

Annex 4

WHO guidelines on good manufacturing practices for blood establishments

1. Introduction
2. Glossary and abbreviations
3. Quality management
 - 3.1 Principles
 - 3.2 Quality assurance
 - 3.2.1 Good manufacturing practice in blood establishments
 - 3.2.2 Quality control
 - 3.3 Product quality review
 - 3.4 Quality risk management
 - 3.5 Change control
 - 3.6 Deviation evaluation and reporting
 - 3.7 Corrective and preventive actions
 - 3.8 Internal audits
 - 3.9 Complaints and product recall
 - 3.9.1 Complaints
 - 3.9.2 Recalls
 - 3.10 Process improvement
 - 3.11 Look-back
4. Personnel
 - 4.1 Organization and responsibilities
 - 4.2 Training
 - 4.2.1 Initial training
 - 4.2.2 Continuous training
 - 4.2.3 Competency
 - 4.3 Personal hygiene
5. Documentation
 - 5.1 Standard operating procedures and records
 - 5.1.1 Standard operating procedures
 - 5.1.2 Records
 - 5.2 Document control
 - 5.2.1 Document management
 - 5.2.2 Record retention and archiving
6. Premises and equipment
 - 6.1 Premises

- 6.1.1 Design and construction
- 6.1.2 Donor areas
- 6.1.3 Production areas
- 6.1.4 Storage areas
- 6.1.5 Laboratories
- 6.1.6 Mobile collection sites
- 6.2 Equipment
 - 6.2.1 Design and construction
 - 6.2.2 Maintenance
 - 6.2.3 Cleaning
 - 6.2.4 Calibration
- 6.3 Computerized systems
- 7. Qualification and validation**
 - 7.1 Qualification of equipment
 - 7.2 Validation of manufacturing processes
 - 7.3 Choosing an appropriate test system to screen for infectious disease
 - 7.4 Assay performance validation
- 8. Management of materials and reagents**
 - 8.1 Materials and reagents
 - 8.2 Receipt and quarantine
 - 8.3 Release of incoming production material and test reagents
 - 8.4 Storage
 - 8.5 Traceability of materials and reagents
 - 8.6 Supplier/vendor management
- 9. Manufacturing**
 - 9.1 Donor registration
 - 9.2 Donor selection
 - 9.2.1 Epidemiological surveillance of the donor population
 - 9.2.2 Information to donors
 - 9.2.3 Questionnaire and interview
 - 9.2.4 Deferral policy and deferral criteria
 - 9.2.5 Physical examination, donor health criteria and donor acceptance
 - 9.3 Collection
 - 9.3.1 Whole blood collection
 - 9.3.2 Collection by apheresis
 - 9.3.3 Safety of donors
 - 9.4 Component preparation
 - 9.4.1 Starting material
 - 9.4.2 Methods of production
 - 9.4.2.1 Centrifugation
 - 9.4.2.2 Separation
 - 9.4.2.3 Freezing
 - 9.4.2.4 Leukocyte reduction
 - 9.4.2.5 Irradiation

- 9.4.3 Blood and blood components
 - 9.4.3.1 Whole blood
 - 9.4.3.2 Red-cell concentrate
 - 9.4.3.3 Platelet concentrate
 - 9.4.3.4 Plasma for transfusion and Plasma for fractionation
 - 9.4.3.5 Cryoprecipitate and Cryo-poor plasma
 - 9.5 Laboratory testing
 - 9.5.1 Screening tests for infectious disease markers
 - 9.5.1.1 Testing requirements
 - 9.5.1.2 Handling of samples and data
 - 9.5.1.3 Testing and post-analytical procedures
 - 9.5.1.4 Test interpretation and follow-up of reactive results
 - 9.5.2 Blood group typing
 - 9.5.3 Retention samples
 - 9.6 Quality monitoring of blood and blood components
 - 9.7 Labelling
 - 9.7.1 Label information
 - 9.7.2 Product name
 - 9.7.3 Expiry date
 - 9.8 Release of product
 - 9.9 Storage
 - 9.10 Distribution
 - 9.11 Shipping
 - 9.12 Returns
10. Contract manufacturing, analysis and services
11. Authors and acknowledgements
12. References

1. Introduction

The World Health Organization (WHO) requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (1) define a quality assurance system based on (i) the existence of a national structure that is independent of manufacturers, (ii) compliance with the process of quality assurance for biological products — i.e. control of starting material(s), production processes and final product(s) — and (iii) strict adherence to the principles of good manufacturing practice (GMP). Since the last revision of these requirements in 1992, two relevant items have been reviewed and new recommendations adopted, namely on virus inactivation and removal of plasma derivatives (2004) (2) and human plasma for fractionation (2007) (3). However, a number of issues, such as the requirement for a quality assurance system in blood establishments, have not yet been addressed. The WHO Expert Committee on Biological Standardization (ECBS), therefore, considered that the development of WHO guidelines on GMP for blood establishments is of highest priority in assisting Member States to meet their needs in this area, as requested by the International Conference of Drug Regulatory Authorities in 2008 (4).

The importance of establishing reliable quality assurance systems for the whole chain of blood collection, processing and distribution of blood components in blood establishments was also emphasized by the Sixty-third World Health Assembly in resolution WHA63.12 on the availability, safety and quality of blood products (5). In that resolution, quality assurance was seen as a necessary measure that would contribute to increased global availability of plasma that meets internationally recognized standards.

Resolution WHA63.12 recognized that a special effort is needed to strengthen globally the technical capacity of national regulatory authorities (NRAs) to assure the appropriate control of blood products. The resolution recalls earlier related resolutions which urged Member States to promote the full implementation of well organized, nationally coordinated and sustainable blood programmes stressing the role of voluntary, non-remunerated blood donations from low-risk populations.

In recent years, safety and quality in the transfusion chain has become an important topic in many countries and regions (6). Blood establishments should establish and maintain quality systems, based on GMP principles, involving all activities that determine quality policy objectives and responsibilities, and should implement them by such means as quality planning, quality control, quality assurance and quality improvement. A GMP approach to manufacturing safe blood components that consistently meet predefined specifications and customers' expectations provides a model that allows for a documented system of incorporating quality into

the entire process. When collecting and processing blood and plasma from human donors, GMP considerations should be addressed in a biological context due to the specific characteristics of materials of human origin.

The guidelines in this document include:

- general GMP topics such as quality management, personnel, documentation, premises and equipment, qualification and validation, materials management, contract manufacturing, and complaints and recalls;
- GMP concepts such as quality risk management and product quality reviews;
- topics specific to the manufacturing of blood components from donor selection to distribution of the final product.

They address current and widely accepted GMP principles that are relevant to the consistent production of safe and assured quality blood components in blood establishments, including related donor safety concerns. The document is intended to serve as guidance for both blood establishments and NRAs when implementing and enforcing these principles. It does not address the practice of transfusion medicine or management of emergencies or crises where specific policies defined by the NRA apply. Aspects of personnel and environmental protection are also not within the scope of this document.

Complementary guidance, especially with respect to the production of plasma for fractionation, is available in the *WHO recommendations for the production, control and regulation of human plasma for fractionation (3)*.

2. **Glossary and abbreviations**

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

apheresis

The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/or filtration into its components, and returning those not required to the donor.

blood collection

The procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution, under conditions designed to minimize microbial contamination, cellular damage and/or coagulation activation of the resulting blood donation.

blood component

A constituent of blood (erythrocytes, leukocytes, platelets, cryoprecipitate and plasma) that can be prepared by various separation methods and under such conditions that it can be used either directly for therapeutic purposes or for further processing/manufacturing.

blood establishment

Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components when intended for transfusion or further industrial manufacturing.

blood products

Any therapeutic substances derived from human blood, including whole blood, blood components and plasma-derived medicinal products.

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.

CJD/vCJD

Creutzfeld-Jakob-Disease/variant Creutzfeld-Jakob-Disease.

closed system

A system developed for aseptic collection and separation of blood and blood components, manufactured under clean conditions, sealed to the external environment and sterilized by a validated and approved method.

computerized system

A system including the input of data, electronic processing and the output of information to be used either for reporting or for automatic control.

contract acceptor

An establishment or institution that performs particular work or services under a contract for a different institution.

contract giver

An establishment or institution that is subcontracting particular work or services to a different institution and sets up a contract defining the duties and responsibilities of each side.

donor

A person in defined good health conditions who voluntarily donates blood or blood components, including plasma for fractionation.

distribution

The act of delivery of blood and blood components to other blood establishments, hospital blood banks or manufacturers of blood- and plasma-derived medicinal products. It does not include the issuing of blood or blood components for transfusion.

first-time (tested) donor

A donor whose blood or plasma is tested for the first time for infectious disease markers in a blood establishment.

good manufacturing practice (GMP)

All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations.

HAV, hepatitis A virus

A non-enveloped single-stranded RNA virus that is the causative agent of hepatitis A.

HBsAg, hepatitis B surface antigen

The antigen on the periphery of the hepatitis B virus.

HBV, hepatitis B virus

An enveloped double-stranded DNA virus that is the causative agent of hepatitis B.

HCV, hepatitis C virus

An enveloped single-stranded, RNA virus that is the causative agent of hepatitis C.

HIV, human immunodeficiency virus

An enveloped, single-stranded RNA virus that is the causative agent of the acquired immunodeficiency syndrome (AIDS).

HTLV 1 and 2, human T-cell lymphotropic virus, types 1 and 2

Enveloped, single stranded RNA viruses that are typically cell-associated.

manufacture

All operational processes or steps — including purchase or selection of materials and products, production, quality control, release, storage and distribution of products and the related controls — used to produce a blood product. This includes also the donation process.

mobile site

A unit or site used for the collection of blood and/or blood components, operating temporarily or at movable locations off-site from a permanent collection site, under the responsibility of a blood establishment.

nucleic acid amplification techniques (NAT)

A testing method to detect the presence of a targeted area of a defined microbial genome that uses amplification techniques such as polymerase chain reaction (PCR).

near-miss event

An incident that, if not detected in a timely manner, would have affected the safety of the recipients or donors.

national regulatory authority (NRA)

WHO terminology for national medicines regulatory authorities. NRAs should promulgate and enforce medicines regulations.

plasma for fractionation

The liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration and/or centrifugation of anticoagulated blood in an apheresis procedure, intended for further manufacturing.

production

All operations involved in the preparation of blood components, from collection through processing to completion as a finished product (blood component).

qualification

A set of actions used to provide documented evidence that any piece of equipment, critical material or reagent used to produce the final product and that might affect the quality or safety of a product works reliably as intended or specified and leads to the expected results.

quality

The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs, and the consistent and reliable performance of services or products in conformity with specified requirements. Implied needs include safety and quality attributes of products intended both for therapeutic use and as starting materials for further manufacturing.

quality assurance

A part of quality management focused on providing confidence that quality requirements will be met.

quality management

The coordinated activities that direct and control an organization with regard to quality.

quality management system

A management system that directs and controls an organization with respect to quality and that ensures that steps, processes, procedures and policies related to quality activities are being followed.

quality risk management (QRM)

A systematic process for the assessment, control, communication and review of risks to the quality of the product across the product's life cycle.

quarantine

The status of starting or packaging materials, intermediate, bulk or finished products that are isolated physically or by other means while a decision is awaited on their release for use or rejection.

regular donor

A person who routinely donates blood, blood components or plasma in the same blood establishment in accordance with the minimum time intervals.

repeat donor

A person who has donated before in the same establishment but not within the period of time considered as regular donation.

repeatedly reactive

A donation is considered to be repeatedly reactive if it is found reactive in a screening test, is retested in duplicate using the same assay, and at least one of the repeat tests is also reactive.

validation

Actions for proving that any operational procedure, process, activity or system leads to the expected results. Validation work is normally performed in advance according to a defined and approved protocol that describes tests and acceptance criteria.

WNV, West Nile Virus

An enveloped single-stranded RNA virus that is the causative agent of West Nile fever.

3. **Quality management**

3.1 **Principles**

Quality is the responsibility of all persons involved in the various processes of the blood establishment. The management of the blood establishment is responsible for a systematic approach to quality and the implementation and maintenance of a quality management system. A quality programme

should be designed to ensure that each product (including plasma for fractionation) is manufactured in the same manner from donor selection through to distribution of the final product.

Quality management involves all activities that determine the quality policy, objectives and responsibilities, and their implementation through quality planning, quality control, quality assurance and quality improvement in order to assure the quality and safety of blood and blood components.

The attainment of the quality policy and objectives is the responsibility of the senior management of the blood establishment and requires the participation and commitment of all staff throughout the entire blood establishment. Senior management should review the quality system at regular intervals to verify its effectiveness and to introduce corrective measures if they are considered necessary.

Within the organizational structure of the blood establishment there should be a quality management unit comprising one or more persons. The quality management personnel should be responsible for ensuring that there is documented evidence that the quality policies, procedures and practices are being fulfilled. Senior management, in coordination with the quality management unit, should develop and implement quality assurance policies and objectives in a manner that provides clear direction to all staff. The quality assurance policies and objectives should be designed to ensure the highest levels of safety and quality in the blood components that are produced from each collection. The policies and procedures should comply with all national and, where appropriate, international regulations and requirements.

Staff should be able to understand the intent of the quality objectives and their own role in accomplishing the objectives. The performance of the quality management system should be evaluated periodically by determining whether the objectives have been or are continuously being met. If there are shortcomings in the quality system, corrections should be made and the quality management unit should be held responsible for monitoring corrective action and continued compliance.

