

Haemovigilance is defined as the organised surveillance procedures related to serious adverse or unexpected events or reactions in donors or recipients and the epidemiological follow up of donors.

The ultimate goal of haemovigilance is to prevent the recurrence of adverse events and reactions. For that purpose, the results of data analysis should be fed back periodically to their providers and communicated to any competent authority, indicating, whenever possible, any preventive or corrective measure to be adopted.

Haemovigilance should also incorporate an early alert/warning system.

Haemovigilance provides useful information on the morbidity of blood donation and transfusion, and gives guidance on corrective measures to prevent the recurrence of some incidents. Moreover, haemovigilance is considered as a part of total health care vigilance, along with pharmacovigilance, and vigilance on medical devices.

The information provided by haemovigilance may contribute to improving the safety of blood collection and transfusion by:

- providing the medical community with a reliable source of information about adverse events and reactions associated with blood collection and transfusion;
indicating corrective measures required to prevent the recurrence of some incidents or dysfunctions in the transfusion process;

- warning hospitals and blood establishments about adverse events and reactions that could involve more individuals than a single recipient, including:
  - those related to the transmission of infectious diseases;
  - those related to blood bags, solutions or blood processing.

**Paragraph 2. Prerequisites for implementation of a haemovigilance network**

Haemovigilance should be a responsibility of the competent national authority for blood safety. Haemovigilance networks should embody operational linkages between clinical departments, hospital blood banks, blood establishments, and national authorities.

**Traceability of blood components**

Traceability, which is a prerequisite for haemovigilance, may be defined as the ability to trace each individual unit of blood or blood components derived from it from the donor to its final destination, whether this is a patient, a manufacturer of medicinal products or disposal, and vice versa.

The essential element for traceability is a unique identification numeric or alphanumeric code for each donation, with a subsidiary code for each component prepared from that donation (Recommendation No. R (96) 11 of the Council of Europe on Documentation and record-keeping to guarantee the traceability of blood and blood components especially in hospital). This unique identifier must be linked with data identifying both the donor and the recipient, so that all patients transfused with a particular donor’s blood or all donors who donated the blood components a patient received may be traced.

Traceability is essential for:

- tracing retrospectively a possibly infectious donor in case of transmission of an agent to a recipient;
principles. chapter 11

- tracing retrospectively a possibly infected recipient in case of infectivity of a donor;
- tracing recipients in case of systemic problems putting recipients at risk of serious adverse reactions or events.

traceability can provide information on the total number of:
- patients that have been transfused;
- blood units or components that have been issued or used;
- blood donors that have provided the transfused blood units or components.

without this information, it is difficult to calculate the incidence of adverse events and reactions and thus to estimate risk. the number of adverse events and reactions, over a given time period, may help in identifying critical issues within the process.

information systems should be available to facilitate rapid traceability by using patients, blood components and donors as data-access keys. to ensure the reliability of the data base, confirmation that the blood component was transfused to the patient for whom it was issued is needed. without this, proving the link between donor and patient would require verification in the patient's notes that the blood component had been transfused. the document confirming the transfusion should also include information on the existence or nonexistence of immediate adverse events or reactions.

by these systems the following data should be made unmistakeably available:

- personal data uniquely identifying the donor and providing a means to contact him/her;
- the blood establishment in which blood or blood component collection has been carried out;
- the date of donation;
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- the blood components produced and additional component information, if appropriate;
- the blood establishment or hospital blood bank to which the blood component has been distributed, if different from the production facility;
- the hospital and the ward to which the blood component has been issued for transfusion;
- the date and time of issue;
- the final fate of the unit; either the identity of the patient who received it or other use (e.g. quality assurance, reagents, discards, etc.);
- the date and starting time of transfusion.

In case of blood components that have not been issued for transfusion, data should be available to identify the facility where the units have been used or disposed of.

**Co-operation between blood establishments, hospital blood banks and clinical departments**

The responsibility of reporting adverse events and reactions does not imply the responsibility for individual patient’s care.

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.

This co-operation is essential to ensure a complete investigation of any adverse event or reaction including uneventful transfusion errors. In the blood establishment and/or in the hospital blood bank, the physician involved may be the one responsible for blood component delivery, or a physician specifically in charge of haemovigilance. Similarly, in the clinical departments, the involved person can be the physician in charge of the patient, or another physician specifically in charge of haemovigilance.
In case of serious adverse reactions in blood recipients, which may be related to the transfused blood components, notification should be sent as soon as possible to the blood establishment where the components have been collected.

Prompt reporting enables the blood establishment to take action to block blood components from related donors, donations or production methods.

Serious adverse reactions include: acute haemolytic transfusion reaction, sepsis due to bacterial contamination, delayed haemolysis, transfusion related acute lung injury, transfusion associated graft versus host disease, transfusion transmitted infectious diseases, anaphylaxis, transfusion-associated circulatory overload.

**Paragraph 3. Types of adverse reactions and adverse events collected in a haemovigilance network**

**Adverse reactions in patients**

Adverse reactions associated with transfusion of blood components are the primary scope of a haemovigilance system, which should collect reports concerning patients of events such as:

- immediate adverse reactions during transfusion, such as haemolysis, non haemolytic febrile transfusion reaction, rash, erythema, urticaria, anaphylactic shock, bacterial contamination, TRALI, Transfusion Associated Circulatory Overload (TACO), acute GvHD, etc.;
- delayed adverse reactions after transfusion, such as haemolysis, post-transfusion purpura, ALT increase, iron overload, etc.;
- bacterial, viral, parasitical or TSE transmission;
- occurrence of alloimmunisation against red cell, HLA or platelet antigens.

The rules for reporting may differ according to the type and severity of adverse reaction. In case of minor reactions such as non haemolytic
febrile transfusion reaction, rash, erythema and urticaria, individual reports should be sent only by the clinical departments to the blood bank, which, depending on the organisation of the haemovigilance network, may send periodic reports to its blood establishment or to the competent authority concerning the incidence of such events.

This applies to any event that may involve several individuals, and to serious hazards. Moreover, in case of viral transmission the extent of required investigations should be clearly defined.

**Adverse reactions in donors**

See also Chapter 3 *Principles of blood collection*.

Adverse reactions in donors in are defined as an unintended response in a donor associated with the collection of blood or blood components.

Adverse reactions in a donor should be fully documented in donor records and Serious Adverse Reactions should also be documented in the Quality System records.

Haemovigilance for donors may:

- allow the creation of a list of adverse events and reactions in relation to blood collection;
- allow analysis of data and enhance safety of blood collection by implementing corrective actions to prevent recurrence of incidents;
- allow analysis of data and improve transfusion safety depending on donor selection (frequency and causes of blood donation exclusion) and epidemiological follow up of donor population (confirmed positive donors in infectious marker screening);
- allow tracing of donors in case of an emerging threat to safety of blood components (such as a new endemic situation).

Adverse events related to blood donation can occur in several fields:

- donor selection: the donor does not fulfil the local medical selection criteria but has been given clearance for donating blood
(with possible consequence on his health or quality of blood components): e.g. insufficient haemoglobin level before donation, insufficient weight;

- blood collection: inappropriate procedure: e.g. inadequate volume of blood lost during blood or blood component donation, inadequate volume of anticoagulant used for apheresis procedure;

- donor suitability: post-donation information may have consequences for the safety of donated blood components.

Both adverse events and reactions in donors may also have consequences on the quality of the donated blood components.

Data concerning adverse reactions and adverse events in donors should be collected and evaluated within the blood establishments and where appropriate reported at least annually to the national haemovigilance system. Information on adverse events and reactions in donors should be considered as part of the haemovigilance system.

**Adverse events**

Adverse events are defined as any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to an adverse reaction in blood recipients or blood donors.

Serious adverse events are those which might (but did not) lead to death or life-threatening, disabling or incapacitating conditions for patients or donors, or which might (but did not) result in prolonged hospitalisation or morbidity. Examples of these serious adverse events are failures to detect an infectious agent, errors in ABO typing, wrong labelling of donor blood samples or blood components, for instance in cases where the components were not transfused. Directive EC 2002/98 requires that these events are to be notified.

“Near-miss” events are a subgroup of adverse events, defined as any error, which if undetected, could result in the determination of a wrong blood group or failure to detect a red cell antibody, or
issue, collection, or administration of an incorrect, inappropriate or unsuitable component, but which was recognised before transfusion took place.

Adverse events include incorrect, inappropriate or unsuitable blood component transfusion which did not lead but could have led to harm to the recipient. For example, administration of a mismatched ABO compatible component or failure to give irradiated components when prescribed.

Notification of adverse events, which are transfusion errors that do not cause an adverse reaction, may help to identify weaknesses in the clinical transfusion process and so reduce risk. The haemovigilance system should inform relevant staff of the importance of adverse event reporting. It should provide a system for reporting new misses with anonymisation to protect individuals from blame and to stimulate voluntary reporting.

Information technology systems may facilitate reporting and analysis of haemovigilance data.

**Device defects**

Reporting of device defects can be viewed as part of haemovigilance (see Standards).

**Paragraph 4. Tracing and recall of potentially infectious donations for HIV, HCV or HBV (look-back)**

**Post-transfusion infection in a recipient reported to the blood establishment**

Hospitals must inform the blood establishment whenever a recipient of blood components develops laboratory tests results and/or disease symptoms, indicating that a blood component may have transmitted an infectious agent (see Standards).
It is important that the blood establishment is informed without delay by the hospital, so to allow further action on implicated donations and donors, in order to prevent harm to other recipients.

Test results from donations of the implicated donors may be re-analysed, or additional or confirmatory tests on archived samples or freshly obtained samples from the implicated donors may be performed with the aim to exclude HIV, HCV or HBV infection in the donor(s). If such analysis reasonably excludes infection, such donor(s) may be re-released for future donations, and (temporarily) blocked components derived from their donations may be re-released.

Where feasible and appropriate, the blood establishment should (temporarily) defer all implicated donors from further donations, and retrieve (temporarily) or quarantine all in-date components for transfusion collected from the implicated donors.

Whenever an implicated donor is found with a confirmed positive test for HIV, HCV or HBV infection, the blood establishment should act accordingly with regard to deferral of the donor and look-back procedure on previous potentially infectious donations and inform the hospital concerned.

The incident should be reported to the national haemovigilance system and/or competent authorities.

**Post donation information**

The blood establishment should (temporarily) block all in-house components from the donor and retrieve all in-date components. The relevant plasma fractionation institute must be notified.

The blood establishment should perform a risk analysis to assess whether the incident indicates a potentially infectious blood component for recipient(s). Test results from donations of the implicated donors may be re-analysed, or additional or confirmatory tests on archived samples or freshly obtained samples from the donor may be performed.
In case a confirmed HBV, HCV or HIV infection is shown in the donor, the blood establishment should defer the donor and undertake look back procedure on previous potentially infectious donations.

**Recall of blood components**

The blood establishment retrieves in-date blood components from the hospital(s) as a precautionary measure in case of a quality deviation (HBV, HCV or HIV). This may be a temporary measure and implies that certain retrieved blood components may be re-released after proper risk analysis and/or additional testing. The measure is taken in order to prevent harm to potential recipients. The relevant plasma fractionation institute must be notified.

**Tracing of recipients of potentially infectious blood donations (look-back)**

The blood establishment initiates a look-back procedure which is aimed at the tracing of recipients of blood components from a potentially infectious blood donation and notification of these recipient(s) by their treating physicians, whenever a blood donation may have taken place within the window period of a (repeat) donor with a confirmed HIV, HBV or HCV infection. Implicated donations include those within a time frame equal to the maximum test specific window period of the infection, preceding a negative screening test result in the donor.

The blood establishment should inform the hospital in writing about the incident and advise the hospital to trace the recipient(s) of the implicated blood component(s) and inform the treating physician about the potentially infectious transfusion. The relevant plasma fractionation institute must be notified.

It is the responsibility of the treating physician to inform the recipient about the potentially infectious transfusion, unless there are medical arguments not to do so. If the recipient is tested, in order to establish or to exclude the infection, the blood establishment should be informed by the
If testing of the recipient is not performed, the blood establishment should also be informed of this by the hospital.

If the recipient is confirmed to be positive for the infection the incident is reported to a national haemovigilance system and/or competent authorities.

Consistent with the recommendations of the competent public health authority, blood establishments should consider the need to trace and notify blood component recipients and/or their physicians in cases where a blood donor subsequently is diagnosed with vCJD infection.

**Paragraph 5. Contract between the blood establishment and hospital for haemovigilance**

In those situations in which blood collection and processing is carried out in facilities located outside the hospitals, the above procedures may be described in the contract(s) between the blood establishment and the hospital(s).

**Minimum information to be captured in the initial incident report at hospital level**

Information about transfused patients must be managed according to the country’s confidentiality requirements. Patient identifiers reported should include at least date of birth, gender, and unique case number. Clinical signs observed should be documented, in a standardised fashion, either specific for a given adverse event or reaction, or the same form for every untoward effect. Clinical outcome of an adverse reaction should be stated.

**Paragraph 6. Reporting haemovigilance data**

**Standardisation of reporting**

Reports of adverse events and reactions should be made in the same way in all the institutions that participate in the haemovigilance network. This implies not only the use of common report forms, but
also a common training programme ensuring among all participants a similar way of interpretation for a given incident, and a common and agreed definition of the different types of adverse events and reactions. In this respect, the persons specifically in charge of haemovigilance may contribute to the standardisation both of reports and of definitions.

In practice, to be achieved, standardisation of reporting requires an active training policy initiated inside the network.

**Data analysis**

All the reports should be carefully analysed before inclusion in the haemovigilance data base which can be exploited at different levels: institutional, regional, national or international. Whatever the magnitude of the network, an individual institution should have permanent access to its own data.

**Information sent to the haemovigilance database**

Information about transfused patients must be managed according to the country’s confidentiality requirements.

**Component information**

This information should include a detailed prescription of the component involved:

- unit number and adequate codes for components;
- description of the component, including:
  - the type of component, i.e. red cell, platelet or plasma;
  - the type of preparation, i.e. from whole blood or from apheresis;
  - other characteristics, i.e. leucocyte depleted, irradiated, plasma reduced, etc.;
  - conditions and duration of storage prior to transfusion.
**Information about severity**

Severity should be graded. A suggested scale is:

<table>
<thead>
<tr>
<th>Severity scale</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No clinical signs</td>
</tr>
<tr>
<td>1</td>
<td>Immediate signs without vital risk and full resolution</td>
</tr>
<tr>
<td>2</td>
<td>Immediate signs with vital risk</td>
</tr>
<tr>
<td>3</td>
<td>Long term morbidity</td>
</tr>
<tr>
<td>4</td>
<td>Death</td>
</tr>
</tbody>
</table>

**Information about imputability**

The possible relationship between the observed adverse reaction and the transfusion of blood components given (imputability) should be identified. A suggested scale is:

<table>
<thead>
<tr>
<th>Imputability scale</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Excluded: When there is conclusive evidence beyond reasonable doubts for attributing the adverse reaction to alternative causes.</td>
</tr>
<tr>
<td>0</td>
<td>Unlikely: When the evidence is clearly in favour of attributing the adverse reaction to causes other than the blood or blood components.</td>
</tr>
<tr>
<td>N/A</td>
<td>Not assessable: When there is insufficient data for causality assessment.</td>
</tr>
<tr>
<td>1</td>
<td>Possible: When the evidence is indeterminate for attributing adverse reaction either to the blood or blood component or to alternative causes.</td>
</tr>
<tr>
<td>2</td>
<td>Likely, Probable: When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.</td>
</tr>
<tr>
<td>3</td>
<td>Certain: When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to the blood or blood component.</td>
</tr>
</tbody>
</table>
Information about the type of adverse events and reactions

Report forms should enable differentiation between adverse events and reactions in patients and donors.

Report forms should include a brief summary describing the event as well as the corrective actions taken.

In order to provide an evaluation of the incidence of untoward effects, each participating institution should provide the number of blood components used per year and the number of patients transfused, together with details of all reported events.

Additional information about the current guidelines and procedures in regard to the use of blood components will be useful in comparison of results from different institutions or even different countries.
Chapter 1

Standards for a quality system for blood establishments

Paragraph 1. The quality system

Each Blood Establishment must develop and maintain a Quality System that is based on EU Good Manufacturing Practices (GMP) Directive 2003/94/EC and meets the requirements identified in the Directive 2005/62/EC.

The quality system must be designed to assure the quality and safety of manufactured blood and blood components and also ensure donor safety and customer service. The system must include a mechanism for evaluation and continuous improvement.

The quality system must cover all activities that influence the quality of the blood and blood components that are produced. This requires the development of clear policies, objectives and responsibilities, and implementation by means of quality planning, quality control, quality assurance and quality improvement in order to ensure the quality and safety of blood and blood components and to provide customer satisfaction.

The quality assurance system must ensure that all critical processes are specified in appropriate instructions, are performed in accordance with the principles of Good Practice and comply with appropriate regulations.
Management must review the system at regular intervals to verify the effectiveness of the system and introduce corrective measures if considered necessary.

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

A Quality Assurance Manager must be identified who will be responsible for the quality assurance function.

**Paragraph 2. Elements of the quality system**

**Validation and change control**

Every blood establishment must have a general policy regarding validation of equipment, facilities, processes, automated systems and laboratory tests. The formal objective of validation is to ensure compliance with the intended use and regulatory requirements.

All procedures, premises and equipment that have influence on the quality and safety of blood and blood components shall be validated prior to introduction.

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

**Personnel and organisation**

Sufficient numbers of appropriately qualified and experienced staff must be available in to perform all necessary tasks.

Only persons who are authorised by defined procedures and documented as such may be involved in the collection, manufacturing and distribution processes, including quality control and quality assurance.
All personnel must have clear, documented and up to date job descriptions. There must be an organisation chart showing the hierarchical structure of the blood establishment and clear delineation of lines of responsibilities.

All personnel must receive initial and continued training appropriate to their specific tasks. Training and competencies must be documented and training records must be maintained.

**Premises**

Premises must be located, constructed, adapted and maintained to suit the operations to be carried out.

Premises must enable effective cleaning and maintenance to minimise risk of contamination.

Processing and storage areas must be secured against the entry of unauthorised persons and must be used only for the intended purpose.

**Equipment and materials**

All equipment must be designed, validated and maintained to suit its intended purpose and must not present any unacceptable risks to donors or operators.

Regular maintenance and calibration must be carried out and documented according to established procedures. Operating instructions must be available and appropriate records kept.

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

All modifications, enhancements or additions to validated systems and equipment must be managed through the blood establishment’s change management procedure. The effect of each change on the system or equipment and the degree of required validation must be determined.
Instructions for use, maintenance, service, cleaning and sanitation must be available according to the instructions for use and operator’s manual.

Procedures must be available for each type of equipment, detailing the action to be taken when malfunctions or failures occur.

New and repaired equipment must meet qualification requirements when installed and authorised before use. Qualification results must be documented.

Only reagents and materials from approved suppliers that meet the documented requirements and specifications may be used. Where applicable by law, materials, reagents and equipment must meet the requirements of Directive 93/42/EC on medical devices in addition to Directive 98/79/EC on in vitro diagnostic medical devices.

Critical materials must be defined and released under the responsibility of QA function before use. The actual release may be performed by an authorised person under the guidance of a validated information technology system.

Inventory records must be kept for traceability.

**Documentation and record keeping**

A document control system must be established for review, revision history and archive of documents including Standard Operating Procedures (SOPs).

Each activity that may affect the quality of the blood and blood components must be described in an SOP.

Documentation must include an SOP governing development and revision of SOPs. This will ensure that work performed is standardised and that there is traceability of all steps in the process.

The recording system must ensure a continuity of documentation of all procedures performed, from the blood donor to the recipient, i.e. each significant step must be recorded in a manner that permits tracing in either direction of a component or procedure from the first step to final disposition.
Records must be retained for a period according to local or national requirements.