Within any blood establishment there should be independent functions for fulfilling quality assurance and quality control responsibilities. The quality assurance function should be independent of manufacturing operations and should assure that all processes are performed and documented. The quality assurance function should be involved in all quality-related matters and in the review and approval of all quality-related documents.

3.2 Quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of the product. It is the

totality of arrangements that are made with the purpose of ensuring that products are of the quality required for their intended use. Quality assurance therefore incorporates GMP, and other elements, including those outside the scope of this guideline — such as product design and development (7).

Quality assurance is that part of quality management that ensures that all critical processes are appropriately described in written instructions (see chapter 5), are performed in accordance with the principles of GMP and comply with the appropriate regulations. The quality assurance system should be fully documented, distributed and explained to everyone involved in the manufacturing processes.

All parts of the quality assurance system should be adequately resourced with competent personnel, suitable premises, and suitable and sufficient equipment and facilities to enable the manufacturing steps to be completed in a safe and quality-compliant manner.

3.2.1 ***Good manufacturing practice in blood establishments***

GMP is the part of quality assurance that ensures that blood products are consistently produced and controlled to the quality standards appropriate to their intended use, as required by predefined specifications and, if applicable, by the marketing authorization. GMP is aimed primarily at diminishing the risks inherent in any blood establishment operation — such as contamination (including cross-contamination), mix-ups, disease transmission or other unexpected adverse outcomes resulting from the use of blood products. GMP is concerned with both production and quality control.

The basic requirements of GMP are the following:

- All manufacturing processes are clearly defined by policies and standard operating procedures, are systematically reviewed in the light of experience, and are shown to be capable of consistently manufacturing products of the required quality that comply with their specifications.
- Qualification of equipment and reagents and validation of processes and methods are performed prior to use in the manufacture of products intended for transfusion or further manufacturing.
- All necessary resources are provided — including appropriately qualified and trained personnel, adequate premises, suitable equipment, appropriate materials, approved procedures and instructions, suitable storage and transport.
- A system is available to maintain traceability of all released products in order to facilitate recall, if necessary, of any product suspected of not conforming to standards, and there is also a system to handle complaints.
- A system is available that addresses process and quality improvement functions and activities.

3.2.2 **Quality control**

Quality control is that part of GMP which is concerned with specifications, sampling and testing. Quality control is also concerned with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that neither materials are released for use nor products released for supply until their quality has been judged to be satisfactory (7). For quality control programmes in blood establishments, refer to sections 9.5 and 9.6.

3.3 **Product quality review**

Regular periodic or rolling quality reviews should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify improvements in both product and process.

A product quality review may also be considered as an instrument for surveying the overall quality status of a blood component and its manufacturing processes, including the collection of starting materials. Such a review should normally be conducted annually and should be documented. In accordance with international and/or NRA requirements and recommendations it may include:

- review of starting materials;
- review of critical in-process controls;
- review of results of quality control and quality monitoring;
- review of all changes;
- review of the qualification status of equipment;
- review of technical agreements and contracts;
- review of all significant deviations, errors and non-conformances, and the corrective actions implemented;
- review of the findings of internal audits and other inspections, and the corrective actions implemented;
- review of complaints and recalls;
- review of donor acceptance criteria;
- review of donor deferrals;
- review of look-back cases.

3.4 **Quality risk management**

Blood establishments should ensure that blood components manufactured in their facilities are of the quality required for their intended use, comply with quality standard requirements, and do not place recipients at risk due to inadequate safety, quality or efficacy throughout the life-cycle of the product. In order to reliably achieve the quality objective, there should

be a comprehensively designed and correctly implemented system of quality assurance that incorporates GMP, quality control and quality risk management (QRM).

An effective QRM approach can ensure the quality of a product by providing proactive means to identify and control potential quality issues. It can also facilitate and improve the decision-making process in cases when quality problems or deviations from standard processes and specifications have to be assessed or planned changes need to be evaluated.

The two primary principles of QRM are:

- The evaluation of the risk to quality and safety should be based on scientific knowledge and ultimately linked to the protection of the donor and/or recipient.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

Examples of the QRM processes and applications can be found in guidelines on QRM, such as the Q9 guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (8). This describes processes and offers a selection of methods and tools for applying the QRM principles.

3.5 **Change control**

A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality, traceability and availability of blood or blood components or that might have an impact on the safety of blood, blood components, donors or recipients. The change control system should guarantee a formal approval of a change before it is implemented. Furthermore it should ensure that the impact of the proposed change is assessed and that all necessary measures — such as qualification and validation, training of personnel, adoption of working instructions, revision of contracts, definition of maintenance tasks, information for third parties and authorities — are defined and completed at the time the change is put into force. The need for additional testing and validation should be determined on a scientific basis. A risk analysis may be appropriate as part of the QRM.

After the implementation of a change, a post-implementation evaluation should be carried out in order to determine whether the introduction of the change has been successful and effective.

The introduction of new equipment, processes and methods should be treated as a change.

3.6 **Deviation evaluation and reporting**

Any deviation from standard operating procedures, validated processes, or non-conformances with specifications or other quality-related requirements should be recorded and investigated. The potential impact on the quality of the product in question, or on other products, should be evaluated.

The evaluation of the cause of the deviation and of related processes that may also be implicated in the deviation should be documented. Review and approval of the investigation as completed should be documented by the quality assurance and/or quality control department as appropriate.

All deviations and non-conformances should be logged in a system that allows for appropriate data review. A data review should be carried out periodically in a manner that allows for tracking and trending of data and that facilitates process improvement.

The handling of deviations and non-conformances should be defined in writing. Actions should be taken within a reasonable time frame in order to avoid any impact on other products manufactured within the same establishment.

Under certain circumstances a product may be accepted after evaluation of a deviation. The documentation should include the justification or rationale for accepting a product manufactured in deviation from a specified requirement, and should be signed by the responsible person.

3.7 **Corrective and preventive actions**

A corrective and preventive action system should be established, implemented and maintained to ensure that there is continuous improvement at the blood establishment. The procedures should include the management of deviations and non-conformances, complaints, events and findings of the quality system management review, inspections and audits, and should ensure the proper recording of all corrective and preventive actions taken.

The corrective and preventive action system should ensure that each quality problem is addressed and corrected and that recurrence of the problem is prevented. Actions should be carried out within a reasonable predefined time frame. The management of the blood establishment should be involved in the review of corrective and preventive actions.

The blood establishment should have methods and procedures in place to collect, document and evaluate data on quality. Product or quality problems should be entered into the corrective and preventive action system. Quality data include all errors, deviations, non-conformances, accidents, near-miss events and complaints. Quality data also include the results of quality control tests

and monitoring activities. Quality data should be reviewed at defined intervals in order to identify product and quality problems that may require corrective action and to identify unfavourable trends that may require preventive action.

3.8 **Internal audits**

In order to monitor implementation and compliance with the quality management system, regular internal audits should be performed according to an established procedure. Internal audits should be conducted by trained, independent and competent persons under the responsibility of the organization's quality assurance unit.

Internal audits should be arranged according to a schedule and should cover all parts of the operations, including data processing systems. Each audit should be carried out according to an approved audit plan that assesses compliance with internal requirements and applicable national and/or international regulations.

All audit results should be documented and reported to the management. Appropriate corrective and preventive actions should be taken in a timely and effective manner and should be assessed for effectiveness after implementation.

The quality assurance department, where the internal audit function resides, should not audit itself but should be subject to an independent audit.

Internal audits are not a substitute for official inspections performed by the competent national authorities who check compliance with national regulations.

3.9 **Complaints and product recall**

3.9.1 **Complaints**

There should be a system in place to ensure that all complaints are handled according to written — and approved — standard operating procedures. The review of the complaint should take account of whether the complaint relates to a quality defect in a blood component. The blood establishment should determine whether a recall should be initiated. The process should be defined in a standard operating procedure. Complaints, adverse events or reactions, as well as any information concerning potentially defective products, should be carefully reviewed and thoroughly investigated in order to find the root cause of the problem. Consideration should be given to determining whether other products are also affected. All investigations and actions should be carried out in a timely manner to ensure that the safety of the recipient is not compromised and that other products manufactured within the same establishment are not affected.

Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions (see section 3.7).

Designated personnel should be responsible for managing complaints and coordinating investigations, actions and measures to be taken within a defined time frame. The unit responsible for quality should be included in this process.

All complaints, with the original details, should be recorded. Records should be retained of all the decisions, investigations and measures taken as a result of a complaint. Complaint records should be reviewed regularly in order to check for unfavourable trends or recurring problems and to ensure continuous quality improvement.

Depending on the national requirements the NRA should be informed.

3.9.2 **Recalls**

An effective written recall procedure should be in place, including a description of the responsibilities and actions to be taken. A recall should always be initiated whenever it is discovered that a product does not meet the release criteria of the blood establishment and NRA. This may happen when information is obtained subsequent to the release of a product and, had this information been known in advance, it would have prevented the blood component from being released. A recall may also be indicated when it is discovered that personnel did not follow standard operating procedures. Corrective actions should take place within predefined time periods and should include the traceability of all relevant components and, where applicable, look-back procedures (see section 3.11).

A qualified person within the blood establishment should be nominated to assess the need for product recall and to initiate, coordinate and document the necessary actions.

Recall operations should be initiated promptly and at any time. Therefore the standard operating procedures should include emergency and “out of hours” contact details. Depending on the national requirements the NRA should be informed.

Recalled products should be destroyed. If recalled products are not destroyed, they should be clearly identified and stored separately in a secure area.

3.10 **Process improvement**

Ideas for potential improvements to any of the systems may come from research, development, brainstorming, or from the management of non-

conformances, events and complaints, from internal or external audit or inspection findings, and from deviations detected during quality monitoring activities.

The process should track corrective or preventive actions that are developed and implemented. An effectiveness check should be in place to determine the impact or effectiveness of any changes. These activities should be documented and reported at least annually to the executive management (in the quality management review report).

3.11 **Look-back**

A written system should be in place for carrying out a look-back procedure. This process should be able to trace the products collected from a donor to the final recipients and from the recipient back to the donor, preferably by means of a computer database.

This standard operating procedure should be followed when it is determined retrospectively that a blood or plasma donation should have been excluded from processing — for instance, because the unit was collected from a donor who was subsequently rejected for reactive viral marker, high-risk behaviour, exposure to CJD/vCJD or other risks related to infectious diseases (*donor look-back*) (3).

If a donor is confirmed to have a disease that is transmissible by blood products or has high-risk behaviour, the donor should be permanently excluded from further donation. All donations from such a donor should be traced and prevented from being used or further manufactured unless they have expired and therefore have already been destroyed. If donations have been used or further processed, procedures should be in place to define appropriate actions. Donor notification and counselling is recommended for purposes of donor health and for the safety of the blood supply.

There should be a process in place for investigating a report of a suspected transfusion-associated reaction in a recipient, in order to identify a potentially implicated donor (*recipient look-back*). The donor of products implicated in transmitting disease or causing recipient harm should be excluded from further donations. All other donations from the implicated donor should be traced and blood components removed from the inventory and recalled, if within the expiry date.

All post-donation information should be recorded and maintained. There should be a system in place to react accordingly and in time to remove unexpired products from distribution in order to assure the safety of recipients.

The recipients of any products identified in the look-back process should be counselled about the risk of having contracted a disease from the potentially contaminated products and should be offered disease marker testing, consultation and medical treatment if indicated. For plasma used for fractionation, the manufacturer of the medicinal product should be notified in case of a look-back (3).

4. Personnel

Sufficient personnel should be available and should be qualified to perform their tasks. They should have the appropriate qualifications and experience and should be given initial and continuous training in order to assure the quality and safety of blood and blood components.

Only persons who are competent in the manufacturing process and have read and understood all relevant standard operating procedures should be involved in the manufacturing and distribution processes, including collection, quality control and quality assurance.

4.1 Organization and responsibilities

Tasks and responsibilities should be clearly documented and understood. Personnel should have clear, current and written job descriptions. There should be an organizational chart showing the hierarchical structure of the blood establishment with clear delineation of lines of responsibility and reporting.

Key personnel include the following functions and their substitutes:

- a “responsible person” (see functions and qualifications below);
- a processing or operations manager, responsible for all processing and operations activities;
- a quality control manager, responsible for all quality control activities;
- a quality assurance manager, reporting findings or quality issues directly to the responsible person and empowered to discontinue operations if quality and safety expectations are not being fulfilled;
- a physician with the responsibility to ensure the safety of donors and the safety of the distributed blood components.

The blood establishment should nominate a “responsible person” who will be responsible for:

- ensuring that approved donor selection criteria are followed;
- ensuring that every unit of blood or blood components has been collected, tested, processed, stored and distributed in compliance with the national regulations in force;
- providing information to the competent national authority;

- ensuring that the required initial and ongoing training of personnel is carried out;
- ensuring that a quality management system and a haemovigilance system (ensuring traceability as well as notification of serious adverse events and reactions) is in place in the blood establishment.

The responsible person should fulfil the qualification requirements according to the national regulations, or should fulfil the following minimum conditions of qualification:

- He/she should hold a diploma, certificate or other evidence of formal qualification in the field of medical or biological sciences awarded on completion of a university course of study or a course recognized as equivalent.
- He/she should have practical experience in relevant areas, preferably for at least two years, in one or more establishments which are authorized to undertake activities related to collection, testing, preparation, storage and distribution of blood and blood components.

Depending on the national legislation, the name of the responsible person may need to be communicated to the NRA.

The quality assurance manager and the processing or operations manager should be different persons, functioning independently. The quality assurance manager is responsible for ensuring that there are appropriate quality systems and protocols in place for the safe and secure release of all materials, equipment, reagents and blood and blood components.