**Data processing system**

All computer software, hardware and backup procedures must be validated before use and checked regularly to ensure reliability. Hardware and software must be protected against unauthorised use or changes.

Systems must be properly maintained at all times. Documented maintenance plans must be developed and implemented. This must include quality assurance system audits.

A backup procedure must be in place to prevent loss of records as a result of expected or unexpected down time or function failures.

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

There must be a hierarchy of permitted user access to enter, amend, read or print data. Methods of preventing unauthorised entry must be in place, such as personal identity codes or passwords which are changed on a regular basis.

**Quality monitoring**

Acceptance criteria must be based on a defined set of specifications for each blood and blood component.

**Quality control**

All quality control procedures must be validated before use.

The results of quality control testing must be continuously evaluated and steps taken to correct defective procedures or equipment.
Standard procedures for the quality control of blood components must be in place. The suitability of each method to provide the intended information must be validated.

Quality control of blood and blood components must be carried out according to a defined sampling plan.

The testing must be performed in accordance with the instructions recommended by the manufacturer of reagents and test kits.

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

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

**Contract management**

Specific written contracts with suppliers must be developed to support tasks, including, component processing or testing, that are performed externally.

**Deviations, complaints, adverse events and reactions, recall, corrective and preventive actions**

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

There must be systems in place to ensure that complaints, adverse events or reactions are documented, carefully investigated for causative factors of the defect and, where necessary, followed by the implementation of corrective actions to prevent recurrence.

All errors and accidents must be documented and investigated in order to identify system problems for correction. This must include the identification of specific corrective and preventative actions.
The corrective and preventive actions system must ensure that existing component nonconformity or quality problems are corrected and that recurrence of the problem is prevented.

An effective recall procedure must be in place, including a description of the responsibilities and actions to be taken and guidance on the situations in which a recall may be required.

**Self inspection, audits and improvement**

Systems of regular self-inspection and internal audits must be in place in order to monitor overall compliance with the quality management system. Self-inspection and audit must be conducted independently by trained and competent persons from within the organisation, according to approved protocols.

All audit results must be documented and reported to management. Appropriate corrective actions must be taken.
Chapter 2

Standards for selection of donors

Paragraph 1. Overview

Measures must be taken to promote the collection of blood and blood components from voluntary non-remunerated donations according to the principles set 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 Biomedecine, CETS No. 164) and its Additional Protocol concerning Transplantation of Organs and Tissues of Human Origin (CETS No. 186).

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 limitation to donation of blood and blood components.

Paragraph 2. Information to be provided to the donor

The following information must be provided to prospective donors of blood or blood components:

a. 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.

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

- For allogeneic donations, self-deferral, and temporary and permanent deferral, and the reasons why individuals are not to 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 would not take place in the presence of a health risk to the individual whether as donor or recipient of the autologous blood or blood components.

c. 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.

d. The reasons why individuals are not to make donations which may be detrimental to their health.

e. Specific information on the nature of the procedures involved in the allogeneic or autologous donation process and their respective associated risks. For autologous donations, the possibility that the autologous blood and blood components may not suffice for the intended transfusion requirements.

f. All blood donors must be provided with accurate and updated information on HIV/AIDS and hepatitis transmission and provide the opportunity for self-exclusion so that those persons who have unsafe sex practices or other risk behaviour exposing them to potential infectious sources will refrain from donating.

g. Information on the option for donors to change their mind about donating prior to proceeding further, or the option to withdraw or self-defer at any time during the donation process, without any undue embarrassment or discomfort.
h. 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.

i. 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.

j. Information why unused autologous blood and blood components will be discarded and not transfused to other patients.

k. 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.

l. Information on the opportunity for donors to ask questions at any time.

**Paragraph 3. Medical assessment of the donor**

All donors must undergo a screening process to assess their suitability. Only healthy persons with a good medical history can be accepted as donors of blood or blood components.

The donor must be properly identified.

The selection process must include an assessment of each donor carried out by a suitably qualified individual, trained to use accepted guidelines and working under the direction of a physician. This assessment involves an interview, a questionnaire and further direct questions if necessary.

**Questionnaire and interview**

The questionnaire must be designed to elicit information relevant to the health and life style of the donor. It must be designed to be understandable by the donor and given to all donors each time they attend. On completion it must be signed by the donor.
A confidential interview must be conducted by specifically trained staff to ask further direct questions to supplement the information in the questionnaire. The person who carries out the assessment must certify that the relevant questions have been asked.

**Donor details**

There must be secure, unique donor identification, contact details and robust mechanisms linking donor to donation.

**Age of the donor**

The age limits for donation are minimum 18 years and maximum 65 years.

Where allowed by national legislation, bleeding donors may be considered at the age of 17.

Bleeding donors over 65 years of age is at the discretion of the responsible physician, as is the recruitment of any first-time donor above the age of 60.

**Donor appearance and inspection**

Special note must be taken in case of plethora, poor physique, debilitation, under-nutrition, anaemia, jaundice, cyanosis, dyspnoea, mental instability, intoxication from alcohol or drugs.

**Paragraph 4. Donor deferral**

Deferred donors must be given a clear explanation of the reasons for deferral.

Tables 2-1, 2-2 and 2-3 list conditions to deferral. Specific conditions for infectious diseases are listed in sections a) to k) of this paragraph.
Table 2-1. Conditions leading to permanent deferral (rejection)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer/Malignant Diseases</strong></td>
<td>Individuals with a malignant disease, or a history of such, are usually permanently deferred. The physician in charge may make exceptions to this rule in selected cases (see Principles).</td>
</tr>
<tr>
<td><strong>Creutzfeldt-Jakob Disease</strong></td>
<td>All individuals who have in the past been treated with extracts derived from human pituitary glands, have been recipients of dura mater or corneal grafts or who have been told of a family risk of Creutzfeldt-Jakob Disease or any other Transmissible Spongiform Encephalopathy.</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>If requiring insulin therapy.</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Any history of injectable drug abuse.</td>
</tr>
<tr>
<td><strong>Heart and blood vessel disease</strong></td>
<td>Persons with a history of heart disease, especially coronary disease, angina pectoris, severe cardiac arrhythmia, a history of cerebrovascular diseases, arterial thrombosis or recurrent venous thrombosis (see also Hypertension).</td>
</tr>
<tr>
<td><strong>Infectious conditions</strong></td>
<td>There are infectious states and diseases necessitating permanent deferral: Carriers of HIV 1/2, HTLV I/II, HBV, HCV Babesiosis&lt;sup&gt;1&lt;/sup&gt; Leishmaniasis (Kala-Azar)&lt;sup&gt;1&lt;/sup&gt; Chronic Q fever&lt;sup&gt;2&lt;/sup&gt; Trypanosomiasis cruzi (Chagas disease)&lt;sup&gt;2&lt;/sup&gt; (see also Infectious diseases) Persons, whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood.</td>
</tr>
<tr>
<td><strong>Xenotransplantation</strong></td>
<td>All recipients.</td>
</tr>
</tbody>
</table>

1 A family history of CJD carries a presumption of family risk unless it is determined that: (a) the affected family member had vCJD, not CJD; or (b) the affected family member did not have a genetic relationship to the donor; or (c) the cause of CJD in the affected family member was iatrogenic; or (d) the donor was tested and is known to have a normal genetic polymorphism for PrP<sup>1</sup>.

2 Deferral requirements may be waived by the blood establishment when the donation is used exclusively for plasma for fractionation.
Table 2-2. Conditions leading to temporary deferral (suspension)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Deferral period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy with biopsy using flexible instruments, inoculation injury, acupuncture, tattooing or body piercing, mucosal splash with blood, tissue or cell transplant of human origin</td>
<td>6 months or 4 months provided a NAT test for hepatitis C is negative.</td>
</tr>
<tr>
<td>Transfusion of blood components</td>
<td>6 months or for 4 months provided a NAT test for hepatitis C is negative. Injection of red cells as part of an approved immunisation programme will need clinical assessment.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Three years off treatment and without an attack.</td>
</tr>
<tr>
<td>Fever above 38 °C, flu-like illness</td>
<td>Two weeks following cessation of symptoms.</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>Acute glomerulonephritis: five years deferral period following complete recovery.</td>
</tr>
<tr>
<td>Medication</td>
<td>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 transfusion centre, be available. Donors treated with prescribed drugs, particularly those with proven teratogenic effect, should be deferred for a period consistent with the pharmacokinetic properties of the drug.</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Two years after having been declared cured.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>6 months after delivery or termination, except in exceptional circumstances and at the discretion of a physician.</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Two years following attack with no evidence of chronic heart disease. The latter complication is a cause for permanent deferral.</td>
</tr>
</tbody>
</table>
Following major surgery patients should not donate until they are fully recovered and fit to be donors, typically about six months.

If no complications, one week (because of possible risk of transient bacteraemia).

6 months following return from tropical areas and then only if they have not suffered an unexplained fever or illness (see Infectious diseases).

1 Exceptions could be made according to national risk assessment.

### Table 2-3. Prophylactic immunisations

<table>
<thead>
<tr>
<th>Inoculations, vaccinations</th>
<th>Deferral period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccines with attenuated bacteria and viruses: BCG, yellow fever, rubella, measles, poliomyelitis (oral), mumps, live attenuated typhoid fever vaccine, live attenuated cholera vaccine</td>
<td>Four weeks</td>
</tr>
<tr>
<td>Vaccines with killed bacteria Cholera, typhoid, capsular polysaccharide typhoid fever vaccine</td>
<td>Accept if well</td>
</tr>
<tr>
<td>Vaccines with inactivated viruses Poliomyelitis (injection), influenza</td>
<td>Accept if well</td>
</tr>
<tr>
<td>Toxoids Diphtheria, tetanus</td>
<td>Accept if well</td>
</tr>
<tr>
<td>Other vaccines Hepatitis A and B vaccine Hepatitis B vaccine Rabies, tick-borne encephalitis</td>
<td>Accept if well and no exposure (see section on jaundice and hepatitis) 1 week in order to prevent vaccine-related positivity in HBs antigen result Accept if well One year if post-exposure</td>
</tr>
</tbody>
</table>
Infectious diseases

a. HIV/AIDS

Persons whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood must be permanently deferred.

Current sexual partners of people with HIV must be deferred.

Previous sexual partners of people with HIV are acceptable after 12 months since the last sexual contact.

b. Brucellosis (confirmed)

Deferral for at least two years following full recovery.

The deferral period does not apply when the donation is used exclusively for plasma fractionation.

c. Chagas disease

Individuals with Chagas disease or who have had Chagas disease must be deferred permanently.

The blood of persons who were born or have been transfused in areas where the disease is endemic should be used only for production of plasma that is used exclusively for fractionation into plasma derivatives unless a validated test for infection with *T. cruzi* is negative.

d. Jaundice and hepatitis

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

Persons who have been in close household contact with a case of hepatitis B infection (acute or chronic) must be deferred for six months from the time of contact unless demonstrated to be immune.

Current sexual partners of people with HBV must be deferred unless demonstrated to be immune.
Previous sexual partners of people with HBV are acceptable after 6 months since the last sexual contact.

e. Malaria

Since questioning the donor as to the country(s) in which he was born, brought up or has visited is essential for effective detection, every blood establishment must have a current map or list of the endemic zones and time frames in the countries concerned.

*Persons who have lived in a malaria area for a continuous period of 6 months or more at any time in life:*

These persons may become asymptomatic carriers of the malaria parasite. Therefore, the following rules must apply to these individuals after each return from a malaria area:

- May be accepted as blood donor if the result of a validated immunological test for antibodies to the malaria parasite, performed at least 4 months after the last visit to a malaria area is negative.
- If the test is repeatedly reactive the donor must 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 must be deferred until the test is performed and negative.

*Persons who give a history of malaria:*

- Must be deferred until asymptomatic and off treatment.
- May be accepted as blood donor if the result of a validated immunological test for antibodies to the malaria parasite, performed at least 4 months since cessation of treatment/last symptoms is negative.
- If the test is repeatedly reactive the donor must be deferred and may be re-evaluated after a suitable period when the antibody test may have reverted negative (a period of 3 years is suggested).

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13 The tests and deferral periods may be waived by the blood establishment when the donation is used exclusively for plasma fractionation.
If the test is not performed the donor should be deferred until the test is performed and negative.

Persons who report an undiagnosed febrile illness consistent with malaria during or within 6 months of the end of a visit to a malaria area:

- May be accepted as blood donor if the result of a validated immunological test for antibodies to the malaria parasite, performed at least 4 months since cessation of treatment/last symptoms 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 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.

All other persons who have visited a malaria endemic area without reporting any clinical symptoms consistent with malaria:

- May be accepted as a blood donor if the result of a validated immunological test for antibodies to the malaria parasite performed at least 4 months after the last visit to a malaria endemic area is negative.
- If the test is repeatedly reactive the donor must be deferred and re-evaluated after a suitable period when the antibody test may have reverted negative (a period of 3 years is suggested).
- If the test is not performed, the donor may be re-accepted once a period of 12 months has elapsed after last return from a malaria area.

f. Q Fever
Deferral until two years following the date confirmed cured.

g. Syphilis
Deferral until one year following the date cured.

14 The tests and deferral periods may be waived by the blood establishment when the donation is used exclusively for plasma fractionation.
h. Toxoplasmosis
Deferral until six months following clinical recovery.

i. Tuberculosis
Deferral until two years after having been declared cured.

j. Variant Creutzfeldt-Jakob disease
Deferral of donors as a preventative measures for vCJD must be based on appropriate risk assessment.

k. West Nile virus
Deferral until 28 days after leaving an area with on-going transmission to humans of the disease. Persons with diagnosis of WNV must be deferred until 120 days after diagnosis.

**Paragraph 5. Specific standards for donors of different types of components**

**Whole blood donors**
A standard donation must not be collected from persons weighing less than 50 kg.

**Quantity of donation**
A standard whole blood donation exclusive of anticoagulants must not exceed 500 mL and usually consists of a donation of 450 mL ± 10%.

**Frequency of whole blood donations**
A maximum of 6 standard donations per year have to be taken from males. Up to 4 standard donations per year have to be taken from females, with a minimum interval between standard donations of two months.

---

35 The tests and deferral periods may be waived by the blood establishment when the donation is used exclusively for plasma fractionation.
These maximum donation rates must never be exceeded under any circumstances, and should only be adopted after careful consideration of the dietary habits of the populations 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.

**Laboratory examination**

- Haemoglobin concentration must be determined each time the donor attends to donate.

- Minimum values before donation:
  - female donors: 125 g/L or 7.8 mmol/L (minimum Haematocrit = 0.38);
  - male donors: 135 g/L or 8.4 mmol/L (minimum Haematocrit = 0.4).

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

**Apheresis donors**

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

Other than in exceptional circumstances (to be decided by the responsible physician), donors for apheresis procedures must meet the criteria for whole blood donations.

People with sickle cell trait must not donate by apheresis.

Donors taking medicinal drugs inhibiting platelet function must be temporarily deferred from donation by platelet apheresis.
Frequency of donation and maximal amounts of removal of plasma and red cells

The collection volume (excluding anticoagulant) for each plasmapheresis procedure must not exceed 16% of the estimated total blood volume. The individual total blood volume must be calculated on the basis of gender, height and weight. Alternatively a collection volume based on 10.5 mL per kg of body weight will meet this requirement.

The volume of plasma (excluding anticoagulant) collected one each occasion must not exceed 750 mL.

- A maximum of 33 plasmapheresis procedures may be performed per donor per year. This equates to a maximum annual collection volume of 25 litres based on the maximum volume of 750 mL plasma (excluding anticoagulant) per procedure.
- Not more than 1.5 L of plasma may be collected from one donor per week.
- In any combined collection of plasma, platelets and/or red cells in one apheresis procedure, the total volume of donated plasma, platelets and red cells must not exceed 13% of total blood volume with a maximum of 650 mL (exclusive of anticoagulant) unless fluid replacement is undertaken.
- The total amount of red cells must not exceed the theoretical amount of red cells that would bring the donor haemoglobin in isovolemic situation below 110 g/L or 6.8 mmol/L.
- The interval between one plasmapheresis or plateletpheresis procedure and a whole blood donation or single unit red cell apheresis (combined or not with plasma and/or platelet collection) must be at least 48 hours. The interval between a whole blood donation, an apheresis red cell collection or failed return of red cells during apheresis, and the next apheresis procedure without red cell collection, must be at least one month. The interval between two single unit red cell collections must be the same as for whole blood collections.
• The interval between whole blood donation and the donation of 2 units of red cells must be at least 3 months. The interval between a 2 unit red cell apheresis and whole blood donation or another 2 unit red cell apheresis must be at least 6 months for women and four months for men. Total red cell loss per year must not exceed that acceptable for whole blood donors.

**Additional requirements for donors undergoing plasmapheresis**

Protein analysis, such as determination of total serum or plasma protein and/or electrophoresis and/or quantitation of single proteins, especially albumin and IgG must be performed; total proteins may not be less than 60 g/L. This analysis must be carried out at suitable intervals but at least annually.

Additional requirements for donors undergoing thrombocytapheresis

• Platelet apheresis must not be carried out on individuals whose platelet count is less than $150 \times 10^9$ per litre.

• Donors must not be subjected to a platelet apheresis procedure more often than once every two weeks.

An exception for donation interval and platelet count may be made in the case of HPA or HLA matched donations, at the discretion of the physician responsible for the procedure.

**Paragraph 6. Post donation information**

Blood donors must be instructed to inform the blood establishment when signs or symptoms occur after a donation, indicating that the donation may have been infectious.
Paragraph 1. Premises for donor sessions

The premises must satisfy common sense requirements for the health and safety of both the staff of the mobile teams and the donors concerned, with due regard to relevant legislation or regulations.

Suitable facilities must be provided to allow interview with each donor assuring privacy and confidentiality.

Before premises are accepted for mobile donor sessions their suitability must be assessed against the following criteria:

- sufficient size to allow proper operation and ensure donor privacy;
- safety for staff and donors;
- the presence of ventilation, electrical supply, lighting, hand washing facilities, reliable communication, blood storage and transport.

Paragraph 2. Equipment used at blood donation sessions

Sterile collection systems must be used for collection of blood and blood components. These must be used in accordance with the instructions of the manufacturer. A check must be made before use, to ensure that the collection system used is not damaged or contaminated, and that it is appropriate for the intended collection. Defects in blood bags must be reported to the supplier and subject to trend analysis.
Paragraph 3. Pre-donation checks

The blood container must be inspected before use for defects, and must be inspected for the prescribed content and appearance of the anticoagulant solution. If one or more bags in any package is found to be abnormally damp all the bags in the package must be rejected.

The donor must be re-identified immediately prior to venepuncture.

Paragraph 4. Labelling

Laboratory samples must be taken at the time of each donation. Procedures must be designed to minimise the risk of microbial contamination of the collected blood or deterioration of the sample, and to prevent potential misidentification of samples.

The blood establishment must minimise the possibility of errors in labelling of blood containers and blood samples.

At the time of the blood donation, the blood container as well as those of the samples collected for testing must be labelled to uniquely identify the blood donation. The labelling system must comply with the relevant national legislation and international agreements.

The blood donation must be identified by a unique identity number which is both eye and machine readable. The labelling system must allow full traceability to all relevant data registered by the blood establishment about the donor and the blood donation.

Careful check must be made of the identity indicator of the donor against the labels issued for that donation.

The manufacturer’s label on the blood containers (blood plastic bags and bag systems) must contain the following eye readable information:

- the manufacturer’s name and address;
- the name of the blood bag and/or the name of the blood bag plastic material;
- the name, composition and volume of anticoagulant or additive solution (if any);
- the product catalogue number and the lot number.
Paragraph 5. Venepuncture, bleeding and mixing

Preparation of the venepuncture site

The skin at the venepuncture site must be free from lesions including eczema.