The processing or operations manager is responsible for ensuring that there are appropriate manufacturing and technical processes and procedures in place for the production of blood or blood components.

The physician should hold a relevant medical degree awarded on completion of a university course of study and should hold any registration or licensure that is required by the national authority.

Responsibilities should be delegated only to individuals who have been trained for the task. Delegation should be in written form and should be reviewed regularly.

4.2 Training

Personnel should receive initial and continuous training that is appropriate to their specific tasks. This training should be carried out by qualified personnel or trainers and should follow prearranged written programmes. Approved training programmes should be in place and should also include:

- relevant principles of transfusion medicine;
- GMP;
- relevant knowledge in microbiology and hygiene.

Training should be documented and training records should be retained.

4.2.1 **Initial training**

Programmes for the initial training of newly recruited personnel or personnel taking over new functions should take into account all relevant tasks and procedures, including general topics such as quality assurance, GMP and computerized systems. The same topics and principles apply to training aimed to reintroduce personnel after a longer absence from the workplace. The time frames should be defined.

The training records should identify at least the trainer, all the specified tasks (including the relevant standard operating procedures) and when the training was completed. The records should be signed by both the trainee and the trainer. Upon completing the training, the personnel should be competent in the tasks in which they have been trained. If a database is used the personnel training profile should be updated annually.

4.2.2 **Continuous training**

Continuous training programmes (theoretical and/or practical training) should be in place to ensure that personnel keep up the skills to carry out their assigned tasks. Such training programmes should take technical and scientific developments into account. Training should also include any changes to standard operating procedures and personnel requirements. Both internal and external training courses may be useful here.

4.2.3 **Competency**

The overall competency of personnel is a result of education, experience and training. As a key factor for the quality and safety of blood and blood products, competency has to be carefully evaluated and continuously monitored.

Upon completion of the initial training, the competency of the personnel should be evaluated and documented. After the initial competency is determined, there should be periodic assessment of competency. The contents of training programmes and their effectiveness should be periodically reviewed and assessed.

4.3 **Personal hygiene**

All personnel, prior to being hired and during employment, as appropriate, should undergo health examinations. Any person shown at any time to

have an illness or open lesions that may adversely affect the quality of the products and/or the safety of the donors should be excluded from the establishment's manufacturing processes until that person's condition is no longer judged to be a risk.

All personnel should be trained in personal hygiene. In particular, personnel should be instructed to wash and disinfect their hands before, during and after activities such as blood collection and production.

Special attention should be drawn to the need to protect donors, employees and products from contamination — especially with blood and any other material of human origin.

To ensure protection of products, donors and employees from contamination, personnel should wear clean protective clothing appropriate for the duties they perform. Soiled protective clothing, if reusable, should be stored in a separate closed container until properly laundered and, if necessary, disinfected or sterilized. Where appropriate, disposable or sterile gloves should be worn when handling items that may come in contact with any blood or blood components.

Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines should not be permitted in areas used for production, testing, storage or distribution, or in other areas where they might adversely affect product quality. Personal hygiene procedures, including the use of appropriate protective clothing and equipment, should apply to all persons entering production areas.

5. **Documentation**

The documentation of procedures and records is essential to the quality assurance system. It ensures that work is performed in a standardized and uniform manner and ensures the traceability of all steps. Written instructions should include all applicable methods and procedures and should be accessible to all authorized personnel.

5.1 **Standard operating procedures and records**

5.1.1 ***Standard operating procedures***

All critical procedures — such as purchase and receipt of starting materials, selection of donors, collection of blood, preparation of blood components, laboratory testing and associated quality control testing, product labelling, storage, release, dispatch, shipping, and recall of final products — should be specified in appropriate written instructions in accordance with the principles of GMP and relevant national regulations. Quality assurance

procedures such as complaint investigations, deviation management, recall of non-conforming products, change control and document control should also be specified in written instructions.

All activities should be carried out according to the standard operating procedures. The standard operating procedures and the processes should be regularly reviewed and updated as necessary in order to improve the quality of products and services delivered. The document review process should itself be documented.

5.1.2 **Records**

Each activity that may affect the quality of blood and blood components should be documented and recorded at the time it takes place. Critical activities should be double-checked, either by a second person or electronically. There should be documentation to ensure that work is performed in a standardized manner according to standard operating procedures and that all critical steps in the process are traceable — especially those that have the potential to affect the quality of the product. The documentation should allow all steps and all data to be confirmed by independent review. All documentation should indicate the person performing the action, the date of the action and the equipment used in the action, where applicable.

Records should be legible, accurate, reliable and a true representation of the results and entries. The legibility of records is of great importance. Handwritten entry of data should be clear. Corrections to any records should be made in a manner that permits the reading and review of the previous entry, the correction, the date of correction and the person responsible for the correction.

Critical manufacturing and laboratory testing records should be reviewed frequently for completeness, legibility and, when appropriate, accuracy by the manager or other designated person.

5.2 **Document control**

All documents should be laid out in an orderly manner with a unique title and reference number, and should indicate the version and the effective date. The content of the document should be clear and should not include superfluous information. Title, nature, purpose and scope should be clearly outlined. Documents should be reviewed, approved, signed and dated by authorized persons. An audit trail should indicate the person responsible for each step of document control.

5.2.1 **Document management**

A document management system should be in place. Documents that outline specific manufacturing steps or other critical steps should be readily

available to the personnel performing these tasks. A document control standard operating procedure should be established for the development, review, approval, distribution, implementation, revision and archival of documents. When a document has been revised, the document management system should function in such a way as to prevent the inadvertent use of documents that have been superseded.

There should be a record of the distribution of each document which also shows at least the work areas or tasks affected by the document. All changes to documents should be acted upon promptly and should be reviewed, dated and signed by a person authorized to do so. Standard operating procedures should be designed, developed and approved, and personnel trained in a consistent manner, prior to implementation.

5.2.2 **Record retention and archiving**

All records, including raw data, which are critical to the safety and quality of blood or blood components, should be kept in a secured storage area according to national regulations, or preferably for at least 10 years. A longer period for retention of records may be required by NRAs, international requirements or by specific contractual agreements. Records of permanently deferred donors should be kept indefinitely.

Outdated standard operating procedures should also be kept in a historic file system. Documents should be archived in a secured area and should be readily accessible for retrieval by authorized personnel if required. The archival and retrieval process, especially if computerized systems are used, should be validated to ensure that all information can be retrieved and read at any time until the end of the required period of retention.

6. **Premises and equipment**

6.1 **Premises**

6.1.1 **Design and construction**

Premises should be located, constructed, adapted and maintained to suit the operations that are to be carried out in them. Premises should be designed to permit effective cleaning and maintenance to minimize risk of contamination. The workflow should be designed and arranged to allow for a logical flow of staff, donors and products in order to minimize the risk of errors. Working areas should not be used as passageways or storage areas.

Ancillary areas should be separated from the donor evaluation area, and from the screening, collection and manufacturing areas. Washing and toilet facilities and, if required, facilities for changing or eating should be maintained in a hygienic and tidy condition.

Production, testing and storage areas should be secured against entry by unauthorized persons.

Lighting, temperature, humidity and ventilation should be appropriate and should not adversely affect production or storage. Premises should be designed and equipped so as to afford maximum protection against the entry of animals, including insects.

Premises should be carefully maintained and cleaned (see sections 6.2.2 and 6.2.3) and where appropriate disinfected according to detailed written standard operating procedures. Cleaning records should be retained.

6.1.2 **Donor areas**

The area for blood donors should be separated from all production and testing areas.

The design of premises should be adequate for the conduct of operations and should allow for the logical flow of donors, in one direction if possible, so that donors who have passed reception, screening and donation do not have to return to a previous area.

The area for donor selection should permit confidential personal interviews to take place with due consideration for the safety of donors and personnel.

Rest and refreshment rooms for donors should be separated from donation or storage areas.

6.1.3 **Production areas**

Blood processing should be carried out in adequate facilities that are suitable for the purpose. The donor area, and production and testing areas should be separated from each other.

Whenever possible, closed systems should be used. Using a validated sterile connecting device creates a functionally closed system.

When the use of a closed system is not possible or not appropriate, the risk of contamination or cross-contamination needs to be minimized. Therefore, the premises used for the processing of blood components in an open process should be designed and qualified as a grade A environment with a grade B background, as defined in the WHO GMP for sterile pharmaceutical products (12). A less stringent environment may be acceptable if the preparation of the product is directly combined with additional safety measures — such as immediate transfusion within a defined and limited time period after processing, or placing the product immediately into storage conditions that prohibit microbial growth. Personnel performing open processing should wear appropriate clothing (i.e. suitable coats, masks or gloves) and should

receive regular training in aseptic manipulations. Aseptic processing should be validated. Environmental monitoring protocols should be applied and evaluated by the quality assurance unit.

The premises used for processing blood components should be kept in a clean and hygienic condition. Monitoring of the microbiological contamination load should be considered for critical equipment surfaces and environments where appropriate, according to a risk-based assessment of the process. Records should be available.

Each area of processing and storage should be secured against entry by unauthorized persons and should be used only for the intended purpose.

6.1.4 **Storage areas**

Storage areas should provide adequate space and should be arranged in a way that allows for dry and orderly placement of stored materials.

Storage conditions should be controlled, monitored and documented to show compliance with the specifications. Equal distribution of temperature throughout the storage facility should be guaranteed and documented. This is particularly important for the critical materials used in processing blood and blood components. Temperature checks should be carried out and recorded at least daily. Appropriate alarms at upper and lower temperature limits should be present and should be regularly checked; the checks should be recorded. Appropriate actions to be taken when there is an alarm should be defined in writing.

Intermediate storage and transport should be carried out under defined conditions to ensure that specifications are met.

Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and materials.

6.1.5 **Laboratories**

Testing laboratories should be designed and constructed so as to minimize the risk of errors and contamination. Laboratory areas should be separated from the processing and final product storage areas. Where nucleic acid amplification testing (NAT) technology warrants, separate premises (rooms) and air handling systems should be considered for performing NAT. Consideration should be given to constructing a separate room for specimen sampling and another room for amplification and nucleic acid detection in order to minimize the risk of contamination or false-positive test results.

6.1.6 **Mobile collection sites**

Premises for mobile collection sites should be adequate in design for the conduct of operations and should allow for the logical flow of staff, donors and products in order to minimize the risk of errors. The blood collection at mobile sites should be planned thoroughly. Ancillary areas (rest and refreshment rooms) should be separated from donation or storage areas, but observation of donors during post-donation refreshment should still be ensured.

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

- sufficient size to allow proper operation and ensure donor privacy;
- safety for staff and donors;
- ventilation, electrical supply, lighting, hand-washing facilities, reliable communication, sufficient space for blood storage and transport, and suitable temperature conditions.

Each site should have an approved plan that details the site layout. The set-up of the mobile collection site should be carried out according to the approved plan.

6.2 **Equipment**

6.2.1 **Design and construction**

All equipment should be designed and installed to suit its intended purpose and should not present any hazard to donors, personnel or blood components. It should allow for effective cleaning, and disinfection is recommended for all surfaces in direct contact with the bag system.

Equipment should be located in a suitable position (e.g. a balance should be positioned on a suitable even surface) where there is no negative impact from the surrounding environment (e.g. direct sunlight may have an impact on optical instruments such as apheresis systems or balances).

6.2.2 **Maintenance**

Maintenance, cleaning and calibration should be performed regularly and should be recorded. Maintenance of equipment should be carried out at intervals according to a documented schedule.

The maintenance programmes should be established on the basis of qualification activities. The intervals should be defined according to the instructions of the manufacturer of the equipment. Where intervals are not defined by the equipment manufacturer, maintenance should be carried out at least annually. Different intervals may be defined on the basis of a risk

assessment. If no regular maintenance activities are recommended by the manufacturer, at least a functional control should be performed according to documented procedures. All maintenance activities should be documented. The maintenance reports of external technical services should be checked and countersigned by the staff of the blood establishment in order to decide if action needs to be taken as a result of the maintenance outcome. The maintenance documents should include sufficient information to determine what types of checks have been performed.

Maintenance should also be carried out on equipment that is not in regular use, including back-up systems.

Instructions for use, maintenance, service, cleaning and sanitization should be available in a language that is understood by the user. There should be written procedures for each type of equipment, detailing the actions to be taken when malfunctions or failures occur. Defective equipment, or equipment that is not in service, should be clearly labelled and if possible removed from the working area.

The maintenance of sterile connecting devices should include a check of the tensile strength. Furthermore, as it is a very critical piece of equipment, there should be regular functional checks of the integrity of the tubing weld.

In general, functional tests should also be considered for other pieces of equipment — such as for balances before use after they have been moved or transported to a mobile site.

A regular maintenance programme, including appropriate intervals, should be in place for all critical laboratory equipment or systems. A procedure should be implemented for releasing equipment after maintenance or intervention.

If the maintenance is contracted out (e.g. to the supplier) the work should be documented. Equipment should be evaluated to determine if it is still capable of expected performance prior to returning it to service for manufacturing blood components.

6.2.3 **Cleaning**

Cleaning procedures should be established and described in a standard operating procedure. Cleaning of equipment should take into consideration the instructions of the manufacturer. A schedule for regular cleaning and disinfection, if necessary, is recommended for all surfaces with direct contact with the bag system (e.g. centrifuge, separator, storage shelves).

Disinfectant solutions with sufficient and approved antimicrobial activity should be used. A cleaning plan should be established that specifies the cleaning intervals and methods to be used for the different equipment and

premises. The cleaning procedures should not impact negatively on the equipment or blood components. Cleaning activities should be documented.

6.2.4 **Calibration**

Measuring instruments and measuring systems used for the collection and further separation of blood and for quality control testing should be calibrated regularly according to the instructions of the manufacturer. Calibration should be carried out and documented according to established standard operating procedures and national regulations. Regular calibration is necessary for temperature probes (e.g. in refrigerators), pipettes, balances, timing devices and haemoglobinometer devices (using control blood and/or cuvettes from the manufacturer). The devices used for calibration, such as the control weight used for the calibration of balances, should be certified for accuracy (by testing against a known standard). If the calibration consists of using a comparison measurement approach with a second device, then the maximum allowed deviation between the two measurements should be defined.

6.3 **Computerized systems**

A computerized system may be described as a functional unit consisting of one or more computers and associated peripheral input and output devices, and associated software that uses common storage for all or part of a programme and for all parts of the data necessary for the execution of the programme (9). A computerized system executes user-written or user-designated programmes, performs user-designated data manipulation (including arithmetic operations and logic operations), and it can execute programmes that modify themselves during their execution. A computer system may be a stand-alone unit or may consist of several interconnected units.

Hardware and software should be protected against unauthorized use or changes.

Critical computerized systems should be validated before use. The system is considered critical if:

- it is directly linked to the decision-making process for blood product manufacturing, blood or blood product testing (donor/recipient), labelling and release;
- it is used to handle or manipulate the related information;
- it has an impact on product quality, information management, storage, or tools for operational decision-making and control.

Periodic revalidation or annual checks to ensure reliability should be performed on the basis of a risk assessment.

There should be procedures for each type of software and hardware, detailing the action to be taken when malfunctions or failures occur. A back-up procedure should be in place to prevent loss of records in case of expected or unexpected downtime or function failures. The archival and retrieval process should be validated to ensure the accuracy of the stored and retrieved data.

Once in routine operation, critical computer systems should be maintained in a validated state. Any change should be handled through the formal change control system which includes qualification and/or validation activities. Applicable documentation should be revised and personnel should be trained before the change is introduced into routine use. Any software updates should be evaluated in advance and there should be procedures to validate or verify the acceptability of the update installation.

The manual entry of critical data, such as laboratory test results, should require independent verification and release by a second person. When a computerized system is used, an audit trail should be guaranteed.

7. Qualification and validation

7.1 Qualification of equipment

All equipment should be qualified and used in accordance with validated procedures.

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

The extent of qualification depends on the critical nature and complexity of the equipment. For some equipment, installation qualification and calibration may be sufficient. More complex equipment may need a more thorough approach to qualification and validation and should include the instruments, the associated operation(s) and the software involved.

Further guidance on qualification and validation is given in the WHO guidelines on validation (10) and in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) *Recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation* (11).

7.2 Validation of manufacturing processes

All critical processes in the manufacture of blood and blood components should be validated before implementation according to a predefined protocol of tests and acceptance criteria. Critical processes include donor

selection and determination of suitability, component preparations, donor testing for infectious diseases (see also section 7.3), ABO blood typing and antibody screening where applicable (e.g. for red-cell concentrates), labelling, storage and distribution.

Validation studies, including statistically based sampling where feasible, should be conducted to ensure that products are produced with consistent quality characteristics. Acceptance criteria should be based on a defined set of specifications for each blood component, including a set of quality control tests — such as measurement of weight respective to volume, residual blood cells (depending on product specifications), haemoglobin, and relevant coagulation factors (e.g. Factor VIII) and/or total protein/IgG content where applicable — established by the blood establishment or the NRA (see also sections 9.4.3 and 9.6). Data should be available to ensure that the final product is able to meet specifications.

Likewise, apheresis systems, including software, should be qualified and maintained. Apheresis procedures should be validated. Validation criteria with regard to the quality of blood components may, depending on the product, include weight, yield, content of residual white blood cells, haemoglobin and relevant coagulation factors. Validation studies of new apheresis procedures should also evaluate possible risks of activation of the coagulation, fibrinolysis, and complement systems potentially induced by the material in contact with blood. Such studies are usually performed by the manufacturer of the apheresis systems to support the licensing by the regulatory authorities.

7.3 Choosing an appropriate test system to screen for infectious disease

The quality of the screening of blood donations for markers of infection depends on a number of conditions being fulfilled:

- Only test systems designed and validated for blood donor screening should be used. Other systems, such as tests validated for diagnostic purposes only, should not be used.
- All test systems should be validated by the manufacturer.
- Before implementing a test system for routine analysis, the laboratory should prove by validation that the manufacturer's specifications are met (in principle this also applies if in-house tests are used).
- The laboratory should show that, on routine application of test systems, specified performance is reached and is consistently maintained.

Screening of blood donations generally requires such test systems to aim for high sensitivity even though this may be achieved at the expense of specificity. Although this may result in an increased proportion of false-

positive results, it is important in ensuring that all components with true-positive test results are detected and not released. In case of new assays or techniques, precise specifications must be established by testing samples of appropriate populations (e.g. donors, recipients, seroconverted recipients) and by comparing the results generated by the existing test system and by the new one.

Validation of a test system involves four main elements:

- assay reagents which should include quality control material (e.g. positive quality control sample, negative quality control sample, calibrators);
- equipment;
- software, if applicable;
- procedure and handling (test method).

Validation records should not only present proof that the scope and desired specifications are met, but should also provide precise descriptions of all key material, key equipment and conditions of processing (e.g. temperature and time of incubation, rounds per minute in centrifugation). In addition, instructions for handling and processing, by which assay specifications are met, should be put in writing and should be provided with the test system.

Test system specifications that need to be established and/or met by the manufacturer are:

- specificity;
- sensitivity;
- accuracy (degree of closeness of measurements to the true value);
- repeatability (replicates of series);
- reproducibility (replicates of series, variation by operator, by day or by lot of reagents);
- known interferences (e.g. haemolytic sera, lipemic sera);
- lower and upper limits of detection (serial dilution).

Apart from testing appropriate donor/recipient populations, appropriate reference materials should be used to define the performance specifications of a test system. These reference materials should be traceable to the WHO international standard or reference reagents, when available for a specific marker.

The necessary documentation should be available for each test system and should include at least the following information:

- a description of the test system (reagents, controls, devices etc.), equipment and diluents (if applicable);
- safety instructions;

- a description of the assay principle;
- specifications;
- a description of the sampling procedure, sampling plan, sample handling and test procedure;
- internal quality controls (positive and negative), run with every series of donor samples;
- recommended calibration material and calibration frequency (e.g. change of reagent lot);
- primary reading of measurement (format e.g. optical density);
- interpretation of the measurement and/or conversion to result;
- acceptance criteria, cut-off, reference values, limits, pro-zone, grey zone.

Where feasible, the test system should be approved for blood screening by the NRA.

7.4 Assay performance validation

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

- the performance specifications of the system established by the kit manufacturer are met by the laboratory;
- laboratory personnel are thoroughly instructed, trained and competent to operate the test system.

Prior to first-time use, critical equipment, including related computer systems, should be thoroughly qualified. Installation qualification, operational qualification and performance qualification should be carried out and fully documented. This work may involve suppliers and/or third parties. It is strongly recommended that any performance qualification should be performed by the end-user (and not by a third party) since this is intended to demonstrate that the process works as designed.

In addition, a demonstration showing that the test system performance specifications are constantly met in routine donor testing is required. The means by which this may be achieved are:

- inclusion of internal and external quality control materials with every test series;
- previously tested samples collected for use as an internal panel for periodical in-process quality control;
- monitoring measurements of controls (for instance, graphically by using a Levi-Jennings diagram);
- statistically establishing the standard deviation of control measurements;

- implementation of deviation rules (warning range, control range, Westgard rules) to govern corrective actions;
- monitoring trends in control measurements on external standard or reference material;
- successful participation in external quality assessment schemes (proficiency testing) by all qualified members of staff.

8. Management of materials and reagents

8.1 Materials and reagents

Only reagents and materials from approved suppliers that meet documented requirements and specifications should be used. Materials and reagents should meet the legal requirements for medical devices. The management procedures for materials, reagents and supplies should define the specifications for acceptance of any elements that may influence the quality of the final blood component. Receipt logs or records for these critical materials should indicate their acceptability on the basis of the defined specifications and should identify the person accepting them.

8.2 Receipt and quarantine

Appropriate checks (e.g. attached certificates, expiry date, lot number, defects) should be performed on received goods in order to confirm that they correspond to the order and meet the specifications. Damaged containers should be carefully checked to detect possibly affected materials. Incoming critical materials (such as sterile solutions, blood bag systems and testing reagents) should be physically or administratively quarantined immediately after receipt and until they are released for use. Where the quarantine status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. When labels are applied to the containers to indicate their status, the use of different colours may be helpful. Any system replacing physical quarantine (e.g. a computerized system) should provide equivalent security.

8.3 Release of incoming production material and test reagents

Critical material should be received under quarantine and then evaluated for acceptability. After acceptability has been determined, the materials should be released by an authorized person for use in manufacture. The actual release may be performed by an authorized person or under the guidance of a validated computer system. The minimum criteria for the release should be the availability — and check of — certificates or other acceptability records generated by the manufacturer and containing sufficient information to determine product acceptance.

Similarly, each new lot of testing kits should be evaluated by the laboratory to check compliance with predetermined performance standards before release for routine analysis.

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

8.4 **Storage**

Materials and reagents should be stored under the conditions established by the manufacturer and in an orderly manner that permits segregation by batch or lot and stock rotation. Storage and use should follow the “first-expiring first-out” principle (i.e. the material that entered storage first should be used first). The use of the expiry date as an alternative inventory management technique is also acceptable.

Where special storage temperature conditions are required, these should be provided, checked and regularly monitored.

8.5 **Traceability of materials and reagents**

Inventory records should be kept for traceability. The records should document which batch or lot of materials or reagents have been used for the collection, processing or testing of the blood units or blood components. Inventory of critical supplies such as donation labels with serial numbers should be strictly controlled to avoid mix-ups or mislabelling due to uncontrolled excess labels.

8.6 **Supplier/vendor management**

All materials and reagents relevant for the quality of the products should be purchased or obtained only from qualified suppliers. The relationship between the two parties (i.e. contract giver and contract acceptor) should be defined in a contract. The blood establishment as contract giver is responsible for assessing the competence of the supplier (contract acceptor).

The contracting process should include:

- a qualification review prior to awarding the contract to ensure that the supplier meets the organizational needs and complies with GMP requirements;

- the setting of appropriate specifications that adequately define the quality of the service or goods;
- appropriate checks on received goods to confirm that they meet specifications;
- checks to ensure that goods in use continue to meet specifications;
- notification of changes to requirements from either party prior to implementing any changes that may affect the quality of the services or goods provided;
- regular contact with suppliers in order to help understand and resolve problems.

9. Manufacturing

9.1 Donor registration

Upon presentation at the blood establishment, donors should positively identify themselves by stating their full name, address and date of birth. Each donor should also provide proof of a permanent place of residence, including a telephone number where appropriate, so that they can be contacted after donation, if necessary.

Proof of identity with a photograph — such as an identity card, passport or driver's licence — should be provided, especially in the case of first-time donors. A careful check of the identity of the donor should be repeated prior to each step that is relevant to the quality of the products and the safety of donors, but at least before donor selection and venipuncture.

If electronic databases are used to maintain donor information, double checks or another validated method to confirm accuracy of information entered manually should be implemented.

9.2 Donor selection

Blood and blood components should be obtained from healthy donors who are carefully selected using a systematic and validated process consisting of review of the donor's health assessment, social behaviour history (the donor questionnaire) and medical examination. This evaluation, along with a review of the results of the infectious disease screening laboratory test, should be used to make sure, prior to the release of any blood component, that the donor presents no increased risk for transmission of infectious agents. NRAs are pivotal in establishing a harmonized framework for donor selection criteria, taking into consideration the types of products, the relevant infectious risks, and the epidemiological data for disease prevalence in the country. The review of these combined data may be used in developing donor selection criteria. The NRA should also be part of

any decision-making process intended to modify the donor selection and donation-testing procedures.

Regulatory agencies and professional organizations have respectively published regulations and recommendations on the criteria for the selection of donors of whole blood and blood components (see, for instance, the Council of Europe's *Guide to the preparation, use and quality assurance of blood components*) that can be used as a reference (13). Such guidance documents also explain critical points that should be considered when processing blood and blood components.

Whenever possible, blood donations should be collected through a donation system involving regular and repeat donors. Obtaining blood from regular and repeat donors is a major contribution to ensuring optimal historical medical information about the donors, and therefore to detecting potential risk factors.

9.2.1 ***Epidemiological surveillance of the donor population***

To ensure optimal long-term safety of blood components, blood establishments should maintain continuous epidemiological surveillance of the donor population. The objective of this surveillance is to know, as precisely as possible, the prevalence and incidence, and their respective trends, of infectious markers that are relevant to the safety of blood components. This enables countermeasures to be taken in a timely manner. The system should be able to gather epidemiological data not only at national/regional levels but also among donor populations that provide blood at individual blood establishments within a country or region. Consideration should be given to the travelling patterns of the donor population with respect to possible transmission of infectious diseases (i.e. malaria, Chagas disease, vCJD, etc.).

The information from epidemiological surveillance can furthermore be used:

- to detect, among donor populations of various collection centres, differences that may be associated with objective differences in viral markers within donor populations;
- to detect differences in the donor selection and screening processes at collection centres;
- to detect trends in infectious markers which may reflect either a change in the rate of viral markers in the population or a possible deviation in the donor selection or screening process at specific collection sites;
- to assess the relevance of any preventive measures such as a strengthened donor selection process, additional deferral criteria, or implementation of additional screening tests to avoid contamination of blood components.