The venepuncture site must be prepared using a defined and validated disinfection procedure. The antiseptic solution must be allowed to dry completely before venepuncture. The prepared area must not be touched with fingers before the needle has been inserted.

The effectiveness of the disinfection procedure must be monitored and corrective action taken where indicated.

Successful venepuncture and proper mixing

The needle must be inserted into the vein at the first attempt.

A second venepuncture with a new needle in the other arm is acceptable.

Where an anticoagulant solution is used in the collection, the collection bag must be mixed gently immediately after start of collection and at regular intervals during the whole collection period. The flow of the blood must be sufficient and uninterrupted.

The maximum collection time for acceptance of the donation for component processing must be specified and controlled. Donations that exceed the maximum time period must be recorded and discarded.

If duration of the bleeding is longer than 12 minutes, the blood must not be used for the preparation of platelets.

If the duration of the bleeding is longer than 15 minutes, the plasma must not be used for direct transfusion or the preparation of coagulation factors.

When manual mixing is used, the blood bag must be inverted every 30-45 seconds. When an automated mixing is used, an appropriately validated system is required.
At completion of the donation, the donation number must be checked on all records, blood bags and laboratory samples. Donation number labels of a given donation that have not been used must be destroyed via a controlled procedure. Procedures to prevent mislabelling must be in place.

Each activity associated with the donation must be recorded. This also applies to any unsuccessful donations, the rejection of a donor, adverse reactions and adverse events. An authorised interviewer must sign the donor selection records and final assessment.

**Paragraph 6. Handling of filled containers and samples**

The blood container must be checked after donation for any defect. During separation from the donor a completely efficient method of sealing the tube is obligatory.

The blood bag and corresponding samples must not be removed from the donor’s bedside until labelling has been checked and found to be correct.

After collection, blood bags must be promptly placed into controlled temperature storage and transported to the processing site under temperature conditions appropriate for the component that will be prepared. Validation data must be available to demonstrate that the storage after collection and method of transport maintains the blood within the specified temperature range throughout the period of transportation.

**Paragraph 7. Special requirements for apheresis**

Separation and collection of blood components by cell separators requires premises of suitable size, regular service and maintenance of the machines, and adequately trained personnel for operating such machines.

The volume of extracorporeal blood must not exceed 13% of the donor’s estimated blood volume.
The donor must be observed closely during the procedure and a physician familiar with all aspects of apheresis must be available in order to provide assistance and emergency medical care procedures in case of adverse reaction.

Collection of adequate granulocyte yields by apheresis, requires premedication of the donor. Potential of risk to the donor must be evaluated against anticipated benefit to the intended recipient.

**Return of red blood cells of donors undergoing manual apheresis**

Since the biggest inherent danger in manual apheresis is an accidental interchange between two bags of concentrated red blood cells during their centrifugation and return to individual donors, a robust identification system must be in place.

**Paragraph 8. Repository of archive samples**

If archive samples from the donations are kept, then procedures must be in place prescribing the use and final disposal thereof.
Chapter 4

Standards for blood component preparation, storage and distribution

Paragraph 1. Processing

Preparation of blood and blood components must follow the principles of Good Manufacturing Practice (GMP) and comply with appropriate regulations.

The premises used for the processing of blood components must be kept in a clean and hygienic condition and the microbial contamination load on critical equipment, surfaces and in the environment of the processing areas must be monitored.

Procedures must detail the specifications for any materials that will influence the quality of the final blood component. In particular, specifications must be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

Procedures must be developed and validated for all processing activities. These must include time limits for the processing of blood components.

Sterile connecting devices must be used in accordance with a validated procedure. The resulting weld must be checked for satisfactory alignment and the integrity validated. When validated, connections made using sterile connecting devices are regarded as closed system processing.
Paragraph 2. Component labelling and information

Before use all blood components must be labelled with relevant information as to identity. The type of label to be used as well as the labelling methodology must be established in written procedures. Critical information must be provided in machine readable format to eliminate transcription errors.

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

Paragraph 3. Release of blood components

Each blood establishment must be able to demonstrate that a blood or blood component has been approved for release by an authorised person preferably assisted by validated information technology systems. The specifications for release of blood components must be defined, validated, documented.

Where release is subject to computer-derived information the following requirements must be met:

- The computer system must be validated to be fully secure against the possibility of blood and blood components which do not fulfil all test or donor selecting criteria, being released.
- The manual entry of critical data, such as laboratory test results, must require independent verification by a second authorised person.
- The computer system must block the release of all blood or blood components considered not acceptable for release. There must also be a means to block the release of any future donation from the donor.

In the absence of a computerised system for component status control, or in the event of computer system failure, the following requirements must be met:

- The label of a blood component must identify the component status and must clearly distinguish released from non-released (quarantined) component;
• Records must demonstrate that before a component is released, all current donor declaration forms, relevant medical records and test results have been verified by an authorised person;

• Before final component release, if blood or blood component(s) have been prepared from a donor who has donated on previous occasions, a comparison with previous records must be made to ensure that current records accurately reflect the donor history.

There must 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.

In the event that a final component fails release due to potential impact on patient safety then all other implicated components must be identified and appropriate action must be taken. A check must be made to ensure that (if relevant) other components from the same donation(s) and components prepared from previous donations given by the donor(s) are identified. The donor record must be immediately updated to ensure, where appropriate, that the donor(s) cannot make a further donation.

**Paragraph 4. Storage and distribution**

Storage and distribution routines must take place in a safe and controlled way in order to assure component quality during the whole storage period and to exclude identification errors of blood components.

All transportation and storage actions, including receipt and distribution, must be defined by written procedures and specifications.

Storage conditions must be controlled, monitored and checked. Appropriate alarms must be present and regularly checked; the checks must be recorded. Appropriate actions on alarms must be defined.

Intermediate storage and transport must be carried out under defined conditions to ensure that defined requirements are met.
Storage areas must provide effective segregation of quarantined and released materials or components. There must be a separate area for storage of rejected components and materials.

Prior to distribution, blood components must be visually inspected. There must be a record identifying the person distributing and the institution receiving the components.

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

**Paragraph 5. Ionising irradiation**

The protocol must ensure that no part of the component receives a dose less than 25 Gray or more than 50 Gray. Exposure time must be standardised for each radiation source and re-validated at suitable intervals.

Red cell components may be irradiated up to 14 days after collection and thereafter stored until the 28th day after collection. Exceptions are defined in specific monographs.

Regular dose-mapping of equipment must be performed. The exposure time must 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. The exposure time must be reviewed at regular intervals.

Radiation indicators must be used as an aid to differentiating irradiated from non-irradiated blood and blood components. A defined procedure must ensure the segregation of components that have not been irradiated from those which have been irradiated.
Paragraph 6. Leucocyte depletion

Processes used for leucocyte depletion must be validated. The validation must be carried out by the blood establishment using the manufacturer's instructions against the requirements for Leucocyte depletion and other quality aspects of the components including plasma for fractionation.

For quality control, an appropriate validated method must be used for Leucocyte counting.

Paragraph 7. Bacterial safety

A systematic programme to assure the bacterial safety of blood collection and processing procedures must be in place.
Chapter 5

Component monographs

Part A. Whole blood components
Part B. Red cells components
Part C. Platelet components
Part D. Plasma components
Part E. White cell components
Component monographs

Part A. Whole blood components
**Paragraph 1. Whole Blood**

1. **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 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.

2. **Preparation**

   By definition no preparation is required to achieve whole blood.

3. **Requirements and quality control**

   Table 5A-1 lists the requirements. Additional testing might be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
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<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
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<tr>
<td>Anti-HIV 1 &amp; 2</td>
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</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>450 mL ± 50 mL volume excluding anticoagulant. A non-standard donation should be labelled accordingly</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 45 g per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

1 Where different from "All units" the frequency of control is an indication of minimal frequency and suitable statistical process control should be used to minimize the risk of a product deviation.
4. Storage and transport

*Whole Blood* for transfusion must be kept at a controlled temperature, between +2 °C and +6 °C. The storage time depends on the anticoagulant/preservative solution used. For example in CPDA-1, the storage time is 35 days. Validated transport systems must ensure that at no time during a maximum transit time of 24 hours does the temperature exceed +10 °C.

*Whole Blood* for preparation of blood components may be kept up to 24 hours in conditions validated to maintain temperature between +20 °C and +24 °C, which is a prerequisite for the production of platelet preparations from whole blood.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Compatibility of Whole Blood for transfusion with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Micro aggregates are formed on storage.

Whole Blood for transfusion is not recommended in:

- anaemia without blood volume loss;
- plasma intolerance;
- intolerance due to alloimmunisation against leucocyte antigens.

Adverse reactions

- 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;
- graft versus host disease (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 component is 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);
• circulatory overload;
• iron overload.

Paragraph 2. Whole Blood, Leucocyte-Depleted

1. Definition and properties

*Whole Blood, Leucocyte-Depleted (LD)* is a component derived from *Whole Blood* by removing the leucocytes to a maximum residual content. *Whole Blood, LD* contains a minimum haemoglobin content of 43 g. *Whole Blood, LD* normally contains less than $1.0 \times 10^6$ of leucocytes.

2. Preparation

Generally a filtration technique is used to produce *Whole Blood, LD*. Pre-storage leucocyte depletion within 48 hours after donation is the standard.

3. Requirements and quality control

Table 5A-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).
### Guide to the preparation, use and quality assurance of blood components

**Table 5A-2**

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
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<tbody>
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<td>Grouping</td>
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<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>450 ± 50 mL volume excluding anticoagulant</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td></td>
<td>A non-standard donation should be labelled accordingly</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 43 g per unit</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes²</td>
<td>&lt; 1 × 10⁶ per unit by count</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

### 4. Storage and transport

*Whole Blood, LD* must be kept at a controlled temperature between + 2 °C and + 6 °C. The storage time depends on the anticoagulant/
preservative solution used. For example in CPDA-1 the storage time is 35 days.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

Compatibility of Whole Blood, LD with the intended recipient must be verified by suitable pre-transfusion testing.
RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

*Whole Blood, LD* is not recommended in:

- anaemia without blood volume loss;
- plasma intolerance.

**Adverse reactions**

- 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;
- graft versus host disease (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 component is 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);
- circulatory overload;
- iron overload.
Component monographs

Part B. Red cell components
Paragraph 1. Red Cells

1. Definition and properties

Red Cells is obtained by removal of a major part of the plasma from Whole Blood.

Red Cells also contains the greater part of the whole blood leucocytes (about 2.5 to 3.0 × 10⁹ cells) and a varying content of platelets depending on the method of centrifugation.

2. Preparation

For the preparation, plasma is removed from Whole Blood after centrifugation.

3. Requirements and quality control

Table 5B-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

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<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>280 ± 50 mL</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.65 - 0.75</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>minimum 45 g per unit</td>
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</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
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</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.
4. Storage and transport

Red Cells must be kept at a controlled temperature between +2 °C to +6 °C. The storage time depends on the anticoagulant/preservative solution used. For example in CPDA-1, the storage time is 35 days.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Micro aggregates are formed on storage.

Compatibility of Red Cells with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells are not recommended in:

- plasma intolerance;
- intolerance due to alloimmunisation against leucocyte antigens;
- exchange transfusion in newborns unless supplementary plasma is added.

Adverse reactions

- 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;
- graft versus host disease (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 component is 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);
• circulatory overload;
• iron overload.

Paragraph 2. Red Cells, Buffy Coat Removed

1. Definition and properties

Red Cells, Buffy Coat Removed (BCR) is a red cell component prepared by the removal of a major part of the plasma and the buffy coat layer from Whole Blood.

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

Red Cells, BCR normally contains less than $1.2 \times 10^9$ of leucocytes and a varying content of platelets depending on the method of centrifugation.

2. Preparation

Red Cells, BCR is derived from whole blood by centrifugation. The plasma and 20 to 60 mL of the buffy coat layer are removed from the whole blood after centrifugation, resulting in the loss of 10 to 30 mL of the whole blood’s red cells. Sufficient plasma is retained to give a haematocrit of 0.65 to 0.75.

3. Requirements and quality control

Table 5B-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).
Guide to the preparation, use and quality assurance of blood components

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>250 ± 50 mL</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.65-0.75</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 43 g per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;1.2 × 10&lt;sup&gt;9&lt;/sup&gt; per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

1 Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

2 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

### 4. Storage and transport

*Red Cells, BCR* must be kept at a controlled temperature between +2 °C to +6 °C. The storage time depends on the anticoagulant/preservative solution used. For example in CPDA-1, the storage time is 35 days.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

### 5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown
on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

Compatibility of Red Cells, BCR with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, BCR are not recommended in:

- plasma intolerance (may not concern units with a low plasma content unless IgA incompatibility is present);
- exchange transfusions in newborns unless supplementary plasma is added.
Adverse reactions

- 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;
- graft versus host disease (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 component is 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);
- circulatory overload;
- iron overload.

**Paragraph 3. Red Cells, in Additive Solution**

1. **Definition and properties**

*Red Cells, in Additive Solution (AS)* is a red cell component prepared by the removal of the plasma from whole blood with subsequent addition of an appropriate additive solution.
Red Cells, AS contains a minimum haemoglobin content of 45 g. The haematocrit is 0.50 to 0.70.

Red Cells, AS also contains the greater part of the whole blood leucocytes (about 2.5 to 3.0 × 10⁹ cells) and a varying content of platelets depending on the method of centrifugation.

2. Preparation

Whole Blood is collected with CPD as the anticoagulant solution. After centrifugation of the whole blood, plasma is removed and the additive solution is immediately added to the red cells and carefully mixed.

3. Requirements and quality control

Table 5B-3 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Table 5B-3

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>to be defined for the system used</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.50-0.70</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 45 g per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.
4. Storage and transport

*Red Cells, AS* must be kept at controlled temperature between + 2 °C to + 6 °C during storage. Depending on the anticoagulant/additive system the storage time may be extended up to the approved limit of the additive solution system.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed + 10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Micro aggregates are formed on storage.

Compatibility of Red Cells, AS with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, AS is not recommended in:

- plasma intolerance;
- intolerance due to alloimmunisation against leucocyte antigens;
- exchange transfusion in newborns unless used within 5 days of donation, with the additive solution replaced by fresh frozen plasma on the day of use.

Adverse reactions

- 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;
- graft versus host disease (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 component is 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);
circulatory overload;
iron overload.

**Paragraph 4. Red Cells, Buffy Coat Removed, in Additive Solution**

**1. Definition and properties**

*Red Cells, Buffy Coat Removed, in Additive Solution (BCR-AS)* is a red cell component prepared by the removal of a major part of the plasma and the buffy coat layer from *Whole Blood* with subsequent addition of an appropriate nutrient solution.

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

*Red Cells, BCR-AS* contains less than $1.2 \times 10^9$ of leucocytes and a varying platelet content depending on the method of centrifugation.

**2. Preparation**

*Red Cells, BCR-AS* are 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 whole blood’s red cells. The additive solution is immediately added to the red cells and carefully mixed.

**3. Requirements and quality control**

Table 5B-4 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).
Table 5B-4

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>to be defined for the system used</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.50-0.70</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 43 g per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes</td>
<td>&lt; 1.2 × 10⁹ per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>content²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4. Storage and transport

*Red Cells, BCR-AS* must be kept at controlled temperature between +2 °C to +6 °C during storage. Depending on the anticoagulant/additive system the storage time may be extended up to the approved limit of the additive solution system.

Validated transport systems must ensure that at all time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown
Guide to the preparation, use and quality assurance of blood components

on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

Compatibility of Red Cells, BCR-AS with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, BCR-AS is not recommended in:

- plasma intolerance;
- intolerance due to alloimmunisation against leucocyte antigens.
Adverse reactions
- 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;
- graft versus host disease (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 component is 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);
- circulatory overload;
- iron overload.

Paragraph 5. Red Cells, Leucocyte-Depleted

1. Definition and properties

Red Cells, Leucocyte-Depleted (LD) is a red cell component derived from whole blood donation, Red Cells or Red Cells, BCR by removing the leucocytes.

Red Cells, LD contains a minimum haemoglobin content of 40 g. The haematocrit is 0.50 to 0.70.

Red Cells, LD contains less than 1.0 × 10^6 of leucocytes.
2. Preparation

Generally a filtration technique is used to produce Red Cells, LD. Leucocyte depletion within 48 hours after donation is the standard.

Red Cells, LD can be produced:

- by leucocyte filtration of whole blood with subsequent centrifugation and removal of plasma;
- by leucocyte filtration of a red cell component.

3. Requirements and quality control

Table 5B-5 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>To be defined for the system used</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.50-0.70</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 40 g per unit</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content²</td>
<td>&lt; 1 × 10⁶ per unit by count</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
</tbody>
</table>
Standards. Chapter 5

<table>
<thead>
<tr>
<th>Haemoglobin</th>
<th>Minimum 40 g per unit</th>
<th>1% of all units with a minimum of 4 units per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

1 Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

2 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4. Storage and transport

*Red Cells, LD* must be kept at controlled temperature between +2 °C to +6 °C during storage. Depending on the anticoagulant/additive system the storage time may be extended up to the approved limit of the additive solution system.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
6. Warnings

Compatibility of Red Cells, LD with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, LD are not recommended in:
- plasma intolerance.

Adverse reactions
- circulatory overload;
- haemolytic transfusion reaction;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against red cell and HLA (very rarely) antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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 component is 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);
• iron overload.

**Paragraph 6. Red Cells, Leucocyte-Depleted in Additive Solution**

1. **Definition and properties**

   *Red Cells, Leucocyte depleted in Additive solution (LD-AS)* is a red cell component derived from whole blood donation, from *Red Cells, AS* or *Red Cells, BCR-AS* by removing the leucocytes to a maximum residual content.

   *Red Cells, LD-AS* contains a minimum haemoglobin content of 40 g. The haematocrit is 0.50 to 0.70.

   *Red Cells, LD-AS* contains less than $1.0 \times 10^6$ of leucocytes.

2. **Preparation**

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

   *Red Cells, LD-AS* can be produced:
   
   • by leucocyte filtration of whole blood with subsequent centrifugation and removal of plasma and immediate addition of the additive solution followed by carefully mixing;
   
   • by leucocyte filtration of *Red Cells, AS* or *Red Cells, BCR-AS*. 


3. Requirements and quality control

Table 5B-6 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Table 5B-6

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>To be defined for the system used</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.50-0.70</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content²</td>
<td>&lt; 1 x 10⁶ per unit by count</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 40 g per unit</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.
4. Storage and transport

Red Cells, LD-AS must be kept in controlled temperature between +2 °C to +6 °C during storage. Depending on the anticoagulant/additive system the storage time may be extended up to the approved limit of the additive solution system.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Compatibility of Red Cells, LD-AS with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, LD-AS are not recommended in:

- plasma intolerance (may not apply to units with a low plasma content).

Adverse reactions

- haemolytic transfusion reaction;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- anaphylaxis;
- alloimmunisation against red cell and HLA (very rarely) antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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 component is stored for less than 96 hours at +4 ºC;
- 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);
• circulatory overload;
• iron overload.

**Paragraph 7. Red Cells, Apheresis**

**1. 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 Cell, Aph* contains a minimum haemoglobin content of 40 g. The haematocrit is 0.65 to 0.75, and 0.50 to 0.70 if an additive solution is used.

Leucocyte content of *Red Cells, Aph* might vary. When leucocyte depleted, *Red Cells, Aph* normally contain less than $1.0 \times 10^8$ leucocytes.

**2. Preparation**

For preparation of *Red Cells, Aph* whole blood is removed by an appropriate apheresis machine from the donor and anticoagulated with a citrate-containing solution. The plasma is returned to the donor. Either one or two units of *Red Cells, Aph* can be collected during a single procedure.

*Red Cells, Aph* can be used either unmodified or after additional processing e.g. adding of an additive solution or leucocyte depletion.

**3. Requirements and quality control**

Table 5B-7 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).
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<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>To be defined by the system used</td>
<td>1% of all units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.65-0.75</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haematocrit (if additive solution)</td>
<td>0.50-0.70</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 40 g per unit</td>
<td>4 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content (if leucocyte depleted)</td>
<td>&lt; 1 x 10⁶ per unit by count</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Haemolysis at the end of storage</td>
<td>&lt; 0.8% of red cell mass</td>
<td>4 units per month</td>
</tr>
</tbody>
</table>

1 Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

2 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4. Storage and transport

Red Cells, Aph must be kept at controlled temperature between + 2 °C to + 6 °C during storage. Depending on the anticoagulant/additive
system the storage time may be extended up to the approved limit of the additive solution system.

*Red Cells, Aph* to be stored must be collected and prepared in a functionally closed system. If prepared or filtered by methods under which the system has been opened, the storage time is limited to 24 hours at +2 °C to +6 °C.

Validated transport systems must ensure that at no time during a maximum transit time of 24 hours did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number. If two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution (if appropriate);
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
Guide to the preparation, use and quality assurance of blood components

- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

Compatibility of Red Cells, Aph with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

Red Cells, Aph is not recommended in:

- plasma intolerance (may not apply to units with a low plasma content unless IgA incompatibility is present).

Adverse reactions

- circulatory overload;
- haemolytic transfusion reaction;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against red cell and HLA (very rarely after leucocyte-depletion) antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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 component is 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);
• iron overload.

Paragraph 8. Red Cells, Washed

1. Definition and properties

Red Cells, Washed (W) is derived from secondary processing of a red cell component or whole blood with sequential washing and resuspension of the red cells in an additive solution.

Most of the plasma, leucocytes and platelets are removed. The amount of residual plasma will depend upon the washing protocol. The haematocrit can be varied according to clinical need.

2. Preparation

After centrifugation of the primary component and removal of 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 must be performed at a controlled temperature.

3. Requirements and quality control

Table 5B-8 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).
Table 5B-8

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>To be defined for the system used</td>
<td>All units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.65-0.75</td>
<td>All units</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 40 g per unit</td>
<td>All units</td>
</tr>
<tr>
<td>Haemolysis at end of the process</td>
<td>&lt; 0.8% of red cell mass</td>
<td>All units</td>
</tr>
<tr>
<td>Protein content of final supernatant</td>
<td>&lt; 0.5 g per unit</td>
<td>All units</td>
</tr>
</tbody>
</table>

1 Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

4. Storage and transport

*Red Cells, W* must be kept at controlled temperature between +2 °C and +6 °C during storage.

When an open system has been used for washing the storage time should be as short as possible after washing and must never exceed 24 hours.

If a closed system and a suitable additive solution are used, storage times may be prolonged subject to validation.

Validated transport systems must ensure that at no time did the temperature exceed +10 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown
on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date and time of expiry;
- the name of the anticoagulant solution;
- the name and volume of the washing solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

Compatibility of Red Cells, W with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should not be transfused with red cells from RhD positive donors.

Adverse reactions

- haemolytic transfusion reaction;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
Paragraph 9. Red Cells, Cryopreserved

1. Definition and properties

*Red Cells, Cryopreserved (Cryo)* is a red cell component derived by secondary processing of a red cell component or whole blood. The red cells are frozen, preferably within 7 days of collection, using a cryoprotectant, and stored at –60 °C to –80 °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 0.65 to 0.75.

2. Preparation

Two methods are in general use for preparation of *Red Cells, Cryo*. One is a high glycerol, the other a low glycerol technique. Both methods require a washing/deglycerolisation procedure.
3. Requirements and quality control

Table 5B-9 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 185 mL</td>
<td>All units</td>
</tr>
<tr>
<td>Haemoglobin (supernatant)²</td>
<td>&lt; 0.2 g per unit</td>
<td>All units</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.65-0.75</td>
<td>All units</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Minimum 36 g per unit</td>
<td>All units</td>
</tr>
<tr>
<td>Osmolarity²</td>
<td>&lt; 340 mOsm/L</td>
<td>1% of all units with a minimum of 4 units per month. If less, each unit.</td>
</tr>
<tr>
<td>Residual leucocytes content³</td>
<td>&lt; 0.1 × 10⁹ cells per unit</td>
<td>1% of units with a minimum of 4 units per month. If less, each unit.</td>
</tr>
<tr>
<td>Sterility</td>
<td>Sterile</td>
<td>1% of all units with a minimum of 4 units per month. If less, each unit.</td>
</tr>
</tbody>
</table>

¹ Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² Final suspending solution.

³ These requirements shall have been deemed to have been met if 90% of the units tested fall within the values indicated.
Since cryopreservation allows prolonged storage, serum and/or plasma samples obtained at collection must also be stored to enable future testing for newly discovered markers of transmissible diseases at the time of thawing of the component.

4. Storage and transport

Red Cells, Cryo in frozen state

These must be constantly maintained at:
- – 60 °C to – 80 °C if stored in an electrical freezer when a high glycerol method is used;
- – 140 °C to – 150 °C if stored in vapour phase liquid nitrogen, when a low glycerol method is used.

The storage may be extended to at least ten years if the correct storage temperature can be guaranteed.

Thawed reconstituted Red Cells, Cryo

*Red Cells, Cryo* must be stored at + 2 °C to + 6 °C. The storage time must be as short as possible after washing and never exceed 24 hours when an open system has been used.

If transport in the frozen state is unavoidable, storage conditions must be maintained. Transport of thawed reconstituted red cells is limited by the short storage time. Storage conditions must be maintained during transport.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements.

The following information must be traceable for each frozen unit:
- the producer’s identification;
- the unique identity number;
Standards. Chapter 5

- 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 temperature of storage.

Labelling of the reconstituted component

After thawing and reconstitution (washing), the date of expiry must be changed to the date (and time) of expiry, and the name and volume of the cryoprotective solution must be changed to the name and volume of the additive solution (if any). The following information must be shown on the label of the reconstituted component or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the name of the blood component;
- the ABO and RhD group;
- blood group phenotypes other than ABO and RhD (optional);
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information if appropriate;
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must not be used for transfusion if there is abnormal haemolysis or other deterioration;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Compatibility of Red Cells, Cryo with the intended recipient must be verified by suitable pre-transfusion testing.

RhD negative female recipients of child bearing age or younger should preferably not be transfused with red cells from RhD positive donors.

When Red Cells, Cryo are processed in an open system, the risk of bacterial contamination is increased and therefore extra vigilance is required during transfusion.

Adverse reactions

- circulatory overload;
- haemolytic transfusion reaction;
- anaphylaxis;
- alloimmunisation against red cell and HLA (very rarely) antigens;
- sepsis due to inadvertent bacterial contamination;
- viral transmission (hepatitis, HIV, etc.) is possible despite careful donor selection and screening procedures;
- protozoal transmission (e.g. malaria) may occur in rare instances;
- transmission of other pathogens that are not tested for or recognised;
- iron overload.
Component monographs

Part C. Platelet components
Paragraph 1. Platelets, Recovered, Single Unit

1. Definition and properties

_Platelets, Recovered, Single Unit (Rec, SU)_ is a platelet component derived from a whole blood donation. It contains the majority of the original whole blood platelet content suspended in plasma.

_Platelets, Rec, SU_ contains more than $60 \times 10^9$ platelets.

_Platelets, Rec, SU_ contains up to $0.2 \times 10^9$ leucocytes if prepared by the platelet-rich plasma method, and up to $0.05 \times 10^9$ leucocytes if prepared by the buffy coat method.

_Platelets, Rec, SU_ can be used for neonatal and infant transfusion. In order to achieve a “standard adult dose” 4 to 6 units of _Platelets, Rec, SU_ Platelets, Recovered, Single unit have to be transfused.

2. Preparation

Preparation from platelet-rich plasma (PRP)

A unit of whole blood stored up to 24 hours in conditions validated to maintain temperature between +20 °C and +24 °C is centrifuged so that an optimal number of platelets remain in plasma and the number 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 leaving 50-70 mL of it with the platelets; finally the platelets are allowed to disaggregate and are then resuspended.

Preparation from buffy coat

A whole blood unit stored for up to 24 hours in conditions validated to maintain temperature between +20 °C to +24 °C is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with leucocytes. The buffy coat is separated and further processed to obtain a platelet concentrate. Single buffy coats diluted with plasma are centrifuged so that platelets remain in the supernatant but red cells and leucocytes are sedimented to the bottom of the bag.
3. Requirements and quality control

Table 5C-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, must be carried out prior to the issue and transfusion of this component.

### Table 5C-1

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
<td></td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
<td></td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
<td></td>
</tr>
<tr>
<td>Platelet content per final unita</td>
<td>&gt; 60 × 10⁹</td>
<td>1% of all units with a minimum of 10 units per month</td>
<td></td>
</tr>
<tr>
<td>Residual leucocytes per final unita</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. prepared from buffy-coat</td>
<td>&lt; 0.05 × 10⁹</td>
<td>1% of all units with a minimum of 10 units per month</td>
<td></td>
</tr>
<tr>
<td>b. prepared from PRP</td>
<td>&lt; 0.2 × 10⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf lifea</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
<td></td>
</tr>
</tbody>
</table>

1 Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation. (see next page)
2 These requirements shall be deemed to have been met if 75% of the units tested fall within the values indicated.

3 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4 Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.

4. Storage and transport

*Platelets, Rec, SU* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be + 20 °C to + 24 °C under constant agitation.

The maximum storage time for *Platelets, Rec, SU* is five 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* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, they must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if platelets are pooled the original donations must be traceable;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
• the name of the anticoagulant solution;
• additional component information: irradiated, etc. (if appropriate);
• the volume of the blood component;
• the number of platelets (average or actual, as appropriate);
• the temperature of storage;
• that the component must be administered through a 150-200 μm filter.

6. Warnings

Platelets, Rec, SU are not recommended in:
• plasma intolerance;
• RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions
• 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;
• graft versus host disease (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;
- circulatory overload.

**Paragraph 2. Platelets, Recovered, Pooled**

1. **Definition and properties**

*Platelets, Recovered, Pooled (Rec, Pool)* is a platelet component derived from 4 to 6 fresh whole blood donations which contains the majority of the original platelet content in a therapeutically effective dose suspended in plasma.

*Platelets, Rec, Pool* contain a minimum platelet content of $2 \times 10^{11}$.

*Platelets, Rec, Pool* contain a maximum of $1 \times 10^9$ leucocytes.

2. **Preparation**

*Platelets, Rec, Pool* can be produced:

- directly from whole blood derived buffy coats, which is the method of choice;
- by secondary processing after pooling of 4-6 *Platelets, Rec, SU*.

**Preparation from buffy coat**

A whole blood unit stored in conditions validated to maintain temperature between $+20 \, ^\circ\text{C}$ to $+24 \, ^\circ\text{C}$ for up to 24 hours is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with leucocytes. The buffy coat is separated and further processed so that usually 4 to 6 blood group compatible buffy coats are pooled in a sterile manner and resuspended with plasma. After careful mixing, the buffy coat pool is centrifuged (soft spin) so that platelets remain in the supernatant but red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet containing supernatant is immediately transferred into a suitable platelet storage bag in a sterile manner.

**Preparation of Platelets, Recovered, single units**

4-6 units of *Platelets, Rec, SU* prepared by the PRP-method are connected and pooled. If storage for longer than 6 hours is intended, the pooling must be undertaken in a sterile manner.
3. Requirements and quality control

Table 5C-2 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.

Table 5C-2

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content per final unit²</td>
<td>Minimum 2 × 10¹⁰</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content³</td>
<td>&lt; 1 × 10⁶ per final unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life⁴</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation. (see next page)
2 These requirements shall be deemed to have been met if 75% of the units tested fall within the values indicated.

3 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4 Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at +22 °C.

4. Storage and transport

*Platelets, Rec, Pool* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be +20 °C to +24 °C under constant agitation.

The maximum storage time for *Platelets, Rec, Pool* is five days. Storage may be extended to 7 days in conjunction with appropriate detection or reduction of bacterial contamination.

When an open system has been used for preparation of *Platelets, Rec, Pool* the storage time must not exceed 6 hours.

During transportation the temperature of *Platelets, Rec, Pool* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if platelets are pooled the original donations must be traceable;
- the name of the blood component;
Standards. Chapter 5

- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution
- additional component information: irradiated, number of donations combined to make the pool, etc. (if appropriate);
- the volume of the blood component;
- the number of platelets (average or actual, as appropriate);
- the temperature of storage;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

*Platelets, Rec, Pool are not recommended in:
- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions
- circulatory overload;
- haemolytic reaction due to transfusion of ABO-incompatible plasma in the component;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA and red cell antigens;
• alloimmunisation against HPA antigens;
• transfusion related acute lung injury (TRALI);
• post-transfusion purpura;
• graft versus host disease (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.

Paragraph 3. Platelets, Recovered, Pooled, Leucocyte-Depleted

1. Definition and properties

*Platelets, Recovered, Pooled, Leucocyte-Depleted (Rec, Pool, LD)* is a leucocyte-depleted platelet component derived from 4 to 6 fresh whole blood donations which contains the majority of the original platelet content in a therapeutically effective dose suspended in plasma.

*Platelets, Rec, Pool, LD* contain a minimum platelet content of $2 \times 10^{11}$.

*Platelets, Rec, Pool, LD* contain a maximum leucocyte content of $1.0 \times 10^6$ cells.

2. Preparation

*Platelets, Rec, Pool, LD* are 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 whole blood derived buffy coats, which is the method of choice;
- by secondary processing after pooling of 4-6 Platelets, Rec, SU.

**Preparation from buffy coat**

A whole blood unit stored in conditions validated to maintain temperature between +20 °C to +24 °C for up to 24 hours is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with leucocytes. The buffy coat is separated and further processed so that usually 4 to 6 blood group compatible buffy coats are pooled in a sterile manner and resuspended with plasma. After careful mixing, the buffy coat pool is centrifuged (soft spin) so that platelets remain in the supernatant but red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet containing supernatant is immediately filtered and transferred into a suitable platelet storage bag in a sterile manner.

**Preparation from Platelets, Recovered, single units PRP method**

4-6 units of Platelet, Rec, SU prepared by the PRP method are connected, pooled, immediately filtered and transferred into a suitable platelet storage bag. If storage for longer than 6 hours is intended, the preparation must be undertaken in a sterile manner.

**3. Requirements and quality control**

Table 5C-3 lists the requirements for the final component. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards of screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.
Table 5C-3

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content(^2)</td>
<td>Minimum 2 × 10¹⁰ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes(^3)</td>
<td>&lt; 1 × 10⁶ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life(^4)</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

---

1 Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

2 These requirements shall be deemed to have been met if 75% of the units tested fall within the values indicated.

3 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

4 Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.
4. Storage and transport

Platelets, Rec, Pool, LD must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be +20 ºC to +24 ºC under constant agitation.

The maximum storage time for Platelets, Rec, Pool, LD is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination.

When an open system has been used for preparation of Platelets, Rec, Pool, LD the storage time must not exceed 6 hours.

During transportation the temperature of Platelets, Rec, Pool, LD must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; If platelets are pooled the original donations must be traceable;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, number of donations combined to make the pool, etc. (if appropriate);
- the volume of the blood component;
the number of platelets (average or actual, as appropriate);
the temperature of storage;
that the component must be administered through a 150-200 μm filter.

6. Warnings

*Platelets, Rec, Pool, LD* are not recommended in:

- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions

- circulatory overload;
- haemolytic reaction due to transfusion of ABO-incompatible plasma in the component;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA (very rarely after leucocyte-depletion) and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Paragraph 4. Platelets, Recovered, Pooled, in Additive Solution

1. Definition and properties

Platelets, Recovered, Pooled, in Additive Solution (Rec, Pool, AS) is a platelet component derived from 4 to 6 fresh whole blood donations which contains the majority of the original platelet content in a therapeutically effective dose suspended in a mixture of plasma (30-40%) and an additive solution (60-70%).

Platelets, Rec, Pool, AS contains a minimum platelet content of $2 \times 10^{11}$. Platelets, Rec, Pool, AS contains a maximum of $0.3 \times 10^9$ leucocytes.

2. Preparation

Platelets, Rec, Pool, AS is prepared from whole blood derived buffy coats. A whole blood unit stored in conditions validated to maintain temperature between $+20 \degree C$ to $+24 \degree C$ for up to 24 hours is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with leucocytes. The buffy coat is separated and further processed so that usually 4 to 6 blood group compatible buffy coats 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 platelets remain in the supernatant but red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet containing supernatant is immediately transferred into a suitable platelet storage bag in a sterile manner.

3. Requirements and quality control

Table 5C-4 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out.
either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.

### Table 5C-4

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content²</td>
<td>Minimum 2 × 10¹¹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content³</td>
<td>&lt; 0.3 × 10⁹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life⁴</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 75% of the units tested fall within the values indicated.

³ These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

⁴ Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.
4. Storage and transport

*Platelets, Rec, Pool, AS* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be +20 °C to +24 °C under constant agitation.

The maximum storage time for *Platelets, Rec, Pool, AS* is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination and depending on the type of additive solution. When an open system has been used for preparation of *Platelets, Rec, Pool, LD* the storage time must not exceed 6 hours.

During transportation the temperature of *Platelets, Rec, Pool, AS* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if platelets are pooled the original donations must be traceable;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, number of donations combined to make the pool, etc. (if appropriate);
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- the volume of the blood component;
- the number of platelets (average or actual, as appropriate);
- the temperature of storage;
- that the component must be administered through a 150-200 μm filter.

6. Warnings

*Platelets, Rec, Pool, AS* is not recommended in:

- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions

- circulatory overload;
- haemolytic reaction due to anti-A, -B in case of incompatible transfusions;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Paragraph 5. Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution

1. Definition and properties

*Platelets, Recovered, Pooled, Leucocyte-Depleted, in Additive Solution (Rec, Pool, LD-AS)* is a leucocyte-depleted platelet component derived from 4 to 6 fresh whole blood donations which contains the majority of the original platelet content in a therapeutically effective dose suspended in a mixture of plasma (30-40%) and an additive solution (60-70%).

*Platelets, Rec, Pool, LD-AS* contains a minimum platelet content of $2 \times 10^{11}$.

*Platelets, Rec, Pool, LD-AS* contains a maximum of $1.0 \times \times 10^6$ leucocytes.

2. Preparation

*Platelets, Rec, Pool, LD-AS* is prepared from whole blood derived buffy coats and leucocyte-depleted by filtration. Pre-storage leucocyte filtration within 6 hours of preparation is recommended.

A whole blood unit stored in conditions validated to maintain temperature between +20 °C to +24 °C for up to 24 hours is centrifuged so that platelets are primarily sedimented to the buffy coat layer together with leucocytes. The buffy coat is separated and further processed so that usually 4 to 6 blood group compatible buffy coats 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 platelets remain in the supernatant but red cells and leucocytes are effectively sedimented to the bottom of the bag. The platelet containing supernatant is immediately filtered and transferred into a suitable platelet storage bag in a sterile manner.

3. Requirements and quality control

Table 5C-5 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).
Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content²</td>
<td>Minimum 2 × 10¹¹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content³</td>
<td>&lt; 1 × 10⁶ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured⁴ (+ 22 ºC) at the end of the recommended shelf life</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 75% of the units tested fall within the values indicated.

³ These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

⁴ Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 ºC.
4. Storage and transport

*Platelets, Rec, Pool, LD-AS* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be +20 °C to +24 °C under constant agitation.

The maximum storage time for *Platelets, Rec, Pool, LD-AS* is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination and depending on the type of additive solution.