When donations from first-time donors are used to prepare blood components, epidemiological data on this specific donor group should be included in the estimate of the risk for infectious diseases transmitted by blood. It has been shown that first-time donors, who may occasionally include test-seeking persons, constitute a group that in some situations is more likely to have bloodborne viral markers than regular donors who have already gone through a selection/deferral process.

It is currently advisable to collect and analyse epidemiological data at the collection sites for HIV1/HIV2, hepatitis C virus (HCV) and hepatitis B virus (HBV) since they historically represent the major pathogenic risks associated with blood components. It is the responsibility of the NRA to define whether this list should be modified or should include additional criteria such as emerging infectious agents, on the basis of local or regional epidemiology. For the current three recommended markers, only confirmed positive tests (i.e. tests which are repeatedly reactive in a screening test and positive in at least one confirmatory test) should be recorded, reported and analysed.

9.2.2 **Information to donors**

Potential new donors should be informed (ideally both verbally and in writing) that it is necessary to respond to questions about their medical history and personal behaviour so that it can be determined whether they are eligible for blood donation. Written information can be a leaflet explaining infectious risks associated with blood products, and the impact of social behaviour on infectious risks or infectious risk factors. This information is usually provided by a licensed physician, or by a designated qualified person under the direct supervision of a licensed physician. The information should clearly explain the deferral criteria that exclude a donor from donating blood or plasma. It is important to ensure that the reasons for deferral are well understood by the candidate donor.

The candidate donor should be asked to sign a form of informed consent to give blood in which he/she acknowledges understanding the moral and legal responsibilities and possible risks associated with donating blood, as well as the occasional complications that may occur. The declaration of consent should also include a statement that the donor authorizes the release of his/her blood and blood components for transfusion or further manufacturing.

Donors should be informed to contact the blood establishment if there is an unexpected event after the donation, such as illness or the discovery of new information not disclosed during the health screening.

9.2.3 **Questionnaire and interview**

The interview assessment of each donor should be carried out by a qualified person who is trained in the use of donor selection criteria using a validated

written questionnaire with direct questions if necessary. In order to obtain relevant and consistent information about the donor's medical history (concerning illnesses and drug use) and general health, it is recommended that the donor should review, complete and sign a predefined questionnaire that is adapted to the type of donor (e.g. first-time donor or repeat donor). The questionnaire should cover questions about the medical history of the donor, his/her travel habits, risk behaviours, use of medication, and other medical treatment. A list of countries may be provided to assist the donor to complete the questionnaire with regard to earlier residency or travel. Similarly, a list of drugs that may pose a threat to the recipient or may be an indication of poor donor health may also be provided. The NRA may provide requirements for such lists.

The questions should be drafted in such a way that donors may easily identify whether they are in good health. The questionnaire may be administered in several ways, such as:

- by a person reading questions to the donor and recording the responses;
- by the donor reading the questions and recording the responses;
- by computerized written questions presented to the donor with the donor recording the responses;
- by the computer reading the questions to the donor and the donor recording the responses;
- by other validated methods that ensure that the donor understands the question, how to completely answer the question and how to record the response to the question.

There should be a link between the donor, the donor questionnaire and the collected products. After the donor's history has been reviewed, the collected components should be identified in a way that links the products to the history records but maintains the confidentiality of the donor. The product should be identified by a unique donation number linked to the donor name but the product information should not include the donor name except as required by the NRA in cases such as autologous donations.

After reading the donor information and/or answering the questionnaire, donors who are at risk of carrying a disease transmissible by blood should be able to exclude themselves voluntarily and confidentially. Such confidential self-exclusion should also be possible after the donation (e.g. by phone). There should be a means of documenting both the reason for self-deferral and the determination of the need for temporary or permanent deferral. These records should be retained in a similar manner to all donor screening records.

Donor identification and information, the donor selection interview and the donor assessment should all take place before each donation. The premises

and layout of the blood establishment (or the mobile collection unit) should allow for adequate confidentiality during the donor interview and selection process so as not to discourage the candidate donor from answering questions about personal or private behaviour; otherwise the safety of the blood donation could be compromised.

The minimum intervals between two donations should be defined and should then be audited or reviewed for compliance with the waiting period prior to each donation.

9.2.4 ***Deferral policy and deferral criteria***

As part of the blood establishment's deferral policy, a list of permanent or temporary deferral criteria used for potential donors should be clearly defined, made public, and incorporated in the educational material for donors and the establishment's procedures. It should also be determined whether the donor has previously been deferred, and reasons for any deferral should be reviewed so that a decision may be made on whether to accept the donor for current donation. A donor who is deferred should be informed of the reason for deferral, encouraged not to donate at other facilities while deferred and informed that the reason for the deferral may be shared with other health professionals or government agencies according to NRA recommendations or other legal requirements.

Both acceptance and deferral criteria for the donation of blood should be formulated by the NRA and should be national requirements that are applied nationwide. Within the scope of their role of establishing and implementing effective national regulations, NRAs should enforce such criteria.

Examples of the major permanent deferral criteria found in international guidelines include:

- clinical or laboratory evidence of bloodborne infectious diseases such as acute or chronic infection with HIV, HCV or HBV (in certain jurisdictions donors with elevated titres of anti-HBs may be acceptable);
- past or present intravenous drug use;
- persistent bacterial or protozoal infections.

Other deferral criteria, either permanent or temporary, may include:

- a sexual relationship between men;
- men or women who are engaged in prostitution;
- subjects with haemophilia or other clotting-factor defects;
- sexual partners of any of the above or of someone the donor suspects may carry the above risk factors;
- jaundice within the 12 months prior to donation, since this may be a clinical sign of hepatitis A, B or C;

- transfusion with blood, blood components, plasma products, cellular therapy products or vascularized tissue transplant in the 12 months prior to donation, as blood transfusion and transplantations are risk factors for all bloodborne infections;
- exposure to someone else’s blood, including an accidental needle stick in the 12 months prior to donation;
- tattooing, scarification, ear-piercing or acupuncture in the 12 months prior to donation (since these practices may be vehicles for transmission of viral diseases) unless clear evidence is provided that it was carried out under sterile conditions;
- risk factors for Human T-cell lymphotropic virus (HTLV) infection;
- risk factors for malaria infection (e.g. travel in countries where the prevalence is high);
- a confirmed family history of CJD;
- imprisonment longer than three days within the 12 months prior to donation.

When temporary deferral criteria are used, a specific procedure involving trained personnel should be in place for the reinstatement of donors. There are deferral criteria that are temporary (as long as a risk factor has been identified) but that can be waived after additional controls have been carried out on the donor or the period of deferral has passed. NRAs may recommend or define different deferral criteria and timelines, e.g. when implementing NAT testing for the relevant viruses.

9.2.5 ***Physical examination, donor health criteria and donor acceptance***

A targeted physical examination should be carried out by a licensed physician according to an established procedure prior to the first donation and thereafter before subsequent blood donations, and in case of special apheresis programmes at regular intervals. Depending on national regulations established by the NRA, the physical examination may be performed by a suitably educated and trained physician substitute under the supervision of a licensed physician. NRAs should, usually after consultation with the blood establishment, determine the health criteria and the acceptable limits taken into account during the physical examination — such as measurement of haemoglobin, blood pressure, weight, age, pulse rate and temperature, or any other criteria considered to be of concern for the safety of blood components or donors.

A written standard operating procedure based on the relevant acceptance/deferral criteria should be in place at the blood establishment to control donor acceptance and deferral criteria, in compliance with the NRA. Abnormal donor findings should be referred to the physician who has the

responsibility of making the final decision about the donor's eligibility on the basis of current medical knowledge and national regulations. If the physician has any doubt about the donor's eligibility, the donor should be deferred.

An appropriate computerized record system (or, if that is not available, a manual system) should be in place for donor records (including their medical history and health status), and for the purpose of ensuring traceability of all donations. Such information provides historical perspective of the health status of donors, including previous temporary deferrals, and contributes to reinforcing the judgement about whether the donation would create a risk to the quality and safety of the blood components.

Records should be kept for each activity associated with the selection of the donor. The record should reflect the decision to accept the donor, taking into consideration the medical history, donor deferral history, the donation interval, the answers given in the interview or questionnaire, and the results of the physical examination. The rejection of a donor and the reason for the deferral should be recorded. An authorized interviewer should sign the donor selection records and the final assessment of the donor's suitability.

As with all other manufacturing steps under GMP, donor selection and acceptability procedures should be followed at all times using the validated methods. Any deviations from established procedures and processes may result in products not meeting specifications so such products should be considered as non-conforming products and must not be released for distribution.

9.3 **Collection**

9.3.1 ***Whole blood collection***

Donors should confirm their identity (by a method such as stating name and date of birth) immediately prior to venipuncture. Also prior to venipuncture, a check should be made to ensure that the collection system to be used is not damaged or contaminated, and that it is appropriate for the intended collection. Any abnormal moisture or discoloration suggests a defect and in such a case the collection system should be discarded. An investigation should be conducted to evaluate the extent of the problem and appropriate corrective actions should be taken. The collection systems should be used in accordance with the instructions of the manufacturer. Appropriate hand disinfection and personal hygiene procedures should be in place and should be performed by the personnel before each donation.

A standardized and validated procedure for the preparation of the phlebotomy site should be followed using a suitable disinfection solution

which should be allowed to dry depending on the type of disinfectant. The expiry date of the disinfectant should be checked. If refillable bottles are used, they should be cleaned before being refilled. The date of manufacture and the date of opening of in-house disinfectants should be stated on the label. The prepared skin area should not be touched after the disinfection and before the needle has been inserted. Care should be taken not to lean over or speak over the disinfected skin.

For blood donations, laboratory samples should be taken at the time of donation. Procedures should be designed to minimize the risk of microbial contamination to the unit, such as diverting at least the first 10 ml collected in the tubing into test tubes for testing. Methods should be implemented to minimize the deterioration of the sample, such as refrigeration of the sample if required by the manufacturer's instructions for the sample tube or test kit. The sample labelling process should include steps (such as labelling the tubes immediately at the chair side) to prevent the misidentification of samples. The test samples should be labelled immediately in a manner that links the donor, the samples and the blood component without breaching the confidentiality of the donor.

As soon as the collection process starts, good mixing of the blood with the anticoagulant solution should be ensured to avoid risks of activation of the coagulation cascade. The collection bag should be mixed gently at regular intervals thereafter. The mixing can be done by using a continuously running automatic mixing balance or by periodic manual mixing of the unit at least every 90 seconds. Collection of one standard unit of whole blood should be achieved within 12–15 minutes (depending on the component to be prepared later on), as longer durations may result in activation of the coagulation factors and cellular components.

Records should be kept for each activity associated with the donation, including identification of the person who performed the venipuncture. Records should also show any unsuccessful donation, adverse reactions or adverse events.

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.

The integral blood bag collection tubing should be sealed off at the end as close as possible to the blood bag and then removed.

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

When the donation is completed, all records, blood bags and laboratory samples should be checked for the donation number issued. Donation

number labels that have not been used should be discarded using a controlled procedure. Procedures to exclude misidentification should be in place. After blood collection, the blood bags should be handled in a way that maintains the quality of the blood (see section 9.4.3.1).

A standard operating procedure should be in place describing the actions to be taken following an unsuccessful donation. It should specify how to handle already labelled material and the circumstances under which a second venipuncture might be possible.

As with other GMP manufacturing steps, the donor product collection process should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and therefore such products should be considered non-conforming products and should not be released for distribution.

9.3.2 ***Collection by apheresis***

In automated procedures, whole blood is collected from the donor, mixed with anticoagulant, and passed through an automated apheresis device. The blood component of choice is separated from the other blood components which are returned to the donor in a series of collection/separation and return cycles. The operational parameters of the apheresis system should be implemented in compliance with the instructions of the equipment manufacturer and in compliance with any specified safety requirements of the NRA. In general, the anticoagulant — often 4% sodium citrate or anticoagulant citrate dextrose solution A (ACD-A) — is delivered at a rate that will yield a specified ratio of anticoagulant to blood. The volume of the component collected from the donor during one procedure and over a period of time should be regulated by internal policies based on current medical knowledge and on national regulations set by the NRA. The number of collection/separation and return cycles for each donor depends on the total volume of the component that is to be harvested. To determine the number of cycles to be employed, the equipment requires programming with data inputs such as donor weight, height and haemoglobin values, and the pre-donation platelet count if platelets are to be collected. The amount of time required for the donation procedure depends on the number of cycles. An adequately trained physician should be available during apheresis sessions.

The donor apheresis collection process should be followed at all times using validated methods. Any deviations from the established procedures and processes may result in products not meeting specifications and therefore they should be considered non-conforming products and must not be released for distribution.

9.3.3 **Safety of donors**

All measures should be taken to avoid anything that could adversely affect the donor before, during and after the donation. Special attention should be drawn to the potential risk of transmission of diseases or infections during the collection and sampling processes.

Donors should be given post-donation instructions regarding a period of recovery, such as refraining from certain activities for a while, drinking more fluids than usual and making sure to eat appropriately after the donation. Donors should be advised to refrain from activities such as heavy lifting, operating large items of equipment and other strenuous activities for a period of time until their blood volume has recovered. Donors should also be provided with information on how to obtain medical advice if they experience an adverse donor reaction after leaving the blood establishment.