During transportation the temperature of *Platelets, Rec, Pool, LD-AS* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if platelets are pooled the original donations must be traceable;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, number of donations combined to make the pool, etc. (if appropriate);
- the volume of the blood component;
• the number of platelets (average or actual, as appropriate);
• the temperature of storage;
• that the component must be administered through a 150-200 μm filter.

6. Warnings

*Platelets, Rec, Pool, LD, AS* is not recommended in:

• plasma intolerance;
• RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

**Adverse reactions**

• circulatory overload;
• haemolytic reaction due to anti-A, -B in case of incompatible transfusions;
• anaphylaxis;
• non haemolytic transfusion reactions (mainly chills, fever and urticaria). The incidence is reduced by the use of pre-storage leucocyte depleted platelets;
• alloimmunisation against HLA (very rarely after leucocyte-depletion) and red cell antigens;
• alloimmunisation against HPA antigens;
• transfusion related acute lung injury (TRALI);
• post-transfusion purpura;
• graft versus host disease (GvHD);
• sepsis due to inadvertent bacterial contamination;
• viral transmission (hepatitis, HIV, etc.) is possible despite careful donor selection and screening procedures;
• syphilis transmission;
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- 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.

**Paragraph 6. Platelets, Apheresis**

1. **Definition and properties**

*Platelets, Apheresis (Aph)* is a component obtained by platelet apheresis of a single donor using automated cell separation equipment which contains platelets in a therapeutically effective dose suspended in plasma.

*Platelets, Aph* contains a minimum platelet content of $2 \times 10^{11}$.

*Platelets, Aph* contains a maximum leucocyte content of $0.3 \times 10^9$ cells.

2. **Preparation**

For preparation of *Platelets, Aph* whole blood is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and platelets are harvested from it.

For use in neonates and infants *Platelets, Aph* can be divided into satellite units under sterile conditions.

3. **Requirements and quality control**

Table 5C-6 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.
Table 5C-6

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 ×10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>Standard unit: minimum 2 × 10¹⁰ per unit For use in neonates or infants: minimum 0.5 × 10¹⁰ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content²</td>
<td>&lt; 0.3 × 10⁹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life³</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

1  The frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.
2  These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.
3  Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.

4. Storage and transport

Platelets, Aph must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.
Standards. Chapter 5

Storage temperature must be +20 ºC to +24 ºC under constant agitation. Platelets, Aph must be stored for more than 6 hours must be collected and prepared in a functionally closed system. The maximum storage time for Platelets, Aph is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination.

During transportation the temperature of Platelets, Aph must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume of the blood component;
- the number of platelets (average or actual, as appropriate);
- the temperature of storage;
- the relevant HLA and/or HPA type, if determined;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Platelets, Aph is not recommended in:
- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions
- circulatory overload;
- haemolytic reaction due to transfusion of ABO-incompatible plasma in the component;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Paragraph 7. Platelets, Apheresis, Leucocyte-Depleted

1. Definition and properties

Platelets, Apheresis, Leucocyte-Depleted (Aph, LD) is a leucocyte-depleted platelet component obtained by platelet apheresis of a single donor using automated cell separation equipment which contains platelets in a therapeutically effective dose suspended in plasma.

Platelets, Aph, LD contain a minimum platelet content of $2 \times 10^{11}$.

Platelets, Aph, LD normally contains a maximum content of $1.0 \times 10^6$ leucocytes.

2. Preparation

For preparation of Platelets, Aph, LD whole blood is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and platelets are harvested from it. To reduce the number of contaminating leucocytes centrifugation, filtration or other in-process steps are included in the process. 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 under sterile conditions

3. Requirements and quality control

Table 5C-7 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.
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### Table 5C-7

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>Standard unit: minimum 2 × 10¹¹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td></td>
<td>For use in neonates or infants: minimum 0.5 × 10¹¹ per unit</td>
<td></td>
</tr>
<tr>
<td>Residual leucocytes content²</td>
<td>&lt; 1 × 10⁷ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life³</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

³ Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.

### 4. Storage and transport

*Platelets, Aph, LD* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.
Storage temperature must be +20 °C to +24 °C under constant agitation. *Platelets, Aph, LD* to be stored for more than 6 hours must be collected and prepared in a functionally closed system. The maximum storage time for *Platelets, Aph, LD* is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination.

During transportation the temperature of *Platelets, Aph, LD* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

**5. Labelling**

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume of the blood component;
- the number of platelets (average or actual, as appropriate);
- the temperature of storage;
- the relevant HLA and/or HPA type, if determined;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

*Platelets, Apheresis, LD* is not recommended in:

- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

**Adverse reactions**

- circulatory overload;
- haemolytic reaction due to transfusion of ABO; incompatible plasma in the component;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria). The incidence is reduced by the use of pre-storage leucocyte depleted platelets;
- alloimmunisation against HLA (very rarely) and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Paragraph 8. Platelets, Apheresis, in Additive Solution

1. Definition and properties

*Platelets, Aph, AS* is a component obtained by platelet apheresis of a single donor using automated cell separation equipment which contains platelets in a therapeutically effective dose suspended in a mixture of plasma (30-40%) and an additive solution (60-70%).

*Platelets, Aph, AS* contain a minimum platelet content of $2 \times 10^9$.

Platelets, Aph, AS contain a maximum leucocyte content of $0.3 \times 10^9$ cells.

2. Preparation

For preparation of *Platelets, Aph, AS* whole blood is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and platelets are harvested from it. 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 under sterile conditions.

3. Requirements and quality control

Table 5C-8 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 *Standards for screening for infectious markers*).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.
Table 5C-8

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HLA or HPA</td>
<td>As required</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 x 10^9 of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>Standard unit: minimum 2 x 10^11 per unit For use in neonates or infants: minimum 0.5 x 10^11 per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>Residual leucocytes content^2</td>
<td>&lt; 0.3 x 10^9 per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 °C) at the end of the recommended shelf life^3</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

1 Where different from "All units" the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

2 These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

3 Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 °C.

4. Storage and transport

*Platelets, Aφh, AS* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.
Storage temperature must be +20 °C to +24 °C under constant agitation. Platelets, Aph, AS to be stored for more than 6 hours must be collected and prepared in a functionally closed system. The maximum storage time for Platelets, Aph, AS is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination and depending on the type of additive solution.

During transportation the temperature of Platelets, Aph, AS must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, etc. (if appropriate);
- the volume of the blood component;
- the number of platelets (average or actual, as appropriate);
- the temperature of storage;
6. Warnings

Platelets, Apheresis, AS is not recommended in:

- plasma intolerance;
- RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions

- circulatory overload;
- haemolytic reaction due to anti-A, -B in case of incompatible transfusions;
- anaphylaxis;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Paragraph 9. Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution

1. Definition and properties

Platelets, Apheresis, Leucocyte-Depleted, in Additive Solution (Aph, LD-AS) is a leucocyte-depleted platelet component obtained by platelet apheresis of a single donor using automated cell separation equipment which contains platelets in a therapeutically effective dose suspended in a mixture of plasma (30-40%) and an additive solution (60-70%).

Platelets, Aph, LD-AS contains a minimum platelet content of \(2 \times 10^{11}\).

Platelets, Aph, LD-AS contains a maximum of \(1.0 \times 10^6\) leucocytes.

2. Preparation

For preparation of Platelets, Aph, LD-AS whole blood is removed from the donor by the apheresis machine, anticoagulated with a citrate solution and platelets are harvested from it. Platelets are stored in a combination of plasma and an appropriate nutrient solution. To reduce the number of contaminating leucocytes centrifugation, filtration or other in-process steps are included in the process. 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 under sterile conditions

3. Requirements and quality control

Table 5C-9 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

Demonstration of the swirling phenomenon, based on light scattering by platelets of normal morphology in movement, may be carried out either as a separate quality control procedure or as a routine part of the issue and transfusion of this component.
Table 5C-9

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HLA or HPA</td>
<td>as required</td>
<td>All units</td>
</tr>
<tr>
<td>Volume</td>
<td>&gt; 40 mL per 60 × 10⁹ of platelets</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>Standard unit: minimum 2 × 10¹¹ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td></td>
<td>For use in neonates or infants: minimum 0.5 × 10¹¹ per unit</td>
<td></td>
</tr>
<tr>
<td>Residual leucocytes content²</td>
<td>&lt; 1 × 10⁶ per unit</td>
<td>1% of all units with a minimum of 10 units per month</td>
</tr>
<tr>
<td>pH measured (+ 22 ºC) at the end of the recommended shelf life³</td>
<td>&gt; 6.4</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
</tbody>
</table>

¹ Where different from “All units” the frequency of control is an indication of minimal frequency and statistical process control should be used to minimize the risk of a product deviation.

² These requirements shall be deemed to have been met if 90% of the units tested fall within the values indicated.

³ Measurement of the pH in a closed system is preferable to prevent CO₂ escape. Measurement may be made at another temperature and converted by calculation for reporting pH at + 22 ºC.
4. Storage and transport

*Platelets, Aph, LD-AS* must be stored under conditions which guarantee that their viability and haemostatic activities are optimally preserved.

Storage temperature must be + 20 °C to + 24 °C under constant agitation.

*Platelets, Aph, LD-AS* to be stored for more than 6 hours must be collected and prepared in a functionally closed system. The maximum storage time for *Platelets, Aph, LD-AS* is five days. Storage may be extended to 7 days in conjunction with detection or reduction of bacterial contamination and depending on the type of additive solution.

During transportation the temperature of *Platelets, Aph, LD-AS* must be kept as close as possible to recommended storage temperature and, on receipt, unless intended for immediate therapeutic use, the component must be transferred to storage under recommended conditions.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer's identification;
- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO and RhD group;
- the date of donation;
- the date of expiry;
- the name of the anticoagulant solution;
- the name and volume of the additive solution;
- additional component information: irradiated, etc. (if appropriate);
• the volume of the blood component;
• the number of platelets (average or actual, as appropriate);
• the temperature of storage;
• the relevant HLA and/or HPA type, if determined;
• that the component must be administered through a 150-200 μm filter.

6. Warnings
Platelets, Aph, LD-AS is not recommended in:
• plasma intolerance;
• RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

Adverse reactions
• circulatory overload;
• haemolytic reaction due to anti-A, -B in case of incompatible transfusions;
• anaphylaxis;
• non haemolytic transfusion reaction (mainly chills, fever and urticaria);
• alloimmunisation against HLA (very rarely after pre-storage leucocyte-depletion) and red cell antigens;
• alloimmunisation against HPA antigens;
• transfusion related acute lung injury (TRALI);
• post-transfusion purpura;
• graft versus host disease (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.

**Paragraph 10. Platelets, Cryopreserved**

**1. Definition and properties**

*Platelets, Cryopreserved (Cryo)* is a component prepared by the freezing of *Platelets, Aph, LD* within 24 hours of collection, using a cryoprotectant.

The reconstituted *Platelets, Cryo* contains more than 40% of the original component.

The method provides extended storage of platelets from selected donors and of autologous platelets.

**2. Preparation**

Prepared by secondary processing of *Platelets, Aph, LD*. The component is cryopreserved within 24 hours of collection, using a cryoprotectant. Two methods are in general use for preparation of *Platelets, Cryo*: one is a DMSO (6% w/v), the other a very low glycerol (5% w/v) technique.

Before use the platelets are thawed, washed and resuspended in (autologous) plasma or in a suitable additive solution.

**3. Requirements and quality control**

As indicated for *Platelets, Aph* (Table 5C-6) with the following additions and changes:

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>50-200 mL</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>&gt; 40% of the pre-freeze platelet content</td>
<td>All units</td>
</tr>
</tbody>
</table>
Platelets, Cryo when thawed will not swirl.

4. Storage and transport

Platelets in the frozen state must be constantly maintained at:
- – 80 °C if stored in an electrical freezer;
- – 150 °C if stored in vapour phase liquid nitrogen.

If storage must be extended for more than one year, storage at – 150 °C is preferred.

If transport in the frozen state is unavoidable, storage conditions must be maintained during transportation.

Thawed platelets must be used as soon as possible after thawing. If short intermediate storage is required, the component must be kept at + 20 °C to + 24 °C

Transportation of thawed platelets is limited by the short life of this component. During transportation the temperature of Platelets, Cryo must be kept as close as possible to + 20 °C to + 24 °C.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements.

The following information must be shown on the label or contained in the component information leaflet, as appropriate and must be traceable for each frozen unit:
- the producer’s identification;
- the unique identity number;
- the date of donation;
- the date of expiry;
- the name and volume of the cryoprotective solution;
• additional component information if appropriate;
• the volume or weight of the blood component;
• the temperature of storage.

Labelling of the reconstituted component

After thawing and reconstitution (washing), the date of expiry must be changed to the date (and time) of expiry, and the name and volume of the cryoprotective solution must be changed to the name and volume of the additive solution (if any).

The following information must be shown on the label or contained in the component information leaflet, as appropriate:

• the producer's identification;
• the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
• the ABO and RhD group;
• the date of preparation;
• the name and volume of the cryoprotective solution;
• the name of the blood component;
• additional component information: Leucocyte depleted, irradiated, etc. (if appropriate);
• the date of expiry (and time of expiry when required);
• the volume or weight of the blood component;
• the temperature of storage;
• the HPA type (if determined);
• that the component must be administered through a 150-200 μm filter.
6. **Warnings**

Toxicity of residual cryoprotectant (e.g. DMSO).

RhD negative female recipients of child bearing age or younger should preferably not be transfused with platelets from RhD positive donors.

**Adverse reactions**

- circulatory overload;
- haemolytic reaction due to anti-A, -B in case of incompatible transfusions when thawed platelets are resuspended in plasma;
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- alloimmunisation against HLA (very rarely) and red cell antigens;
- alloimmunisation against HPA antigens;
- transfusion related acute lung injury (TRALI);
- post-transfusion purpura;
- graft versus host disease (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.
Component monographs

Part D. Plasma components
Paragraph 1. Plasma, Fresh Frozen

1. Definition and properties

*Plasma, Fresh Frozen* is a component for transfusion or for fractionation prepared either from *Whole Blood* or from plasma collected by apheresis, frozen within a period of time and to a temperature that will adequately maintain the labile coagulation factors in a functional state.

*Plasma, Fresh Frozen* used as *Human plasma for fractionation* must comply with the specifications of the European Pharmacopoeia monograph *Human plasma for fractionation* (Ph. Eur. monograph 0853).

*Plasma, Fresh Frozen* (FFP) used for clinical transfusion must comply with the specifications given in this monograph (Part D, Paragraph 1).

It must contain, on average, not less than 70 IU Factor VIII per 100 mL and at least similar quantities of the other labile coagulation factors and naturally occurring inhibitors.

It must not contain irregular antibodies of clinical significance.

If leucocyte depleted, the component must contain less than \(1 \times 10^6\) leucocytes.

2. Preparation

a. From whole blood

Plasma is separated from whole blood collected using a blood bag with integral transfer packs, employing hard spin centrifugation, preferably within 6 hours and not more than 18 hours after collection if the unit is refrigerated. Plasma may also be separated from platelet rich plasma. Plasma may also be separated from whole blood, which immediately after donation has been rapidly cooled by a special device validated to maintain the temperature between + 20 °C and + 24 °C and held at that temperature for up to 24 hours.

Freezing must take place in a system that will allow complete freezing within one hour to a temperature below – 30 °C. If *Plasma, Fresh*
Frozen is to be prepared from a single pack whole blood donation, adequate sterility precautions must be adopted.

b. By apheresis

Plasma, Fresh Frozen may be collected by apheresis. The freezing process must commence within six hours of completion of the procedure in a system which allows complete freezing within one hour to a temperature below – 30 °C. Where use is made of a special device validated to rapidly cool the plasma to + 20 °C and + 24 °C and to maintain the temperature in that range, the plasma can be held at that temperature for up to 24 hours prior freezing.

c. Quarantine FFP

This FFP is 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, designed to exclude the risk associated with the window period. A period of six months is generally applied. This may be reduced if NAT testing is performed.

3. Requirements and quality control

Table 5D-1 lists the requirements. Additional testing may be required to comply with national requirements (see also Chapter 9 Standards for screening for infectious markers).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Grouping Only for clinical FFP</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
</tbody>
</table>

1 Unless performed on whole blood used as the source.
2 Unless intended only for fractionation.
Guide to the preparation, use and quality assurance of blood components

Table 5D-1(b)

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Stated volume ± 10%</td>
<td>All units</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Average (after freezing and thawing):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>not less than 70 IU Factor VIII per 100 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Every 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 units in the first</td>
</tr>
<tr>
<td></td>
<td></td>
<td>month of storage</td>
</tr>
<tr>
<td>Residual cells¹</td>
<td>Red cells: &lt; 6.0 × 10⁹/L</td>
<td>1% of all units with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a minimum of</td>
</tr>
<tr>
<td></td>
<td>Leucocytes: &lt; 0.1 × 10⁹/L</td>
<td>4 units per month</td>
</tr>
<tr>
<td></td>
<td>Platelets: &lt; 50 × 10⁹/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1% of all units, with</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a minimum of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 units per month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If leucocyte depleted: &lt; 1 × 10⁶</td>
<td></td>
</tr>
<tr>
<td>Leakage</td>
<td>No leakage at any part of container</td>
<td>All units</td>
</tr>
<tr>
<td></td>
<td>e.g. visual inspection after pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in a plasma extractor, before freezing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and after thawing</td>
<td></td>
</tr>
<tr>
<td>Visual changes</td>
<td>No abnormal colour or visible clots</td>
<td>All units</td>
</tr>
</tbody>
</table>

1 The exact number of units to be tested could be determined by statistical process control.
2 Cell counting performed before freezing.
3 This requirement is deemed to be met if 90% of the units tested fall within the values indicated.

4. Storage and transport

The following storage times and temperatures are permitted:

- 36 months at below – 25 °C;
- 3 months at – 18 °C to – 25 °C.

Storage temperature must be maintained during transport. Unless for immediate use the packs must be transferred at once to storage at the recommended temperature.

In order to preserve labile factors, *Plasma, Fresh Frozen* must be used as soon as possible following thawing. It must not be refrozen.
5. Labelling
The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:
• the producer's identification;
• the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
• the name of the blood component;
• the ABO RhD group (only for clinical FFP);
• the date of donation;
• the date of expiry;
• the name of the anticoagulant solution;
• additional component information: leucocyte depleted, irradiated, quarantined, etc. (if appropriate);
• the volume or weight of the blood component;
• the temperature of storage;
• that the component must be administered through a 150-200 μm filter.

After thawing, the date of expiry must be changed to the appropriate date (and time) of expiry. The temperature of storage must be changed accordingly.

6. Warnings
Transfusion of ABO blood group incompatible plasma may result in haemolytic transfusion reaction.

*Plasma, Fresh Frozen* must not be used in a patient with intolerance to plasma proteins.

Before use the component must be thawed in a properly controlled environment and the integrity of the pack must be verified to exclude
any defects or leakages. No insoluble cryoprecipitate must be visible on completion of the thaw procedure.

Adverse reactions

- 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;
- circulatory overload;
- anaphylaxis and allergic reactions.

Paragraph 2. Plasma, Fresh Frozen, Pathogen Reduced

1. Definition and properties

*Plasma, Fresh Frozen, Pathogen Reduced (PR)* is a component for transfusion prepared from a single donation either of *Whole Blood* or of plasma collected by apheresis, subjected to a pathogen inactivating procedure and frozen within a period of time and to a temperature that will adequately maintain the labile coagulation factors in a functional state.

*Plasma, Fresh Frozen, PR* used for clinical transfusion must comply with the specifications given in this monograph.

It contains, on average, about 50 to 70 per cent of the labile coagulation factors and naturally occurring inhibitors present in fresh unfrozen/thawed plasma.
The pathogen inactivating procedure on average reduces the risk for infection with enveloped viruses (such as HBV, HCV and HIV) at least a thousand fold.

It must not contain irregular antibodies of clinical significance.

If leucocyte-depleted, the component must contain less than $1 \times 10^6$ leucocytes.

### 2. Preparation

*Plasma, Fresh Frozen, PR* is prepared from plasma obtained from whole blood or collected by apheresis as described for *Plasma, Fresh Frozen*. The inactivation procedure is either applied before, or after freezing and thawing of plasma.

Pathogen reduction procedures are performed according to the manufacturers' instructions by one of the following methods: methylene blue, amotosalen and riboflavin methods.¹⁶

### 3. Requirements and quality control

Table 5D-2 lists the requirements. Additional testing may be required to comply with National requirements (see also Chapter 9 *Standards for screening for infectious markers*).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD¹</td>
<td>Grouping Only for clinical FFP</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
</tbody>
</table>

¹⁶ For pools of less than 12 single units, solvent detergent may be used as the pathogen reduction technique but this is not covered in this monograph.
<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Stated volume ± 10%</td>
<td>All units</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Average: not less than 50-70 IU Factor VIII per 100 mL</td>
<td>Every 3 months 10 units in the first month of storage¹</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Average (after freezing and thawing): ≥ 60 % of the potency of the freshly collected plasma unit</td>
<td>Every 3 months 10 units in the first month of storage¹</td>
</tr>
<tr>
<td>Residual cells²</td>
<td>Red cells: &lt; $6.0 \times 10^9$/L Leucocytes: &lt; $0.1 \times 10^9$/L Platelets: &lt; $50 \times 10^9$/L</td>
<td>1% of all units with a minimum of 4 units per month</td>
</tr>
<tr>
<td></td>
<td>If leucocyte depleted: &lt; $1 \times 10^6$/L</td>
<td>1% of all units, with a minimum of 10 units per month³</td>
</tr>
<tr>
<td>Leakage</td>
<td>No leakage at any part of container e.g. visual inspection after pressure in a plasma extractor, before freezing and after thawing</td>
<td>All units</td>
</tr>
<tr>
<td>Visual changes</td>
<td>No abnormal colour or visible clots</td>
<td>All units</td>
</tr>
</tbody>
</table>

1. The exact number of units to be tested could be determined by statistical process control.
2. Cell counting performed before freezing.
3. This requirement is deemed to be met if 90% of the units tested fall within the values indicated.

### 4. Storage and transport

The following storage times and temperatures are permitted:
- 36 months at or below – 25 °C;
• 3 months at –18 °C to –25 °C.
Storage temperature must be maintained during transport. Unless for immediate use, the packs must be transferred at once to storage at the recommended temperature.

In order to preserve labile factors, Plasma, Fresh Frozen, PR must be used as soon as possible following thawing. It must not be refrozen.

5. Labelling
The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

• the producer’s identification;
• the unique identity number; if two or more units are collected from the donor in one session, each component must have a unique component identity number;
• the name of the blood component;
• the ABO RhD group;
• the date of donation;
• the date of expiry;
• the name of the anticoagulant solution;
• the name of the pathogen inactivating compound;
• additional component information: leucocyte-depleted, irradiated, etc. (if appropriate);
• the volume or weight of the blood component;
• the temperature of storage;
that the component must be administered through a 150-200 μm filter.

After thawing, the date of expiry must be changed to the appropriate date (and time) of expiry. The temperature of storage must be changed accordingly.

6. Warnings

Transfusion of ABO blood group incompatible plasma may result in haemolytic transfusion reaction.

*Plasma Fresh Frozen, PR* must not be used:

- in a patient with intolerance to plasma proteins;
- when prepared by amotosalen treatment in neonates undergoing phototherapy;
- when prepared by methylene blue procedure for patients with G6PD deficiency;
- in case of known allergy to the compounds used for or generated by pathogen reduction procedure.

Before use the component must be thawed in a properly controlled environment and the integrity of the pack must be verified to exclude any defects or leakages. No insoluble cryoprecipitate must be visible on completion of the thaw procedure.

Adverse reactions

- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- transfusion related acute lung injury (TRALI);
- viral transmission (hepatitis B and C, HIV) is highly unlikely. Transmission of other pathogens that are not tested for or not sensitive to pathogen inactivation is possible;
- citrate toxicity in neonates and in patients with impaired liver function;
• circulatory overload;
• anaphylaxy and allergic reactions including allergy to the compounds used for or generated by pathogen reduction procedures.

**Paragraph 3. Cryoprecipitate**

**1. Definition and properties**

*Cryoprecipitate* is a component containing the cryoglobulin fraction of plasma obtained by further processing of *Plasma, Fresh Frozen* and then concentrated.

Contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in freshly drawn and separated plasma.

**2. Preparation**

*Plasma, Fresh Frozen* is thawed, either overnight at +2 ºC to +6 ºC or by the rapid thaw-siphon thaw technique. After thawing, the component is re-centrifuged using a hard spin at the same temperature. The supernatant cryo poor plasma is then partially removed. The resulting cryoprecipitate is then rapidly frozen.

When cryoprecipitate is prepared from whole blood derived plasma the maximal final volume of the component is 40 mL.

Alternatively, *Plasma, Fresh Frozen* obtained by apheresis may be used as the starting material, the final component being prepared by 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.
Guide to the preparation, use and quality assurance of blood components

3. Requirements and quality control

Table 5D-3 lists the requirements. Additional testing may be required to comply with National requirements (see also Chapter 9 Standards for screening for infectious markers).

Table 5D-3a

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD¹,²</td>
<td>Grouping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Only for clinical FFP</td>
<td>All units</td>
</tr>
<tr>
<td>anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
</tbody>
</table>

¹ Unless performed on whole blood used as the source.
² Unless intended only for fractionation.

Table 5D-3b

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume¹</td>
<td>30-40 mL</td>
<td>All units</td>
</tr>
</tbody>
</table>
| Factor VIII             | ≥ 70 IU per unit      | Every 2 months:
|                         |                       | a. pool of 6 units of mixed blood groups during first month of storage
|                         |                       | b. pool of 6 units of mixed blood groups during last month of storage |
| Fibrinogen              | ≥ 140 mg per unit     | 1% of all units with a minimum of 4 units per month |
Von Willebrand Factor & Every 2 months:
> 100 IU per unit
a. pool of 6 units of mixed blood groups
during first month of storage
b. pool of 6 units of mixed blood groups
during last month of storage

1 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 volume may be different.

4. Storage and transport

The stability on storage is dependent on the storage temperature. The optimal storage temperature is below – 25 ºC. Approved storage times are:

- 36 months at or below – 25 ºC;
- 3 months at – 18 ºC to – 25 ºC.

Storage temperature must be maintained during transport. The receiving hospital blood bank must ensure that Cryoprecipitate has remained frozen during transit. Unless for immediate use, the Cryoprecipitate must be transferred at once to storage at the temperature stated above.

Before use, Cryoprecipitate must be thawed in a properly controlled environment at + 37 ºC immediately after removal from storage. Dissolving of the precipitate must be encouraged by careful manipulation during the thawing procedure.

In order to preserve labile factors, Cryoprecipitate must be used as soon as possible following thawing. It must not be refrozen.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer's identification;
Guide to the preparation, use and quality assurance of blood components

- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the name of the blood component;
- the ABO group;
- the date of preparation;
- the date of expiry;
- additional component information: Leucocyte depleted, irradiated, quarantined, etc. (if appropriate);
- the volume or weight of the blood component;
- the temperature of storage;
- that the component must be administered through a 150-200 μm filter.

After thawing, the date of expiry must be changed to the appropriate date (and time) of expiry. The temperature of storage must be changed accordingly.

6. Warnings

Before use the component must be thawed in a properly controlled environment and the integrity of the pack must be verified to exclude any defects or leakages.

_Cryoprecipitate_ is not recommended for patients with intolerance to plasma proteins.

Adverse reactions
- non haemolytic transfusion reaction (mainly chills, fever and urticaria);
- transfusion related acute lung injury (TRALI);
- possibility of development of inhibitors to Factor VIII in patients with haemophilia;
in rare instances, haemolysis of recipient red blood cells due to high titre alloagglutinins in the donor have been recorded;

- 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.

**Paragraph 4. Plasma, Fresh Frozen, Cryoprecipitate-Depleted**

1. **Definition and properties**

   *Plasma, Fresh Frozen, Cryoprecipitate-Depleted* is a component prepared from *Plasma, Fresh Frozen* by the removal of 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*.

2. **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.

3. **Requirements and quality control**

   As indicated for *Plasma, Fresh Frozen* (Table 5D-1) with the addition given in Table 5D-4. Additional testing may be required to comply with National requirements (see also Chapter 9 *Standards of screening for infectious markers*).
Table 5D-4

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Stated volume ± 10%</td>
<td>All units</td>
</tr>
</tbody>
</table>

4. Storage and transport

The stability on storage is dependent on the storage temperature. The optimal storage temperature is below – 25 °C. Approved storage times are:

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

Storage temperature must be maintained during transport. The receiving hospital blood bank must ensure that Plasma, Fresh Frozen, Cryoprecipitate-Depleted has remained frozen during transit. Unless for immediate use, the units must be transferred at once to storage at the temperature stated above.

In order to preserve labile factors, Plasma Fresh Frozen, Cryoprecipitate-Depleted, must be used as soon as possible following thawing. It must not be refrozen.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number; if two or more units are collected from the donor in one session, each component must have an unique component identity number;
- the ABO group;
- the date of preparation;
- the name of the anticoagulant solution;
Standards. Chapter 5

• the name of the blood component;
• additional component information: leucocyte depleted, irradiated, quarantined, pathogen reduced, etc. (if appropriate);
• the date of expiry;
• the volume or weight of the blood component;
• the temperature of storage;
• that the component must be administered through a 150-200 μm filter.

After thawing, the date of expiry must be changed to the appropriate date (and time) of expiry. The temperature of storage must be changed accordingly.

6. Warnings

Transfusion of ABO blood group incompatible plasma may result in haemolytic transfusion reaction.

*Plasma Fresh Frozen, Cryoprecipitate-Depleted* is not recommended for patients with intolerance to plasma proteins.

Adverse reactions

• 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;
• circulatory overload.
Component monographs

Part E. White cell components
Paragraph 1. Granulocytes, Apheresis

1. Definition and properties

Granulocytes Apheresis is a component which contains granulocytes suspended in plasma obtained by apheresis of a single donor using automated cell separation equipment.

An adult therapeutic dose of Granulocytes, Apheresis contains between $1.5 \times 10^8$ – $3.0 \times 10^8$ granulocytes/kg body weight of the designated recipient.

Granulocytes, Apheresis has a significant content of red blood cells, lymphocytes and platelets.

Granulocytes, Apheresis must be irradiated.

IMPORTANT NOTICE

Clinical efficacy, indication and dosage of granulocyte transfusion have not been established. Prior to the collection the potential donor of granulocytes needs to receive medication and sedimenting agents will be required during the apheresis procedure. Both of these have potentially severe side effects which are described below. Thus, it is essential to gain the informed consent of the donor. In addition to the recognized complications of routine donor apheresis, the following side effects may occur:

- Hydroxyethyl starch (HES): acts as a volume expander, and 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, cataracts, and peptic ulcer.
- 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 over Acute Myeloid Leukemia (AML)/Myelodysplasia (MDS) development following G-CSF administration are based primarily on reports of increased rates of AML/MDS among women with breast cancer who received chemotherapy or patients with Severe Chronic Neutropenia (SCN) who received G-CSF support. To date registry data from Europe and the United States have not identified any increased risk of AML/MDS including data of over 100 000 healthy individuals who donated PBSC and received G-CSF as pre-treatment, but the median follow-up of these studies is less than 5 years.

2. Preparation

The donor requires pre-treatment with corticosteroid and/or growth factors. *Granulocytes, Apheresis* are collected from a single donor by apheresis. Optimal collection yields will require the use of a sedimenting agent, such as HES, low molecular weight dextran or modified fluid gelatin.

3. Requirements and quality control

Table 5E-1 lists the requirements. Additional testing may be required to comply with National requirements (see also Chapter 9 *Standards for screening for infectious markers*).

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, RhD</td>
<td>Grouping</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HIV 1 &amp; 2</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative by approved screening test</td>
<td>All units</td>
</tr>
<tr>
<td>HLA (when required)</td>
<td>Typing</td>
<td>As required</td>
</tr>
<tr>
<td>Volume</td>
<td>&lt; 500 mL</td>
<td>All units</td>
</tr>
<tr>
<td>Granulocytes content</td>
<td>Achieve clinical dose: e.g. adult patient with 60 kg: 0.9-1.8 × 10^{10} granulocytes per unit</td>
<td>All units</td>
</tr>
</tbody>
</table>

Table 5E-1
4. Storage and transport

This preparation is not suitable for storage and must be transfused as soon as possible after collection. If unavoidable, storage must be limited to the shortest possible period.

The unit must be transported to the user in a suitable container at +20 °C to +24 °C, but without agitation.

5. Labelling

The labelling must comply with the relevant national legislation and international agreements. The following information must be shown on the label or contained in the component information leaflet, as appropriate:

- the producer’s identification;
- the unique identity number;
- the ABO and RhD group;
- the date of donation;
- the name of the anticoagulant solution and additive solutions and/or other agents;
- the name of the blood component;
- additional component information: irradiated,
- the date of expiry (and time of expiry, when required);
- the number of granulocytes;
- the temperature of storage;
- HLA type if determined;
- that the component must be administered through a 150-200 μm filter.
6. Warnings

Because of the possibility of severe adverse effects associated with both the collection (donor side effects) and the transfusion of granulocytes (recipient side effects) the goals of granulocyte transfusion must be clearly defined before a course of therapy is initiated.

As there is significant content of red blood cells, compatibility of donor red cells with the designated recipient must be verified by suitable pre-transfusion testing. RhD negative female recipients of child-bearing potential must 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-immune globulin must be considered.

Attention to HLA compatibility is also required for allo-immunized recipients.

Granulocytes, Apheresis must be irradiated.

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

Administration through a micro-aggregate or leucocyte reduction filter is contraindicated.

The risk of adverse reactions is increased with concomitant administration of Amphotericin B.

Adverse reactions

The adverse reactions associated with the administration of this component are:

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

- 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.
Chapter 6

Standards for blood components for intrauterine, neonatal and infant use

Part A. Components for intrauterine transfusions

Part B. Components for neonatal exchange transfusion

Part C. Components (small volume) for neonatal and infant transfusion

Specially designed blood components are required for intrauterine, neonatal and infant transfusion.

These recipients are particularly prone to the complications of cytomegalovirus infection and appropriate steps to minimise the risk are required.

Methods of preparation, storage and administration of these components should be validated to ensure that the delivered potassium load is within acceptable limits.

If components are split for use in neonates and infants each satellite pack must have a unique unit identity number which allows traceability to the donation.
Standards of blood components for intrauterine, neonatal and infant use

Part A. Components for intrauterine transfusions
Paragraph 1. Red Cells, Leucocyte-Depleted for Intrauterine Transfusion

1. Definition and properties

Red Cells, Leucocyte-Depleted for Intrauterine Transfusion (IUT) is a red cell component for intrauterine transfusion.

Red Cells, IUT has a haematocrit (Ht) of 0.70 to 0.85.

Red Cells, IUT contains less than $1 \times 10^6$ leucocytes per unit.

2. 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, must be compatible with both mother and fetus. In the event that the fetal blood group is not known, a type O RhD-negative donation must be selected unless the mother has blood group antibodies which necessitate the use of another blood group. The red cells must be antigen negative for any relevant maternal antibody.

The component must not contain irregular antibodies of clinical significance.

Red Cells, IUT, must be used within five days from donation.

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

3. Requirements and quality control

As indicated for the source component with the following additions changes given in Table 6A-1.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>0.70-0.85</td>
<td>All units</td>
</tr>
</tbody>
</table>
4. Storage and transport

The storage and transport conditions are as for primary component. The storage time must not be longer than 24 hours after concentration and irradiation and five days from donation.

5. Labelling

The additional and/or amended labelling requirements to those of the primary 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: irradiated;
- the volume or weight of the blood component;
- the haematocrit of the blood component.

6. Warnings

Compatibility of this component with maternal serum/plasma must be verified by suitable pre-transfusion testing.

The rate of transfusion should be controlled to avoid excessive fluctuations in blood volume.

As the fetus is at increased risk of graft versus host disease, the component must be irradiated.

Adverse reactions

Although the component is given to the fetus, adverse reactions may also affect the mother.

The adverse reactions are outlined in the relevant primary component monograph.
In addition the fetus is especially vulnerable to:
- CMV infection;
- citrate toxicity;
- metabolic imbalance (e.g. hyperkalaemia);
- circulatory overload.

**Paragraph 2. Platelets, Leucocyte-Depleted for Intrauterine Transfusion**

1. **Definition and properties**

*Platelets, Leucocyte-Depleted for Intrauterine Transfusion (IUT)* is a platelet component for intrauterine transfusion, obtained from a single donor either by apheresis or from whole blood.

*Platelets, IUT* must be leucocyte depleted, irradiated and may be hyperconcentrated.

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

2. **Preparation**

*Platelets, IUT* is prepared from either *Platelets, Apheresis, LD*, or by the leucocyte-depletion of *Platelets, Recovered*, and where appropriate the collection is from an HPA compatible donor.

The component can be concentrated if necessary by removing part of the supernatant solution by centrifugation. This must be followed by a 1 hour resting period.

If platelets obtained from the mother are to be transfused, then these must be depleted of plasma and re-suspended in an additive solution.

*Platelets, IUT* must be irradiated.

3. **Requirements and quality control**

As indicated for the source component with the following additions changes given in Table 6A-2.
Table 6A-2

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA&lt;sup&gt;1&lt;/sup&gt; Typing</td>
<td></td>
<td>When required</td>
</tr>
<tr>
<td>Volume</td>
<td>50-60 mL</td>
<td>All units</td>
</tr>
<tr>
<td>Platelet content</td>
<td>45-85 × 10&lt;sup&gt;9&lt;/sup&gt; per unit</td>
<td>All units</td>
</tr>
</tbody>
</table>

1 HPA typing of the selected donor, not of the individual component.

4. Storage and transport

Storage and transport as defined for primary component, but must be used within 6 hours after any secondary concentration process.

5. Labelling

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

- if components are split for use in neonates and infants each split must have a unique unit identity number which allows traceability to the donation;
- additional component information:
  - irradiated, plasma or supernatant reduced, etc. (if appropriate);
  - the volume or weight of the blood component;
  - the platelet count;
  - the date and time of expiry.

6. Warnings

As the fetus is at increased risk of graft versus host disease, the component must be irradiated.

Control the rate of transfusion to avoid excessive fluctuations in blood volume.

Monitor for possible bleeding after puncture.
Adverse reactions

Although the component is given to the fetus, adverse reactions may also affect the mother.

The adverse reactions are outlined in the relevant primary component monograph.

In addition the fetus is especially vulnerable to:

- cytomegalovirus infection;
- citrate toxicity;
- circulatory overload.
Standards of blood components for intrauterine, neonatal and infant use

Part B. Components for neonatal exchange transfusion
Paragraph 1. Whole Blood, Leucocyte-Depleted for Exchange Transfusion

1. Definition and properties

*Whole Blood, Leucocyte-Depleted for Exchange Transfusion (ET)* corresponds to *Whole Blood, LD* with the properties as defined in the relevant monograph, selected for neonatal exchange transfusion to be transfused within five days of donation.

2. Preparation

If the maternal antibody is anti-RhD, the component is prepared from type O RhD-negative red cells. If maternal antibody is other than anti-RhD, red cells are selected that are antigen negative for any relevant maternal antibody.

*Whole Blood, ET* must be irradiated:
- if there is a history of prior IUT;
- for all other patients unless compelling clinical circumstances indicate that delay would compromise the clinical outcome.