Throughout the procedure of withdrawal of blood or blood components, the donor should be monitored. Personnel should be educated to provide appropriate aid in case of any adverse reaction. Donors should be kept under post-donation observation (e.g. for 15 minutes or more) prior to leaving the blood establishment and should be offered refreshment to replace fluid loss. If medically required, drinks may be provided to donors during collection (e.g. apheresis). In these circumstances, a suitable container for the drink is required. Donors should remain under observation for anticipated reactions to donation until they are able to articulate that they feel well enough to leave and be unattended. Immediate care should be given to the donor if there is a donor reaction. Information regarding donor reactions and a process to track and trend reactions should be in place in order to evaluate the number, type and severity of reactions. This information should be used to improve donor safety.

9.4 **Component preparation**

The quality of the components is assured by control of all stages of manufacture, including donor identification, collection, separation of components, labelling, storage, packaging and dispatch. The standard operating procedures should describe the specifications for materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

The standard operating procedures for component preparation should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and such products should be considered as non-conforming products and must not be released for distribution.

9.4.1 **Starting material**

The starting materials for preparation of blood components are blood donations collected from suitable donors. Conditions of storage or transport, and the time prior to processing, are contributing factors to the quality of the product. Delays in preparation or unsuitable conditions of storage or transport may adversely affect the quality of the final product. Blood and blood components should be placed in controlled and validated conditions as soon as possible after venipuncture.

Donations and samples should be transported to the processing site in accordance with procedures that ensure both a constant approved temperature and secure confinement. This is especially important when blood is transported from distant collection sites.

Product transport or shipping at appropriate temperatures and temperature monitoring are important to ensure optimal quality. One way to ensure the temperature of products is to use packaging methods validated to keep the blood within the required temperature limits. There should be validation data to demonstrate that the method of transport maintains the blood within the specified temperature range throughout the period of transportation. Alternatively, portable temperature loggers may be used to record the temperature during the transportation of blood to the processing site. Where the blood is not transported by the processing establishment itself, the responsibilities of the transport company should be clearly defined and periodic audits should be conducted to ensure compliance.

9.4.2 **Methods of production**

Blood components may be prepared by using a centrifugation step with subsequent separation, by using another validated preparation method, or by apheresis technology during collection.

Although the use of closed systems is strongly recommended for all steps in component processing, open systems may exceptionally be necessary due to local constraints in an environment specifically designed to minimize the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures (12).

Where sterile connecting devices are used to maintain a functionally closed system they should be correctly used in accordance with a validated procedure. The resulting weld should be checked for satisfactory alignment and for validated integrity.

The critical equipment used for the preparation of blood components should be traceable to the corresponding manufacturing records.

9.4.2.1 Centrifugation

The centrifugation parameters (revolutions per minute, temperature, time, acceleration, deceleration) are important for the composition and characteristics of the specific components. These critical parameters should be defined on the basis of validation data that demonstrate a process that consistently produces quality products. For each run, the centrifugation records should identify the operator and confirm that the centrifugation process was performed according to specifications.

9.4.2.2 Separation

After centrifugation, the bag system should be carefully removed from the centrifuge and placed into a plasma expressor or blood separation system. The different layers of the components (red cells, platelets, plasma) should be transferred to the satellite bags within the closed systems, in a manner designed to optimize the harvest of the intended component while minimizing the carry-over of other component fractions.

Alternatively, blood components can be separated during collection by apheresis technology (see section 9.3.2.).

9.4.2.3 Freezing

Freezing is an important processing step that has an impact on quality, especially of plasma. The rate at which freezing proceeds and the core temperature are both considered to be important parameters. Rapid plasma freezing prevents or reduces the loss of critical constituents such as Factor VIII in frozen plasma that is either recovered or obtained by apheresis.

A system should be in place for ensuring that plasma is frozen to the specified core temperature within the time limit, keeping in mind that the freezing speed will be influenced by the type of plasma container, the freezing equipment and the loading pattern, as well as by the volume of plasma. The validation of the freezing process should consider worst-case scenarios that take into account both minimum and maximum loads and positions in the freezer. Recording the temperature of plasma units and the freezing time during a freezing process allows one to evaluate the freezing capacity of the equipment and ensures a standardized freezing process. Validation studies should be available and should demonstrate that the temperature of a frozen pack reaches the proposed storage temperature following the specifications. As indicated above, the aim is to achieve rapid freezing and thereafter to minimize temperature changes to the frozen plasma.

Freezing of cellular components such as red cells or cellular therapy should follow a well defined, validated procedure that ensures the recovery

and viability of the intended cellular product during thawing and final preparation steps.

9.4.2.4 Leukocyte reduction

Whole blood may be filtered for leukocyte reduction prior to centrifugation. Filtration of whole blood reduces the level of platelet and leukocyte contamination in plasma and red-cell concentrate preparations. Alternatively, components (e.g. red cells, platelets) may be filtered after separation. The introduction of any leukocyte reduction process either by filtration or special centrifugation technique requires careful validation that takes national requirements into account.

In addition to filter properties, the final result of filtration is influenced by several process parameters (e.g. flow rate, temperature, priming and rinsing) and by the properties of the component to be filtered (e.g. storage history of the component, number of leukocytes and number of platelets). The filtration procedure should incorporate manufacturing specifications such as height and temperature. The method should be fully validated under the conditions to be used. Careful attention should be given to the rate of filtration. Rapid or slow filtration may indicate process failures.

Special centrifugation or filtration techniques of leukocyte reduction are used in several apheresis systems. When a standardized procedure is established on the apheresis system, the method should be validated under the conditions to be used.

An appropriate method should be used for leukocyte counting after leukocyte reduction. The method should be validated to ensure linearity, accuracy and reproducibility.

9.4.2.5 Irradiation

Regular dose-mapping of irradiation equipment should be performed. The exposure time should be set to ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose. The common recommended minimum dose is 25 Gy (2500 cGy).

Care should be taken regarding the increased potassium leakage from red cells after their irradiation, either by limiting the shelf-life of the red-cell concentrate or by further manufacturing steps such as washing.

For the radioactive source, allowance should be made at least annually for source decay. A second independent timing device should be used to monitor exposure time.

Radiation indicators should be used as aids to differentiating between irradiated and non-irradiated blood and blood components. A defined

procedure should ensure the separation of components that have not been irradiated from those that have been irradiated, and should ensure they have distinctive labelling.

9.4.3 **Blood and blood components**

Blood components may be obtained using the methods described in section 9.4.2. However, the sequence and the combination of the methods used in the production of blood components may vary from one product to another.

The collection process itself is already crucial for the quality of blood components. Measures such as a reliable arm-cleaning and disinfection procedure, the use of closed and sterile collection systems, and appropriate microbiological controls should be implemented. Time limits should be defined for the processing of blood components.

There are detailed recommendations concerning the preparation and quality assurance of blood components. See for instance *Guide to the preparation, use and quality assurance of blood components* of the Council of Europe (13). In the following sections, examples of the most important blood components are described. Where NRA requirements exist, they should be followed. Specifications of a number of products are described below.

9.4.3.1 **Whole blood**

Whole blood for transfusion is blood that is taken from a donor who has been assessed and found suitable as meeting the blood establishment and NRA acceptance criteria. Whole blood is collected in sterile and pyrogen-free containers with a suitable anticoagulant. It may be used without further processing. In some cases, whole blood for transfusion may also be used after leukocyte reduction.

The temperature of whole blood stored for transfusion should remain controlled between 1° and 6°C or in a more stringent range defined by the NRA. The storage time depends on the anticoagulant/preservative solution used.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- haemoglobin or haematocrit;
- haemolysis at the end of storage.

The primary use of whole blood is as a source material for the preparation of blood components. Transportation and further manufacturing processes

should be developed to maximize the number of components that may be produced from a whole blood donation. After collection, whole blood should be kept at a controlled temperature appropriate to the intended component manufacture and should be delivered to the production site as quickly as possible. If whole blood is collected away from the production site, the validated transport systems should ensure that correct temperatures are maintained throughout the process and that the product is delivered within 24 hours. The period between collection and further processing depends on the product but should not exceed 24 hours.

The whole blood may also be filtrated to reduce leukocyte content prior to further processing.

Components should be manufactured by a method validated as meeting the predefined product specifications.

9.4.3.2 Red-cell concentrate

Red-cell concentrates are obtained from whole blood by centrifugation and removal of plasma with or without buffy coat, depending on the centrifugation parameters. After subsequent addition of an appropriate nutrient solution, the red cells should be stored at 1–6°C as soon as possible. Alternatively, red-cell concentrates may be obtained using an apheresis system and likewise stored at 1–6°C. Red-cell units that exceed 10°C after reaching the storage temperature should be discarded. The red-cell concentrate may be used for transfusion without further processing.

To obtain leukocyte-reduced red-cell concentrates, either whole blood filtration can be applied prior to separation or there can be a post-separation filtration of the red-cell concentrate. A fully validated procedure should be established to determine optimum conditions for use of a leukocyte reduction method.

Red-cell concentrates are stored under the same storage conditions as whole blood. The storage time depends on the anticoagulant/preservative solution used.

Further methods of preparation, such as irradiation or washing, are applied to obtain specific red-cell products, depending on the clinical indication.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). Parameters measured depend on the type of red-cell concentrate product obtained. At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- haemoglobin or haematocrit;
- haemolysis at the end of storage;
- residual leukocytes, if leukocyte reduction is performed.

9.4.3.3 Platelet concentrate

Platelet concentrates are derived from whole blood or are obtained by apheresis.

After collection, whole blood can be kept for up to 24 hours in conditions that are consistent with the preparation of plasma (see section 9.4.3.4.) and validated to maintain a temperature between 20°C and 24°C, following international or NRA recommendations. The whole blood unit is centrifuged so that an optimal number of platelets remain in plasma (platelet-rich plasma, or PRP). Platelet concentrates are then obtained by hard-spin centrifugation of PRP and are then resuspended.

However, if whole blood is centrifuged so that the blood platelets are primarily sedimented to the buffy coat layer, the buffy coat is separated and further processed to obtain a platelet concentrate. Either a single buffy coat or a pool of buffy coats is diluted with plasma or an appropriate nutrient solution, and platelets are concentrated by further centrifugation. The platelet content per unit depends on the method of preparation. Similarly, the residual leukocyte content will vary according to the centrifugation parameters.

Platelet concentrates (both from whole blood and apheresis) should be stored in conditions that guarantee that viability and haemostatic activities are optimally preserved. The storage temperature should be 20–24°C. Continuous gentle agitation of platelets during storage should be sufficient to guarantee the availability of oxygen to the platelets (but should be as gentle as possible). A storage time should be defined in accordance with national regulations set by the NRA; it should normally not exceed five days in the absence of additional measures.

In special circumstances, volume-reduced, split, washed or irradiated platelet concentrates can be prepared for specific treatments.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- platelet content;
- residual leukocytes, if leukocyte reduction is performed;
- pH, measured at the end of the recommended shelf-life.

9.4.3.4 Plasma for transfusion and Plasma for fractionation

Plasma for transfusion is prepared either from whole blood or from plasma collected by apheresis, and is frozen within a defined period of time to a temperature that should adequately maintain the labile coagulation factors

in a functional state, consistent with the intended use of the plasma. In particular, Factor VIII content is critical both as a quality indicator and to assure the efficacy of cryoprecipitate.

If plasma is separated from a unit of whole blood that is refrigerated to 4°C, centrifugation should preferably take place within eight hours of collection (14,15,16).

If the whole blood unit is rapidly cooled to 20–24°C and maintained at this constant temperature after collection, separation can take place within 18–20 hours because such conditions have been found to protect Factor VIII (17).

If plasma is collected by apheresis, the freezing process should begin as soon as possible, and ideally not later than six hours after the completion of the apheresis process. In compliance with NRA requirements, consideration should be given to the time frames of processing with respect to the anticoagulant and device used and the product to be manufactured.

The freezing process should be validated and should take place in a system that will allow complete freezing to a predefined core temperature in a predefined time (see section 9.4.2.3).

Product stability is dependent on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (more than one year) the optimal storage temperature is minus 25°C or colder (18).

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- Factor VIII activity (especially if plasma is used to treat Factor VIII deficiencies);
- residual leukocytes, if leukocyte reduction is performed;
- leakage;
- visual changes.

Virus inactivation and/or quarantine of plasma for transfusion are applied in some countries. Further complementary guidance with respect to virus inactivation is available in *WHO guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products* (2), and in other publications (19,20).

Plasma for transfusion is suitable as source material for the production of fractionated products, and particularly Factor VIII concentrates or other labile factors. Plasma prepared in other ways should meet the specifications of the plasma fractionators and the requirements of the pharmacopoeia

and NRA. Further complementary guidance with respect to the production of plasma for fractionation is available in *WHO recommendations for the production, control and regulation of human plasma for fractionation (3)*.

9.4.3.5 Cryoprecipitate and Cryo-poor plasma

Cryoprecipitate is the cryoglobulin fraction of plasma and contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in plasma. Cryoprecipitate is obtained from fresh frozen plasma that is prepared in a way that protects Factor VIII stability. Plasma is allowed to thaw either overnight at 2–6°C or by a rapid-thaw technique. Following thawing, the supernatant cryo-poor plasma and the cryoprecipitate are separated by hard-spin centrifugation. The cryo-poor plasma is then expressed into a transfer bag. The two components are refrozen to the appropriate core temperature.

Stability during storage depends on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (for two years or longer) the optimal storage temperature is minus 25°C or colder.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays of cryoprecipitate:

- volume;
- Factor VIII activity;
- clottable fibrinogen;
- von Willebrand factor activity (if applicable).

Virus inactivation and/or quarantine are applied in some countries.

Under certain circumstances the use of small pool preparations of cryoprecipitate (by pooling single-donor cryoprecipitate units) may be desired.

9.5 Laboratory testing

9.5.1 Screening tests for infectious disease markers

9.5.1.1 Testing requirements

The following tests, which are considered mandatory by all regulatory agencies, are relevant to the preparation of blood components and should be performed on each individual blood donation:

- an approved test for Hepatitis B surface antigen (HBsAg);
- an approved test for anti-HIV1/HIV2;
- an approved test for anti-HCV.

All three tests have to be negative. Initially reactive donations should be retested in duplicate by the same assay. Products from a repeatedly reactive donation should not be used for therapeutic applications and should normally be destroyed unless useful for non-therapeutic purposes or investigations. A sample of the donation should be evaluated by a confirmatory test. There should be a system for notifying and counselling the donor if confirmation is positive. It is recommended that national algorithms should be developed and used to enable consistent resolution of discordant/indeterminate or unconfirmed results.

In some countries, additional serological testing is required — for instance, anti-HBc testing may be performed on whole blood donations in order to further reduce the risk of exposure of recipients to HBV by contaminated blood or blood components (3). Additional testing for other agents or markers — such as anti-HTLV I/II, anti-T.cruzi or West Nile Virus (WNV) — may be required by the NRA, taking into account the epidemiological situation in any given region or country or the frequency of donating blood. In addition to testing for immunochemical-serological infectious disease markers, NAT testing of blood donations for the virus genomes has been introduced in some countries to increase the chance of identifying infected donors.

During the natural course of infection, viraemia usually occurs significantly at a point earlier than that at which immunochemical markers (antibodies) can be detected in the infected serum. Thus, infection may be detected by NAT up to 50–60 days before seroconversion (i.e. to HCV) occurs. Testing for the presence of nucleic acid may be performed for viruses such as HCV, HBV, HIV, HAV, WNV (where appropriate) and/or Parvovirus B19, and the application of this technology may be extended to other transmissible microbes. NATs require a particularly sophisticated laboratory environment, special equipment and specially trained laboratory personnel. Mainly because of an extraordinary risk of false-positive results due to the so-called “carry-over” (inadvertent transfer of the amplification product DNA to neat donor samples), very stringent handling and logistics are mandatory.

In contrast to testing for the serological markers of individual donor specimens, NAT testing may be performed following current practices by assembling various samples in mini-pools. However, this requires a thoroughly validated system of sample labelling/identification, a validated strategy and pooling process, and a validated algorithm to resolve pool results to individual donors. Hence, a specific logistics system may have to be established not only in the laboratory but also at the blood establishment in order to collect and suitably label samples. Contiguously tracing samples through the whole process from the donor, through pooling (if applicable), testing and release of the donation may present a particularly demanding challenge.

A system should exist in the country or region for approval of test systems, such as an official approval system by the NRA or a delegated laboratory. The required minimal sensitivity of tests for the different antigens/antibodies or nucleic acids should be defined by the NRA.

9.5.1.2 Handling of samples and data

Multiple specimens may be collected from a donor in order to meet all testing requirements (i.e. ABO typing, viral markers, NAT testing). There should be written standard operating procedures that clearly describe the collection, transportation and labelling of donor samples (i.e. whole blood, sera, anti-coagulant, container tubes etc.) and which define the sampling procedure performed on material for analysis (e.g. how and by whom it is done, transfer of samples, accountability of samples). All screening activities, handling of donor specimens, sampling, analysis and data processing should be separated from patient diagnostic testing (21).

Sample labelling at the site of collection and identification during all subsequent processing is critical and should be under control at all times. Each step of handling and processing should be described, as should the conditions of pre-analytical treatment of specimens (e.g. centrifugation), storage and transportation (duration, temperature, type of container, storage after testing).

Serological testing should be performed on samples transferred directly into the analyser from the original sample tube.

Secondary aliquot samples may be used for NAT testing of mini-pools of individual samples.

The following practical points should be considered in order to ensure the traceability and integrity of samples and data:

- At receipt of specimens at the laboratory, positive identification of those received versus those expected should be performed. The integrity of the sample should be checked for compliance with the recommendations made by the manufacturer of the test kit.
- Aliquot samples for analysis should be withdrawn from the donor sample preferably by automated pipetting equipment.
- To provide for positive identification of all aspects (donation, donor specimen, aliquot samples etc.) it may be advisable to use a barcode system. Hence, starting with the donation, barcodes should be used for labelling. In case of failure of the automatic barcode reader system and/or data processors, an appropriate system should be available for manual entry and tracing of data throughout the whole process until release of donations for transfusion. Manual handling of data should include independent repeat entry into the database; the data format should include a check-digit algorithm or an automated test for identity of the two sets of data.

- Pipetting devices and machines should be validated before routine use, and validation reports should be available.
- Calibration of the pipetting devices should be performed periodically and should be documented.

9.5.1.3 Testing and post-analytical procedures

Testing of blood components should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Modifications to the manufacturer's instructions or reagents for donor screening tests should be validated. Where required, prior approval of the NRA should be obtained before the modified method is used for release of a blood component. Laboratory reagents intended for prolonged use should be marked with the preparation date, expiry date, specific storage conditions and signature of the person who prepared them. Instructions for use and storage should be followed.

Screening algorithms should be precisely defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens and to resolve discrepancies in results after retesting. All available measures should be taken to ensure that blood and blood components that are repeat reactive upon screening for an infectious disease marker are excluded from therapeutic use. Repeat reactive material should be stored away from all other blood components in a separate dedicated storage area. Such material should eventually be destroyed to prevent inadvertent re-entry into the transfusion chain.

Test algorithms should provide details for appropriate confirmatory testing. In the case of repeatedly reactive results, clearly defined follow-up instructions should be followed. Actions include:

- notification and deferral of the donor;
- disposal of the indicated donation and of concurrent products;
- tracing and destruction of products which have not yet expired.

If products from the donor have been processed for further manufacture, there should be a procedure in place to assess both the safety of the manufactured products and whether a recall is needed.

Procedures for donor- and/or recipient-initiated look-backs should also be defined. Look-backs should be designed in such a way that the transfusion chain of donor–blood (or blood product)–recipient can be unequivocally reconstructed. The procedure should comprise notification and counselling action where indicated.

The following practical points should be considered in order to ensure that the equipment used for virology testing performs appropriately:

- There should be a mechanism to ensure positive sample identification and linkage to the donor. The preferred method is by sample tubes with barcodes.
- Ideally, the addition of reagent and samples and the testing process should be automated, in order to minimize risk of human errors and to ensure full traceability of the testing process.
- If addition of reagents and samples or preparation of test plates are done manually, full documentation of each addition step should be kept, ensuring identification of the test plate and the location of the reaction well.

9.5.1.4 Test interpretation and follow-up of reactive results

The transfer and interpretation of raw data is a critical step and should therefore be documented and reviewed by a responsible person, as should the test parameters. Traceability and archiving of raw data should be guaranteed (see section 5.2).

The data should be examined by the supervisor, or by another person authorized to do so, before being officially accepted. If computerized systems are used, accepted data should be downloaded directly to the server, or there should be a secure system for manual download which ensures positive release. Manual transcription of results is discouraged as mistakes may be introduced. Acceptance and rejection criteria should be specified.

The following should be given special attention:

- Initial reactive results should be identified by means of a secure and validated system.
- An acceptable system should be in place to confirm repeat reactive results, including sampling, labelling, testing and entry of results.
- Computer algorithms should edit reactive status to repeat reactive, or the editing should be performed by two authorized staff members.
- An appropriate deferral system should exist for repeat reactive results.
- There should be appropriate documentation justifying the re-entry of deferred donors.
- Donors should be informed of the reason for deferral and should be counselled about social behaviours and their status as a future donor.

9.5.2 Blood group typing

Each donation should be tested for ABO and RhD blood groups and at least all first-time donors should be tested for clinically significant irregular red-cell antibodies. When plasma is used for fractionation it should be tested in compliance with the specifications of the fractionator as agreed by the relevant NRA (3).

Testing should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Molecular methods may be used to determine blood groups, as necessary.

The ABO and RhD blood group should be verified on each subsequent donation. A comparison should be made with the historically determined blood group. If a discrepancy is found, the applicable blood components should not be released until the discrepancy has been unequivocally resolved.

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

NRAs may set different (stronger) requirements.

The ABO/RhD labelling of the red-cell concentrates of all first-time donations should be based on two independent ABO/RhD tests.

9.5.3 ***Retention samples***

As specified by the NRA, an aliquot of the original testing sample should be retained from each donation and stored under conditions recommended by the test manufacturer that would permit retesting if indicated. The procedure for additional testing should be validated to ensure the integrity of the sample (including storage conditions) and the test results. The sample volume, the retention vial, the kind of specimen (serum or plasma), the storage conditions and length of storage should each be defined and should be included in the validation to ensure the integrity of test results.

9.6 **Quality monitoring of blood and blood components**

Quality control data should demonstrate that critical manufacturing processes are under control. Blood and blood components should comply with specifications and their testing should be performed using test methods approved by the NRA.

All processes — including data transfers and computerized systems — that have an influence on the quality of the products in the area of collection, preparation or testing of blood and blood components should be validated. For critical processes such as rapid freezing of plasma, the need for revalidation should be defined.

Quality control of blood and blood components should be carried out according to a defined sampling plan based on statistical methods. The sampling plan should take into account different collection and production sites, transport, methods of preparation and equipment used. Acceptance criteria should be based on a defined specification for each type of blood component. As an example for fresh frozen plasma, these data may include monitoring of weight/volume, sterility, Factor VIII activity and residual cell

counts (platelets, leukocytes, erythrocytes). The sampling plan for testing of blood or blood components should take into account that most components are derived from one donor, and should be considered as a single batch.

Whole blood or blood components should not be released for use if the quality control test indicates that the integrity of the product has been compromised.

The work record should identify the test(s) employed so as to ensure that entries, such as the calculation of results, are available for review.

Test results that do not meet the acceptance criteria should be clearly identified to ensure that blood components of that donation remain in quarantine and that relevant samples are selected for further testing. An investigation should be conducted into the cause of failure prior to additional or repeat testing. Where possible, the performance of the test procedures should be regularly assessed by participation in a formal system of proficiency testing.

Where applicable, the practice of pooling samples before testing should be clearly stated and the donations used in the pooled sample should be recorded. Pooling of samples, such as for the measurement of Factor VIII activity in plasma, is acceptable only where comparative data of pooled samples and individual samples have demonstrated assurance of equivalence.

The results of quality monitoring testing should be subject to periodic review and trend analysis. If the results of quality monitoring suggest that the process is not meeting validated parameters and specifications, then corrective and preventive actions should be taken to correct identified problems before product manufacturing and distribution is continued.

9.7 **Labelling**

9.7.1 **Label information**

The collected blood, as well as intermediate and finished blood components, should be labelled with relevant information regarding their identity and release status. The type of label to be used, as well as the labelling methodology, should be established in written standard operating procedures. Whenever possible, machine-readable labels (barcodes) should be used.

The label for a finished blood component should comply with the requirements of the NRA or contain at least the following information:

- the unique donation number (through the use of this number there should be traceability to the donor and all records of the manufacturing steps through to the final product);
- the product name (see section 9.7.2.);

- the required storage conditions;
- the expiry date and, where appropriate, time (see section 9.7.3.);
- the date of collection of the donation(s) from which the blood component was prepared and/or the production date and time (where appropriate);
- the date and time of irradiation (where applicable);
- the ABO and RhD blood group (where appropriate);
- the name or other identification of the component preparation site.

Information regarding the use of the blood product may also be applicable.

For autologous blood components, the label should additionally contain the name and unique identification of the patient as well as the statement “Autologous donation”. In some countries the signature of the donor is also required.

9.7.2 **Product name**

The name of the blood component should be clearly stated on the label and should indicate any further processing such as leukocyte reduction or irradiation.

In addition, the anticoagulant and/or any nutrient or preservative solution should be mentioned on the label.

9.7.3 **Expiry date**

Any final blood product should have its expiry date on its label. It should be also kept in mind that certain processing steps, such as irradiation, have an influence on the expiry date so that relabelling becomes necessary.

The definition of an expiry date should be validated and based on scientific data according to the processing steps applied and the storage conditions, or should be the subject of stability studies.

9.8 **Release of product**

Each blood establishment should be able to demonstrate that a blood component has been evaluated and approved for release by an authorized person, preferably assisted by validated computerized systems. The release criteria and specifications of blood components should be defined, validated, documented and approved by quality assurance. There should be a standard operating procedure that details the actions and criteria that determine whether the blood or blood component can be released. The decision to release the blood components should be made by the responsible person of the establishment; it should be clearly documented and traceability should be ensured. Electronic release of products should be fully validated.

The documented manufacturing processes should be followed at all times using validated methods and procedures. Any deviations from these established procedures and processes may result in products not meeting specifications, in which case they should be considered non-conforming products and must not be released for distribution.

A review of the donor health record, collection and phlebotomy records, consent forms, records of production and test results should be performed and accepted (and should be recorded) prior to the release of the components. The release of products should be arranged in such a way that each component from the donation has been evaluated to ensure conformance with product specifications — such as platelet content in apheresis units, volume in plasma products or appearance for red blood cells — prior to release for distribution. The decision to release the component should not be made on the basis of a review of the collection processes alone.

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

In the absence of a computerized system for product status control:

- the label of a blood component should identify the product status and should clearly distinguish released products from non-released (quarantined) ones;
- records should demonstrate that, before a component is released, all current donor health records, collection and phlebotomy records, consent forms and test results have been verified and accepted by an authorized person.