*Whole Blood, ET* must be used within 24 hours of irradiation.

3. Requirements and quality control

As indicated for *Whole Blood, LD*.

4. Storage and transport

The storage and transport of *Whole Blood, ET* is as in the monograph for *Whole Blood, LD*.

The storage time must not be longer than 24 hours after irradiation and five days from donation.

5. Labelling

The additional and/or amended labelling requirements to those of *Whole Blood, LD* are:
- blood group phenotype, if the antibody is other than anti-RhD;
Standards. Chapter 6

- the modified date and time of expiry;
- additional component information: irradiated.

6. Warnings

Blood group compatibility with any maternal antibodies is essential.

Control the rate of transfusion 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 the newborn undergoing exchange transfusion are:
- metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
- thrombocytopenia;
- cytomegalovirus infection;
- graft versus host disease unless irradiated;
- circulatory overload;
- haemolytic transfusion reaction.

Paragraph 2. Whole Blood, Leucocyte-Depleted, Plasma Reduced for Exchange Transfusion

1. Definition and properties

Whole Blood, Leucocyte-Depleted, Plasma Reduced for Exchange Transfusion (PR, ET). Whole Blood, PR, ET is Whole Blood, ET with a proportion of the plasma removed.

2. Preparation

Whole Blood, LD is selected within five 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 type O RhD-negative donation. If maternal antibody is other than anti-RhD, red cells are selected that are antigen negative for any relevant maternal antibody.

*Whole Blood, PR, ET* must be irradiated if:
- there is a history of prior IUT,
- for all other patients unless compelling clinical circumstances indicate that delay would compromise the clinical outcome.

*Whole Blood, PR, ET* must be used within 24 hours of irradiation.

### 3. Requirements and quality control

As indicated for *Whole Blood, LD* with the following additions or changes as given in Table 6B-2.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>As clinically prescribed or locally defined</td>
<td>All units</td>
</tr>
</tbody>
</table>

### 4. Storage and transport

The storage and transport of *Whole Blood, PR, ET* is as in the monograph for *Whole Blood, LD*.

The storage time must not be longer than 24 hours after irradiation and 5 days from donation.

### 5. Labelling

The 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: irradiated, haematocrit.
6. Warnings

Blood group compatibility with any maternal antibodies is essential.

Control the rate of transfusion 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 the newborn undergoing exchange transfusion are:

- metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
- thrombocytopenia;
- cytomegalovirus infection;
- graft versus host disease unless irradiated;
- circulatory overload;
- haemolytic transfusion reaction.

Paragraph 3. Red Cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma for Exchange Transfusion

1. Definition and properties

Red Cells, Leucocyte-Depleted, suspended in Fresh Frozen Plasma, for Exchange Transfusion (Red Cells, in FFP, ET) is a reconstituted component derived from Red Cells, LD or Red Cells, LD-AS to which Plasma, Fresh Frozen is added.

2. Preparation

Red Cells, LD or Red Cells, LD-AS are selected within 5 days from collection for secondary processing. Supernatant containing additive solution and/or plasma is removed after centrifugation and thawed fresh frozen plasma is added to reach the clinically required haematocrit.
If the maternal antibody is anti-RhD, the component is prepared from type O RhD-negative red cells. If maternal antibody is other than anti-RhD, red cells are selected that are antigen negative for any relevant maternal antibody. The red cells and FFP must be ABO compatible with mother and infant.

Red Cells, in FFP, ET must be irradiated if:
- there is a history of prior IUT;
- for all other patients unless compelling clinical circumstances indicate that delay would compromise the clinical outcome.

Red Cells, in FFP, ET must be used within 24 hours of irradiation.

3. Requirements and quality control

As indicated for the source component (Red Cells, LD; Red Cells, LD-AS and FFP) with the following additions and changes given in Table 6B-3.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirement</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit</td>
<td>As clinically prescribed or locally defined</td>
<td>All units</td>
</tr>
</tbody>
</table>

4. Storage and transport

The storage and transport of Red Cells, in FFP, ET is as in the monograph for Red Cells, LD or Red Cells, LD–AS.

In addition, storage time must not be longer than 24 hours after reconstitution and irradiation and 5 days from the red cell donation.

5. Labelling

The additional and/or amended labelling requirements to those of the reconstituting components are:
- a new unique identity number by which the original donations’ identity numbers must 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: irradiated, haematocrit.

6. Warnings

Compatibility of Red Cells, in FFP, ET with the intended recipient must be verified by suitable pre-transfusion testing. Blood group compatibility with any maternal antibodies is essential.

Control the rate of transfusion to avoid excessive fluctuations in blood volume.

Adverse reactions

The side effects are those of the two constituting components.

Particular concerns in the context of the newborn undergoing exchange transfusion are:

• metabolic imbalance including: citrate toxicity, hypocalcaemia, hyperkalaemia, hypoglycaemia, hypokalaemia;
• thrombocytopenia;
• cytomegalovirus infection;
• graft versus host disease unless irradiated;
• circulatory overload;
• haemolytic transfusion reaction.
Standards of blood components for intrauterine, neonatal and infant use

Part C. Components (small volume) for neonatal and infant transfusion
Paragraph 1. Red Cells for Neonatal and Infant Small Volume Transfusion

1. 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 primary component.

2. Preparation

Red Cells for Neonatal and Infant Small Volume Transfusion are prepared by the secondary processing of Red Cells, BCR; Red cells, BCR-AS; Red Cells, LD or Red Cells, LD-AS. The selected component is divided into 3 to 8 satellite packs by using a closed or functionally closed system. The component may be irradiated where clinically indicated.

3. Quality control

Quality control of the primary component is stated in the relevant component monograph. Additional quality control of the final component is given in the Table 6C-1.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirements</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>25-100 mL per unit</td>
<td>All units</td>
</tr>
</tbody>
</table>

4. Storage and transport

Storage and transport requirements as for primary red cell component. The storage time must not exceed that of the original component. If the component is irradiated, it must be used within 48 hours.
5. Labelling

The additional and/or amended labelling requirements to those of the primary red cell component are:

- if components are split for use in neonates and infants each satellite pack must have a unique unit identity number which allows traceability to the donation;
- the name of the blood component;
- additional component information: irradiated, etc. (if appropriate);
- the volume or weight of the component;
- the date and time of expiry.

6. Warnings

Transfusion rates must be carefully controlled.

Not for rapid transfusion or large volume transfusion unless used within 5 days from red cell donation.

Adverse reactions

Adverse reactions are those of the primary component selected for secondary processing. In addition of particular concern for the infant are:

- metabolic imbalance (e.g. hyperkalaemia in massive transfusion or if rapidly transfused);
- citrate toxicity;
- circulatory overload;
- cytomegalovirus infection;
- GvHD.
Chapter 7

Standards for autologous pre-deposit transfusion

Paragraph 1. General overview
Autologous blood components obtained from pre-operative donations must be collected, prepared and stored in the same conditions as allogeneic donations.

For these reasons, predeposit autologous donation must be carried out in or under the control of blood establishments or in authorised clinical departments which are subject to the same rules and controls of this activity as blood establishments.

Role of the physician in charge of collection
The physician in charge of blood collection takes the final responsibility for ensuring that the patient’s clinical condition allows preoperative blood donation.

Where autologous donation is contra-indicated, the physician in charge of blood collection informs the patient and the physician in charge of the patient.

Informed consent
Patients must be informed:
• about the autologous transfusion procedure, and the risks and benefits thereof;
about the biological tests, including virological markers, that will be performed;
• that allogeneic transfusion will be used in addition to autologous if needed;
• that unused units will be destroyed.

This information must lead to written informed consent being obtained.

In paediatrics, the information must be given to the child and the parents, and the parents must give a written informed consent.

**Contra-indications of predeposit donations**

Any active bacterial infection is an absolute contra-indication.

**Paragraph 2. Predeposit blood components preparation, storage and distribution**

**Blood typing and microbiological screening of autologous blood components**

Blood typing and microbiological screening must be the same as the minimum required for allogeneic components.

**Preparation of autologous blood components**

The methods used for the preparation must be the same as for allogeneic components.

**Labelling of autologous blood components**

The label on the container must state, in addition to the information valid for allogeneic blood components, the following:
• the statement: 'AUTOLOGOUS DONATION';
• the statement: 'STRICTLY RESERVED FOR';
  • family name and first name,
  • date of birth,
  • identity number of the patient.
Standards. Chapter 7

Storage and handling of autologous blood components

Autologous blood components must be stored under the same conditions as, but separate from, allogeneic components.

Pre-transfusion tests must be carried out as for allogeneic components.

Release procedures must include a confirmation of identity:

- on the components labels,
- on the prescription document,
- and at the bedside.

Untransfused autologous blood components must not be used for allogeneic transfusion or plasma fractionation.
Chapter 8

Standards for blood group serology

Paragraph 1. General overview
The below listed prescriptions should be followed for pre-analytical, analytical and post-analytical procedures:

- For pre-analytical procedures, it is necessary to ensure and document that the reagents used are in-date and have been stored according to specifications.
- All samples used must be correctly labelled and suitable for the analysis to be performed.
- Appropriate performance checks must be carried out on equipment on a daily basis.
- Analytical procedures must be performed according to the manufacturer’s instructions, or adaptations must be fully validated.

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

Paragraph 2. Blood group serology testing of blood donations

ABO and RhD testing must be performed on all donations.

- The ABO and RhD labelling of the red cell concentrates of all first time donations must be based upon two independent ABO and RhD tests.
The ABO and RhD blood group must be verified on each subsequent donation and a comparison must be made with the historically determined blood group.

If a discrepancy is found, the applicable blood components must not be released until the discrepancy is unequivocally resolved.

All first time donors and repeat and regular donors with a history of transfusions or pregnancy since the last donation, must be tested for clinically significant irregular red cell antibodies. Where applicable, the blood or blood component must be labeled accordingly.

**Paragraph 3. Validation of reagents**

The validation of reagents must detect deviation from the established minimal quality requirements (specifications). In the EU, blood group reagents are considered as *in vitro* diagnostic devices and must be CE marked. EU Directive 98/79/EC classified the ABO RhD, Kell test serum and A and B cells in list A. The manufacturer must have a full Quality System certified by an authorised body and submit an application containing all the control results for each lot.

An evaluation of quality is performed on samples before purchasing batches of commercial reagents. Prospective purchasers must require potential suppliers to provide them with full validation data for all lots of reagents. Each lot of reagent must be validated by the purchaser and the results should be as good as the specifications contained in the manufacturers monograph. Minimum potency standards for anti-A, anti-B and anti-RhD must be used in the assessment of blood grouping reagents.

**Paragraph 4. Quality control**

Quality control procedures in blood group serology for equipment, reagents and techniques must be established.

Laboratories undertaking blood group serology testing must participate in a regular external quality assurance programme.
Chapter 9

Standards for screening for infectious markers

Paragraph 1. Selection and validation of infectious markers tests

Only tests that have been licensed or evaluated and considered suitable by the responsible Health Authorities can be used. In the EU, these reagents are considered as *in vitro* diagnostic devices and must be CE marked. EU Directive 98/79/EC classifies the HIV, HTLV, hepatitis B and hepatitis C screening tests in list A. The manufacturer must have a full Quality System certified by an authorised body and submit an application containing all the control results for each lot.

Screening test for infectious markers must be performed in accordance with the instructions provided by the manufacturer of reagents and test kits.

All laboratory assays and test systems, including modifications, for infectious disease marker screening used by blood establishments must be validated before introduction to ensure compliance with intended use of the test.

All techniques and modification to techniques in use must be validated.

Correct determination of negative and positive controls as provided by and in accordance with manufacturer’s instructions is a minimum requirement.
Guide to the preparation, use and quality assurance of blood components

Paragraph 2. Mandatory serological screening tests

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),
- hepatitis B surface antigen (HBsAg) assay which will detect at least 0.5 IU/mL of HBsAg.

Appropriate quality control measures must be in place when screening for infectious markers. Specific requirements are shown in Table 9-1.

Table 9-1. Quality control of mandatory serological screening tests

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirement</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HIV 1/2 screening sensitivity</td>
<td>Detection of weak positive serum(^1)</td>
<td>Each plate/run</td>
</tr>
<tr>
<td>Anti-HCV screening sensitivity</td>
<td>Detection of weak positive serum(^1)</td>
<td>Each plate/run</td>
</tr>
<tr>
<td>HBsAg screening test</td>
<td>detection of 0.5 IU/mL standard</td>
<td>Each plate/run</td>
</tr>
</tbody>
</table>

\(^1\) Where possible the weak positive control should not be the one provided by the manufacturer.

Laboratories undertaking infectious disease testing of blood donations must participate in a regular external quality assurance programme.

Paragraph 3. Additional serological screening tests

National authorities may also require additional screening tests such as Treponema pallidum haemagglutination assay (TPHA) or ELISA for syphilis, antibody to human T-cell lymphotropic virus types I (anti-HTLV-1) and II (anti-HTLV-II), antibody to hepatitis B core antigen (anti-HBc).

Appropriate quality control measures must be in place when screening for infectious markers. Specific requirements are shown in Table 9-2.
Table 9-2. Quality control of additional serological screening

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirement</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis: TPHA or ELISA</td>
<td>Detection of weak positive serum¹</td>
<td>Each plate/run</td>
</tr>
<tr>
<td>Anti-HTLV I/II screening test</td>
<td>Detection of weak positive serum¹</td>
<td>Each plate/run</td>
</tr>
<tr>
<td>Anti-HBc screening test</td>
<td>Detection of weak positive serum¹</td>
<td>Each plate/run</td>
</tr>
</tbody>
</table>

¹ Where possible, the weak positive control should not be the one provided by the manufacturer.

**Paragraph 4. Management of reactive results in serological screening tests**

If any of the repeat tests are reactive, then the donation is deemed repeatedly reactive. The donation must not be used for transfusion or manufacture of medicinal products. Samples from the donation must be sent to a certified/accredited medical microbiology reference laboratory for confirmation.

Initially reactive donations must be retested in duplicate by the same assay unless otherwise recommended by the manufacturer.

Algorithms to enable consistent resolution of repeatedly reactive donations must be in place. In the event that the repeatedly reactive donation is confirmed positive, the donor must be notified and a further sample obtained to reconfirm the results and the identity of the donor. The results of confirmatory testing identifying evidence of ongoing infection must be discussed with the donor and the donor must be deferred from donation, and referred for appropriate care.

The above rules do not necessarily apply to all donations found repeatedly reactive for anti-HBc. Additional testing, e.g. for HBs-antibody and/or HBV-DNA might enable some repeatedly reactive donations to be used clinically.
In the event that a confirmed HBV, HCV or HIV infection is shown in a repeat donor, the blood establishment must undertake a look back procedure on previous potentially infectious donations. This must include the following:

- The blood establishment must inform the hospital in writing about the incident and advise the hospital to trace the recipient(s) of the implicated blood component(s) and inform the treating physician about the potentially infectious transfusion.
- The relevant plasma fractionation organisation must be notified.
- If the recipient is confirmed to be positive for the given infection the incident must be reported to the national haemovigilance system and/or competent authority.

**Paragraph 5. Nucleic acid amplification techniques**

If screening of blood donations by Nucleic Acid Amplification Techniques (NAT) is required by National Authorities for release of blood components, the NAT assays must be validated to detect 5000 IU/mL for HCV-NAT and 10 000 IU/mL for HIV-NAT (as defined for the single donation by WHO standards).

Appropriate quality control measures must be in place when screening for infectious markers. Specific requirements are shown in Table 9-3.

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirement</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV-NAT</td>
<td>Detection of 5000 IU/mL HCV-RNA per donation</td>
<td>Internal control for each NAT reaction</td>
</tr>
<tr>
<td>HIV-NAT</td>
<td>Detection of 10 000 IU/mL HIV RNA per donation</td>
<td>Internal control for each NAT reaction</td>
</tr>
</tbody>
</table>

1 As defined by WHO standards.
**Paragraph 6. Selective screening of donations**

Testing of selected donations for antibody to cytomegalovirus (anti-CMV) may be undertaken. When performed the assay and test system must be fully validated. Confirmation of reactive results and notification of reactive donors is not necessary.

Testing of selected donations for malaria antibody may be undertaken. When performed the assay and test system must be fully validated.

Appropriate quality control measures must be in place when screening for infectious markers. Specific requirements are shown in Table 9-4.

**Table 9-4. Quality control of selective screening tests**

<table>
<thead>
<tr>
<th>Parameter to be checked</th>
<th>Requirement</th>
<th>Frequency of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CMV screening test</td>
<td>Detection of weak positive serum¹</td>
<td>Each plate/run</td>
</tr>
<tr>
<td>Malaria antibody test</td>
<td>Detection of weak positive serum¹</td>
<td>Each plate/run</td>
</tr>
</tbody>
</table>

¹ Where possible the weak positive control should not be the one provided by the manufacturer.
Chapter 10

Standards for transfusion

Paragraph 1. Pre-transfusion measures
Prior to any transfusion of blood components, appropriate indications must be considered and documented.

Identification of patient at blood sampling
Samples for blood typing and compatibility testing must be clearly labelled and uniquely identify the patient.

The phlebotomist’s signature must be on the blood order.

Blood group serological investigations
a. Blood typing
The ABO and RhD blood type and, when needed, other blood types, must be determined on the patient’s blood sample before transfusions except in emergencies when a delay may be life threatening and typing may be carried out in parallel with transfusion of the blood components.

The laboratory must have a reliable and validated procedure for blood typing which will include double checking of data at the time of issuing a report on the blood group, and other serological findings, for inclusion in the patient’s clinical record.
b. Compatibility testing

The compatibility between donor red cells and recipient’s plasma or serum must be assured in transfusions of components containing amounts of red cells visible to the naked eye.

Compatibility testing must be carried out on a sample taken no more than 4 days before the proposed transfusion for patients who have been transfused or pregnant during the last three months.

When clinically significant red cell alloantibodies are present in the patient’s circulation, red cells which lack the corresponding antigens must be selected for transfusion whenever possible.

Compatibility testing between donor red cells and recipient’s plasma or serum must be done in all cases with irregular red cell antibodies.

c. Type and screen

A type and screen procedure, where used as a replacement for compatibility testing, must include:

- a reliable and validated, preferably by computer, checking procedure when the blood units are delivered;
- reagent red cells which cover all antigens, preferably homozygous, corresponding to the vast majority of clinically important antibodies;
- sufficiently sensitive techniques for the detection of red cell antibodies;
- laboratory records of tests performed and of the destination of all units handled (including patient identification);
- a sample of the serum used for cross-matching or antibody screening must be retained for a period of time as determined by national regulations.
Paragraph 2. Transfusion

Safety measures

Procedures must be in place to assure the safety of each step in the transfusion process.

The person who administers blood components to a patient must identify the patient correctly.

The identification number and nature of the units transfused must be noted in the patient’s record so that the donors can be traced if necessary.

Clinical surveillance

Observation of the patient during and after transfusion is essential to ensure that early signs and symptoms of a possible transfusion reaction are promptly identified.

Confirmation of transfusion must be sent back to hospital blood bank.

Handling and storage of blood

Once the infusion set is inserted into the blood component pack, the infusion must generally be completed in no more than 6 hours. If the transfusion is disconnected, it must not be restarted and the unit should be discarded because of risk of bacterial contamination.

Warming of blood

If indicated, blood can be warmed. In that case a specifically designed commercial device must be used according to the manufacturer’s instructions. Blood warming devices must be properly maintained, and validated to ensure that the correct temperature of the blood is achieved.

Addition of medicinal products or infusion solutions to components

Because of the risk of damage to the blood components medicinal products or infusion solutions must not be added to blood units.
Guide to the preparation, use and quality assurance of blood components

Handling of frozen units

If thawing in a water bath, steps must be taken to prevent contamination of the administration ports.

After thawing of frozen plasma or cryoprecipitate the content must be inspected to ensure that all the contents have been dissolved and that the container is not damaged. Containers which leak must be discarded. Thawed preparations should be transfused as soon as possible and must not be refrozen.

Adverse reactions

Procedures must be in place for the management, investigation and reporting of adverse reactions.
Chapter 11

Standards for haemovigilance

Paragraph 1. Overview

Haemovigilance procedures must be in place, ensuring the organised surveillance of serious adverse or unexpected events or reactions in recipients of blood and blood components.

Haemovigilance procedures must be in place, ensuring both the organised surveillance of serious adverse or unexpected events or reactions in donors and the epidemiological assessment of infections in donors.

The results of haemovigilance analysis must be fed back periodically to the providers of haemovigilance data and communicated to the field and to relevant competent authorities, including recommendations on preventive or corrective measures.

Paragraph 2. Prerequisites for implementation of a haemovigilance network

Haemovigilance must be a shared responsibility of the professionals in the field and the competent national authorities for blood safety.

Traceability of blood components

There must be procedures in place ensuring full traceability, allowing the tracing of each individual unit of blood or blood components derived from it, from the donor to its final destination, whether this is a patient, a manufacturer of medicinal products or disposal, and vice versa.
Traceability must also cover cases in which the blood unit or component is not transfused to a patient, but is used for the manufacturing of medicinal products or for research and investigational purposes, or disposed of.

Hospitals must 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.

**Confidentiality of haemovigilance data**

Any database of haemovigilance reports must operate in compliance with applicable regulations on confidentiality of individual medical patient and donor data. Individual reports must be anonymised.

**Paragraph 3. Device defects**

When a causality assessment suggests that a device had at least a possible role in causing an adverse reaction/event the manufacturer or his authorised representative must be notified at the same time as the competent authority, even if at the time of the reporting the full causality may not necessarily be established.

**Paragraph 4. Post-transfusion infection reported to the blood establishment**

Hospitals must inform the blood establishment whenever a recipient of blood components develops laboratory tests results and/or disease symptoms, indicating that a blood component may have been infectious for hepatitis (B or C) or HIV.

The blood establishment must request relevant information from the hospital about the infection and the recipient's course of disease and possible risk factors in the recipient for the infection.

The blood establishment physician must establish a plan of investigation, the results of which must be recorded.

The incident must be reported to the national competent authorities.
Annex

Table 1. Blood volume of women in mL as calculated according to the ICSH formula. The weights and heights corresponding to the minimum acceptable blood volumes of 3,233 mL, 3,400 mL and 3,567 mL are indicated on grey backgrounds.

<table>
<thead>
<tr>
<th>kg</th>
<th>50</th>
<th>51</th>
<th>52</th>
<th>53</th>
<th>54</th>
<th>55</th>
<th>56</th>
<th>57</th>
<th>58</th>
<th>59</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>kg</th>
<th>50</th>
<th>51</th>
<th>52</th>
<th>53</th>
<th>54</th>
<th>55</th>
<th>56</th>
<th>57</th>
<th>58</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td>158 cm</td>
<td>3,340</td>
<td>3,368</td>
<td>3,396</td>
<td>3,423</td>
<td>3,450</td>
<td>3,476</td>
<td>3,503</td>
<td>3,529</td>
<td>3,555</td>
<td>3,581</td>
</tr>
<tr>
<td>159 cm</td>
<td>3,355</td>
<td>3,383</td>
<td>3,411</td>
<td>3,438</td>
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<td>3,492</td>
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<td>3,545</td>
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<tr>
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<tr>
<td>165 cm</td>
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<td>3,474</td>
<td>3,503</td>
<td>3,531</td>
<td>3,559</td>
<td>3,586</td>
<td>3,613</td>
<td>3,640</td>
<td>3,667</td>
<td>3,693</td>
</tr>
<tr>
<td>166 cm</td>
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<td>3,489</td>
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<td>3,656</td>
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<td>167 cm</td>
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<td>3,645</td>
<td>3,672</td>
<td>3,699</td>
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<tr>
<td>169 cm</td>
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<td>3,534</td>
<td>3,563</td>
<td>3,592</td>
<td>3,620</td>
<td>3,648</td>
<td>3,676</td>
<td>3,703</td>
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<td>170 cm</td>
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<td>3,607</td>
<td>3,636</td>
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<td>3,692</td>
<td>3,719</td>
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<tr>
<td>172 cm</td>
<td>3,550</td>
<td>3,579</td>
<td>3,608</td>
<td>3,637</td>
<td>3,666</td>
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<td>3,723</td>
<td>3,750</td>
<td>3,778</td>
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<td>173 cm</td>
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<td>3,624</td>
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Guide to the preparation, use and quality assurance of blood components

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

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## List of definitions

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<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Additive solution</td>
<td>Solution specifically formulated to maintain beneficial properties of cellular components during storage.</td>
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<td>Adverse event</td>
<td>Any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to an adverse reaction in blood recipients or blood donors.</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>Unintended response in donor or in patient associated with the collection or transfusion of blood or blood components.</td>
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<tr>
<td>Allogeneic donation</td>
<td>Blood and blood components collected from an individual and intended for transfusion to another individual, for use in medical devices or as source material for manufacturing into medicinal products.</td>
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<tr>
<td>Antibody quantitation</td>
<td>Technique routinely used to measure the level of antibody, i.e. anti-RhD (or anti-c) antibody in maternal sera.</td>
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<tr>
<td>Antiglobulin testing technique</td>
<td>The direct antiglobulin test (direct Coombs' test) and the indirect antiglobulin test. It detects antibody or complement bound to red cells <em>in vivo</em>.</td>
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<tr>
<td>Anti-IgA antibodies</td>
<td>IgG or occasionally IgM anti-IgA produced by a IgA-deficient patient. Severe anaphylactoid transfusion reactions can occur in such patients.</td>
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<tr>
<td>Apheresis</td>
<td>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.</td>
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</table>
**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 donation**
Blood and blood components collected from an individual, intended solely for subsequent autologous transfusion to the individual.

**Autologous donors**
Individuals may donate blood for their own use if the need for blood can be anticipated and a donation plan developed.

**Autologous transfusion**
Transfusion in which the donor and the recipient are the same person and in which predeposited blood and blood components are used.

**Automated system**
A broad range of systems including, but not limited to, automated manufacturing equipment, automated laboratory equipment, process control, manufacturing execution, laboratory information management, manufacturing resource planning, and document management systems. The automated system consists of the hardware, software and network components, together with the controlled functions and associated documentation. Automated systems are sometimes referred to as computerized systems.

**Blood**
Whole Blood collected from a single donor and processed either for transfusion or further manufacturing.

**Blood component**
Therapeutic components of blood (red cells, white cells, platelets, plasma) that can be prepared by centrifugation, filtration, and freezing using conventional blood bank methodology.

**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 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 when intended for transfusion. This does not include hospital blood banks.

**Blood product**  Any therapeutic product derived from human blood or plasma.

**Buffy coat**  Blood component prepared by centrifugation of a unit of whole blood which contains a considerable proportion of the leucocytes and platelets.

**Buoyant density centrifugation**  Technique for separation based on density differences between cells.

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

**Cell free plasma**  Plasma obtained by cross-flow filtration, when 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 might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

**Counter current centrifugation (elutriation)**  Technique where cells are subjected simultaneously to a liquid flow and a centrifugal force in opposite directions tend to be separated according to their size.

**CPD-Adenine (CPDA)**  Citrate-Phosphate-Dextrose with Adenine is a preservative-anticoagulant solution used for whole blood collection.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Cryoprecipitate</td>
<td>Plasma component prepared from fresh frozen plasma by freeze-thaw precipitation of proteins and subsequent concentration and resuspension of the precipitated proteins in a small volume of the plasma.</td>
</tr>
<tr>
<td>Cryoprecipitate-depleted plasma</td>
<td>A component prepared from plasma by removal of cryoprecipitate.</td>
</tr>
<tr>
<td>Cryopreservation</td>
<td>Prolongation of the storage life of blood components by freezing.</td>
</tr>
<tr>
<td>Cryopreserved platelets</td>
<td>A component prepared by the freezing of platelets and stored.</td>
</tr>
<tr>
<td>Cytapheresis</td>
<td>An apheresis procedure intended for the collection of a cellular component of blood, such as red cells, leucocytes or platelets.</td>
</tr>
<tr>
<td>Depth and surface filtration</td>
<td>Technique of filtration using a filter bed of fibres: owing to the specific properties of platelets and granulocytes as well as the low flexibility of lymphocytes, these cells are more easily trapped in such a filter than are red cells.</td>
</tr>
<tr>
<td>Distribution</td>
<td>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 the issuing of blood or blood components for transfusion.</td>
</tr>
<tr>
<td>Donor</td>
<td>A person in normal health with a good medical history who voluntarily gives blood or components for therapeutic use.</td>
</tr>
<tr>
<td>Donor Deferral</td>
<td>Suspension of the eligibility of an individual to donate blood or blood components, such suspension being either permanent or temporary.</td>
</tr>
<tr>
<td>Febrile transfusion reactions</td>
<td>A febrile response associated with the administration of blood or blood components.</td>
</tr>
<tr>
<td>First time donor</td>
<td>Someone who has never donated either blood or component.</td>
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</table>
Guide to the preparation, use and quality assurance of blood components

**Fresh frozen plasma**  A component prepared from whole blood or from plasma collected by apheresis frozen to a temperature that will maintain the labile coagulation factors in a functional state.

**Glycerol**  Propanetriol, used as a cell-cryoprotective agent for the storage of red cells in the frozen state.

**Granulocytes**  A component consisting primarily of granulocytes suspended in plasma, obtained by single-donor apheresis.

**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 are 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.

**Inspection**  Formal and objective control according to adopted standards to assess compliance with a given directive and other relevant legislation and to identify problems.

**Leucocyte depletion**  The removal of leucocytes from blood.

**Qualification**  As part of validation means the action of verifying that any personnel, premises, equipment or material works correctly and delivers expected results.
<table>
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<tr>
<th>Term</th>
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<td>Are procedures that irreversibly impede proliferation of pathogens.</td>
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<td>Technologies (PRT)</td>
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<tr>
<td><strong>Peripheral blood stem cells (PBSC)</strong></td>
<td>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).</td>
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<tr>
<td><strong>Plasma</strong></td>
<td>The liquid portion of anticoagulated blood remaining after separation from the cellular components.</td>
</tr>
<tr>
<td><strong>Platelets, recovered</strong></td>
<td>A component derived from fresh whole blood which contains the majority of the original platelet content.</td>
</tr>
<tr>
<td><strong>Red cells (apheresis)</strong></td>
<td>Red cells from apheresis red cell donation.</td>
</tr>
<tr>
<td><strong>Red cells</strong></td>
<td>A component obtained from a single whole blood donation by removal of part of the plasma, without further processing.</td>
</tr>
<tr>
<td><strong>Red cells, buffy coat removed</strong></td>
<td>A component prepared from a single whole blood donation by the separation of part of the plasma and the buffy-coat layer from the red cells.</td>
</tr>
<tr>
<td>(Red cells: BCR)</td>
<td></td>
</tr>
<tr>
<td><strong>Red cells, cryopreserved</strong></td>
<td>Red cells of a single whole blood donation with most of the plasma removed, deep frozen using a cryoprotectant solution.</td>
</tr>
<tr>
<td><strong>Red cells, in additive solution</strong></td>
<td>A component prepared from a single whole blood donation by separation of part of the plasma with subsequent suspension of the red cells in appropriate nutrient solution.</td>
</tr>
<tr>
<td>(Red cells: AS)</td>
<td></td>
</tr>
<tr>
<td><strong>Red cells, in additive solution, buffy coat removed</strong></td>
<td>A component prepared from a single whole blood donation by separation of part of the plasma and buffy-coat, and with subsequent resuspension of the red cells in an appropriate nutrient solution.</td>
</tr>
<tr>
<td>(Red cells: AS-BCR)</td>
<td></td>
</tr>
<tr>
<td><strong>Red cells, leucocyte-depleted</strong></td>
<td>A component obtained by removing the majority of leucocytes from red cells.</td>
</tr>
<tr>
<td><strong>Regular donor</strong></td>
<td>Someone who routinely donates their blood or plasma (i.e. within the last two years), in accordance with minimum time intervals, in the same donation centre.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Repeat donor</td>
<td>Someone who has donated before but not within the last two years in the same donation centre.</td>
</tr>
<tr>
<td>RhD Immunoglobulin</td>
<td>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.</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Method to assess and characterise the critical parameters in the functionality of and equipment, system or process.</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>Any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for donors or recipients or which results in, or prolongs, hospitalisation or morbidity.</td>
</tr>
<tr>
<td>Serious adverse reaction</td>
<td>Unintended response in donor or in recipient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs hospitalisation or morbidity.</td>
</tr>
</tbody>
</table>
| Standard operating procedures (SOPs) | Detailed documents:  
(1) covering all Good Manufacturing Practice-compliant activities;  
(2) containing specifications where appropriate;  
(3) process/procedure based;  
(4) modular, and  
(5) reflecting current practice. They must be updated as appropriate, and new techniques must be evaluated and validated before being introduced, to ensure conformation with quality criteria. |
| 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. |
| **Validation** | Means the establishment of documented and objective evidence that the pre-defined requirements for a specific procedure or process can be consistently fulfilled. |
| **Validation plan** | A description of the validation activities, responsibilities and procedures. It describes specifically how a certain validation is to be done. |
| **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** | Single unprocessed blood donation. |
| **Xenotransplantation** | Xenotransplantation is defined as any procedure that involves the transplantation or infusion into a human recipient of live animal cells, tissues or organs, or human body fluids, cells, tissues or organs that have \textit{ex vivo} contact with live animal cells, tissues or organs. |
Guide to the preparation, use and quality assurance of blood components

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag</td>
<td>Antigen</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Amino Transferase</td>
</tr>
<tr>
<td>AS</td>
<td>Additive Solution</td>
</tr>
<tr>
<td>AS-BCR</td>
<td>Additive Solution-Buffy Coat Removed</td>
</tr>
<tr>
<td>BCR</td>
<td>Buffy Coat Removed</td>
</tr>
<tr>
<td>BPAT</td>
<td>Batch Pre-Acceptance Testing</td>
</tr>
<tr>
<td>BSA</td>
<td>Bovine Serum Albumin</td>
</tr>
<tr>
<td>BSE</td>
<td>Bovine Spongiform Encephalopathy</td>
</tr>
<tr>
<td>CD-P-TS</td>
<td>European Committee on Blood Transfusion</td>
</tr>
<tr>
<td>CETS</td>
<td>Council of Europe Treaty Series (formerly ETS: European Treaty Series)</td>
</tr>
<tr>
<td>CJD</td>
<td>Creutzfeldt-Jacob Disease</td>
</tr>
<tr>
<td>CMV</td>
<td>CytoMegaloVirus</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide used as a cell-cryoprotective agent for the storage of platelets and stem cells in the frozen state</td>
</tr>
<tr>
<td>DQ</td>
<td>Design qualification</td>
</tr>
<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines and Healthcare</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbsent assay</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FTA</td>
<td>Fluorescent Treponemal Antibody</td>
</tr>
<tr>
<td>GCSF</td>
<td>Granulocyte Colony Stimulating Factor</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
</tbody>
</table>
Guide to the preparation, use and quality assurance of blood components

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTS</td>
<td><em>Ad hoc</em> working group on the guide to the preparation, use and quality assurance of blood components</td>
</tr>
<tr>
<td>GVHD</td>
<td>Graft-Versus-Host Disease</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HBcAb</td>
<td>Hepatitis B core Antibody</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface Antigen</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>Hct</td>
<td>Haematocrit</td>
</tr>
<tr>
<td>HES</td>
<td>HydroxyEthyl Starch</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leucocyte Antigen</td>
</tr>
<tr>
<td>HPA</td>
<td>Human Platelet Antigen</td>
</tr>
<tr>
<td>HPCs</td>
<td>Haematopoietic Progenitor Cells</td>
</tr>
<tr>
<td>HTLV</td>
<td>Human T Leukaemia Virus</td>
</tr>
<tr>
<td>IQ</td>
<td>Installation qualification</td>
</tr>
<tr>
<td>ISBT</td>
<td>International Society for Blood Transfusion</td>
</tr>
<tr>
<td>IU</td>
<td>International Unit</td>
</tr>
<tr>
<td>LISS</td>
<td>Low Ionic Strength (Salt) Solution</td>
</tr>
<tr>
<td>NAT</td>
<td>Nucleic Acid Amplification Techniques</td>
</tr>
<tr>
<td>OQ</td>
<td>Operational Qualification</td>
</tr>
<tr>
<td>Ph. Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PQ</td>
<td>Performance Qualification</td>
</tr>
<tr>
<td>PRP</td>
<td>Platelet Rich Plasma</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>SAGM</td>
<td>Saline Adenine Glucose Mannitol solution</td>
</tr>
<tr>
<td>SOPs</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>TA</td>
<td>Transfusion-Associated</td>
</tr>
<tr>
<td>TACO</td>
<td>Transfusion Associated Circulatory Overload</td>
</tr>
<tr>
<td>TPHA</td>
<td><em>Treponema pallidum</em> Haemagglutination Assay</td>
</tr>
<tr>
<td>TRALI</td>
<td>Transfusion Related Acute Lung Injury</td>
</tr>
<tr>
<td>TTP</td>
<td>Thrombotic Thrombocytopenic Purpura</td>
</tr>
<tr>
<td>vCJD</td>
<td>Variant Creutzfeld Jacob Disease</td>
</tr>
</tbody>
</table>
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

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)
Guideline to the preparation, use and quality assurance of blood components

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
Resolution 812 (1983) of the Parliamentary Assembly on acquired immune deficiency syndrome (AIDS)
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 Res (2008) 5 on donor responsibility and on limitation to donation of blood and blood components

N.B. The figures in brackets indicate the year of adoption by the Committee of Ministers
Guide to the preparation, use and quality assurance of blood components

List of publications

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

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)

1992  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

1993  Survey of blood transfusion services of central and eastern 
       European countries and their co-operation with western 
       transfusion services  
       Report by H.T. Heiniger

1993  The collection and use of human blood and plasma in Europe by 
       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)
Guide to the preparation, use and quality assurance of blood components

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

1997 Activities of blood banks in relation to bone marrow transplantations  
Study Director: I.M. Francklin; Group members S. Koskimies, R. Kroczyk, 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

Report by Dr Rejman

2000 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 Dr van der Poel

2005 Collection, testing and use of blood and blood products in Europe – 2002 data  
Report by Dr van der Poel

2007 Collection, testing and use of blood and blood products in Europe – 2003 data  
Report by Dr van der Poel

2008 Collection, testing and use of blood and blood products in Europe – 2004 data  
Report by Dr van der Poel
The use of blood components represents the only therapy available for many seriously ill patients who suffer from acute or chronic diseases.

To provide all those working in the field of transfusion medicine – from blood services to hospital departments to regulators – with a compendium of measures designed to ensure the safety, quality and efficacy of blood components, the Council of Europe has developed a guide as a technical annex to its Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components. The Guide contains recommendations on blood collection, blood components, technical procedures, transfusion practices and quality systems for blood establishments. It represents the basis for a large number of national regulations, as well as for the blood directives of the European Commission.

This is the 16th Edition of the Guide, compiled by leading European experts under the aegis of the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS). This Steering Committee was created in 2007 by the Council of Europe to pursue its activities in the field of blood transfusion following the transfer of these activities to the European Directorate for the Quality of Medicines & HealthCare (EDQM).

The EDQM is a Directorate of the Council of Europe, an international organisation founded in 1949 that covers almost the entire continent of Europe. The Council of Europe aims to develop common democratic and legal principles based on the European Convention on Human Rights and other reference texts on the protection of individuals.