If blood or blood components have been prepared from a donor who has donated on previous occasions, a comparison with previous records — specifically the ABO/RhD and infectious disease marker test results — should be made before final product release to ensure that current records accurately reflect the donor history.

Where release is subject to computer-derived information, the following points should be checked:

- Computer systems should be validated so that they are fully secure against the possibility of blood and blood components which do not fulfil all test or donor selection criteria being released.
- The manual entry of critical data, such as laboratory test results, should require independent verification by a second authorized person.
- There should be a hierarchy of permitted access to enter, amend, read or print data. Methods of preventing unauthorized entry should be in place, such as personal identity codes or passwords which are changed on a regular basis.

- Computer systems should prevent the release of all blood or blood components considered not acceptable for release. It should be possible to prevent the release of any future donation from a donor.

In the event that the final product fails release due to noncompliance with the specified requirements and therefore due to potential impact on recipient safety, all other implicated components should be identified and appropriate action should be taken. A check should 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. There should be an immediate updating of the donor record(s) to ensure that the donor(s) cannot make any further donation, if appropriate.

There should be a defined procedure for the exceptional release of nonstandard blood and blood components under a planned non-conformance system. The decision to allow such a release should be made by the responsible person; the decision should be clearly documented and traceability should be ensured. Products that cannot be released should be destroyed and the record of destruction should be retained.

9.9 Storage

Standard operating procedures should describe the receipt, handling and storage of material, blood and blood components. There should be a system in place to maintain and control storage conditions, including any transportation that may be required. Autologous blood and blood components should be stored separately. Storage areas for blood components to be dispatched should be located near an entrance or exit to facilitate dispatch and to limit the number of persons entering the main working areas. Only authorized persons should have access to storage areas.

Storage conditions should be controlled, monitored and checked. The personnel authorized should be trained to be aware of the correct storage temperature ranges and alarm settings. Temperature records should be available to demonstrate that the blood components are stored at the required temperature throughout the storage area. A temperature monitoring and recording system that is independent from the temperature regulation system should be in place. Appropriate alarms should be present (upper and lower limits) and regularly checked; the checks should be recorded. Depending on the method of measuring the temperature, a delay of the alarm may be acceptable in order to avoid an alarm being triggered by opening a door or taking out a product, but any such delay should be reasonably justified. If the temperature sensor is placed in a reference solution, no delay of the alarm should be accepted. Appropriate actions on alarms should be defined, and a person should be authorized to decide on the use or rejection of affected

products. Temperature excursions may occur and each event should be evaluated using the deviation management system (see section 3.5).

An alternative storage area of appropriate temperature is recommended for recovery in case of temperature control failure of the primary system. Areas for storage should be secured against the entry of unauthorized persons and should be used only for the intended purpose. Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and material. If a temporary mechanical or electrical failure affects control of storage temperatures, an examination of the records should be made to evaluate the impact on plasma or blood component quality.

For the main blood components, the common storage temperatures are as follows:

- red-cell concentrate: 1–6°C;
 - plasma for transfusion: minus 25°C or colder;
 - platelets: 20–24°C;
- or in a more stringent range defined by the NRA.

Higher storage temperatures (e.g. minus 20°C) might be acceptable for plasma for transfusion but may result in a significantly shorter shelf-life.

Storage of platelets should also be controlled. Besides the temperature, the continuous agitation is very important. Based on the manufacturer's instructions, the moving velocity should be set in a way that obtains an optimal quality of the product. The moving velocity should be part of the qualification of the equipment.

During the whole collection and manufacturing process it should be ensured that blood or blood components are never placed in direct sunlight or near a heating source.

All storage equipment should be subject to qualification, cleaning and preventive maintenance. Thermometers or temperature sensors should be calibrated annually. The temperature deviation to the standard measuring device should not exceed 1°C.

9.10 Distribution

Prior to distribution, blood components should be visually inspected. There should be a record that identifies the person distributing and the customer receiving the components. Dispatch of blood components should be made by authorized personnel.

At the time of dispatch, there should be a procedure in place to ensure that all blood components being issued have been formally released for

use. A standard operating procedure on packaging should be available stating how the contents should be packaged, the materials to be used, and the amount of any cooling elements and their storage conditions before use.

9.11 Shipping

Distribution should take place in a safe and controlled way in order to assure product quality during transport. All transportation and intermediate storage actions, including receipt and distribution, should be defined by written standard operating procedures and specifications.

The shipping containers should be of sturdy construction in order to resist damage and should be validated to maintain acceptable storage conditions for the blood and blood components (e.g. by using appropriate cooling elements or insulation during transport). The transportation and storage conditions for blood components, the packaging format and the responsibilities of the persons involved should be in accordance with standard operating procedures agreed between the sites in question.

9.12 Returns

Blood components should not be returned to stock for subsequent distribution, unless:

- the procedure for return of a blood component is regulated by contract;
- for each returned blood component, it is proven that the agreed storage conditions have consistently been met;
- the integrity of the container has been maintained (i.e. unopened);
- sufficient material is available for compatibility testing.

In case of medical urgency, components may be returned and subsequently distributed using a defined procedure.

The records should indicate that the blood component has been inspected and found to be acceptable before re-issue.

10. Contract manufacturing, analysis and services

In blood establishments, all tasks that have an influence on the quality of collected blood and the manufacture of blood components — such as component processing, testing or information technology support — and which are performed externally by another party, should be subject to a specific written contract. The contract should ensure that the contract acceptor meets GMP requirements in all disciplines relevant to the contract giver's activities.

The contract giver is ultimately responsible for ensuring that processes are in place to assure the control of outsourced activities and the quality of purchased materials. These processes should incorporate QRM and should include:

- assessing (prior to outsourcing operations or selecting material suppliers) the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g. audits, material evaluations, qualification);
- defining the responsibilities and communication processes for quality-related activities of the parties concerned;
- monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and identification and implementation of any improvements needed;
- monitoring of incoming ingredients and materials to ensure that they are from approved sources using the agreed supply chain.

Details should be specified in a technical quality agreement or contract.

The contract or agreement should:

- clearly establish the duties of each party;
- state the responsibilities of each party;
- mention any technical arrangements;
- define the flow of information, especially regarding deviations and changes;
- define the handling and archiving of documents, samples and other relevant materials and information;
- state that any of the duties given to the contract acceptor should not be passed to a third party without evaluation and approval of the contract giver;
- permit the contract giver and competent authorities to visit and inspect the facilities of the contract acceptor.

The contract giver should provide the contract acceptor with all necessary information to enable compliance with expectations regarding services or goods. This assures that the work or service is performed in compliance with existing regulations. The overall responsibility for the work and duties carried out externally lies always with the contracting company.

The contract should be agreed and signed by quality assurance representatives from both parties and should be kept up to date.

11. **Authors and acknowledgements**

These guidelines were developed under the coordination of Dr A Padilla, Scientist, Quality Assurance and Safety of Medicines (Blood Products and Related Biologicals), World Health Organization, Geneva, Switzerland.

The drafting group was formed of:

Mr JW Atkins, National Institutes of Health (NIH), Bethesda, MD, USA; Dr A Padilla, World Health Organization, Geneva, Switzerland; Dr C Schärer, Swissmedic, Bern, Switzerland; Mrs D Schmidkunz Egger, Swissmedic, Bern, Switzerland; Dr G Werner, Paul-Ehrlich-Institut (PEI), Langen, Germany.

Contributions were also solicited from:

Ms S Douglas, Therapeutic Goods Administration (TGA), Melbourne, Australia; Mr L Fields, Food and Drug Administration (FDA), Rockville, MD, USA; Dr D Kaesermann, Swissmedic, Switzerland; Dr J Morenas and Dr F Teskrat, Agence française de sécurité sanitaire des produits de santé (AFSSAPS), Saint-Denis, France; Dr W Schwarz, PEI, Germany; Dr U Unkelbach, PEI, Germany; Dr L van Loosbroek, GMP Consultant, Netherlands; Mr L Young, Health Canada, Ottawa, Canada.

Comments, advice and information given during the preparation and consultation process for developing these guidelines were received from the following experts:

Dr F Agbanyo, Health Canada, Ottawa, Canada; Dr M Farag Ahmed, National Organization for Drug Control & Research (NODCAR), Agousa, Egypt; Lic. MP Álvarez, Centro para el Control Estatal de la Calidad de los Medicamentos (CECMED), La Habana, Cuba; Dr J Ansah, National Centre of Blood Transfusion, Accra, Ghana; Dr C Bianco, America's Blood Centers, Washington DC, USA; Dr V Bogdanova, Federal Medical and Biological Agency (FMBA), Moscow, Russian Federation; Dr T Burnouf, Human Protein Process Sciences, France; Dr M Cheraghali, Dr Amini and Dr Maqsoodloo, Iranian Blood Transfusion Organization, Tehran, Islamic Republic of Iran; Dr JR Cruz, Regional Advisor, WHO, AMRO/PAHO, Washington, USA; Dr F Darwish, Central Blood Bank, Manama, Kingdom of Bahrain; Dr R Davey, FDA, Rockville, MD, USA; Professor S Diop, National Centre of Blood Transfusion, Dakar, Senegal; Dr D El Sherif, Central Administration of Pharmaceutical Affairs (CAPA), Cairo, Egypt; Dr J Epstein, FDA, Rockville, MD, USA; Dr P Ganz, Health Canada, Ottawa, Canada; Mr A Gould, Medicines Prequalification Programme, WHO, Geneva, Switzerland; Dr I Hamaguchi, National Institute of Infectious Diseases (NIID), Tokyo, Japan; Dr M Heiden, PEI, Langen, Germany; Dr S Hindawi, Blood Transfusion Service, Jeddah, Saudi Arabia; Dr Ho Jung Oh, Korea Food and Drug Administration (KFDA), Seoul, Republic of Korea; Dr M Jutzi, Swissmedic, Bern, Switzerland; Dr H Klein, NIH, Bethesda, MD, USA; Mrs AC Madukwe, National Agency for Food and Drug Administration and Control (NAFDAC), Lagos, Nigeria; Ms GN Mahlangu, Medicines Control Authority, Harare, Zimbabwe; Dr G Michaud, FDA, Rockville, MD, USA; Dr F Moftah, Blood Transfusion Service, Ministry of Health and Population, Agousa, Egypt; Dr Z Mukhtar, National Institute of Health, Islamabad, Pakistan; Dr C Munk and Dr P Strengers, International Society of Blood Transfusion (ISBT), Amsterdam, Netherlands; Dr P Murray, NIH, Bethesda, MD, USA; Dr K Nabae, Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr L Oliva, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), Buenos Aires, Argentina; Dr R Perry, International Plasma Fractionation Association (IPFA), Amsterdam, Netherlands; Dr I Prosser, TGA, Canberra, Australia; Dr I Sainte-Marie, AFSSAPS, Paris, France; Professor R Seitz, PEI, Langen, Germany; Dr G Silvester, European Medicines Agency (EMA), London, UK; Dr G Smith, TGA, Canberra, Australia; Dr D Teo, Blood Services

Group, Singapore; Ms A Turner, National Blood Authority, Canberra, Australia; Dr A van Zyl, GMP Inspectorate, WHO, Geneva, Switzerland; Dr I von Hoegen, Plasma Protein Therapeutics Association (PPTA), Brussels, Belgium; Dr T Vuk, Croatian Institute of Transfusion Medicine, Zagreb, Croatia; Dr E Zhiburt, International Society of Blood Transfusion (ISBT), Moscow, Russian Federation; Dr P Zorzi, AFSSAPS, Paris, France.

12. References

1. WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. In: *WHO Expert Committee on Biological Standardization. Forty-third report*. Geneva, World Health Organization, 1994 (WHO Technical Report Series, No. 840, Annex 2).
2. WHO Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. In: *WHO Expert Committee on Biological Standardization. Fifty-second report*. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 924, Annex 4).
3. WHO Recommendations for the production, control and regulation of human plasma for fractionation. In: *WHO Expert Committee on Biological Standardization. Fifty-sixth report*. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 941, Annex 4).
4. Recommendations of the 13th International Conference of Drug Regulatory Authorities (ICDRA), Bern, 16-19 September 2008. *WHO Drug Information*, 2008, 33(4) (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/Recommendations_13ICDRA.pdf, accessed 11 January 2011).
5. Resolution WHA63.12. Availability, safety and quality of blood products. In: *Sixty-third World Health Assembly, Geneva, 17-21 May 2010, Volume 1, Resolutions*. Geneva, World Health Organization, 2010 (WHA63/2010/REC/1).
6. *Estandares de trabajo para servicios de sangre*. Washington, DC, Organizacion Panamericana de la Salud/Pan American Health Organization, Area de Tecnologia y Prestacion de Servicios de Salud, 2005.
7. Good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908, Annex 4).
8. *ICH Q9: Guideline on quality risk management*. Geneva, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2005.
9. ISBT guidelines for validation of automated systems in blood establishments. *Vox Sanguinis*, 2010, 98(1):1–19.
10. Supplementary guidelines on good manufacturing practices: validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937, Annex 4).
11. *PIC/S recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation*.

Geneva, Pharmaceutical Inspection Cooperation Scheme, 2007
(Document PI 006-3).

12. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902, Annex 6).
13. *Guide to the preparation, use and quality assurance of blood components*, 14th edition. Technical annex to Council of Europe Recommendation No. R (95) 15 on the preparation, use and quality assurance of blood components. Strasbourg, European Directorate for the Quality of Medicines and HealthCare (EDQM), 2008.
14. Hughes C et al. Effect of delayed blood processing on the yield of factor VIII in cryoprecipitate and factor VIII concentrate. *Transfusion*, 1988, 28:566.
15. Carlebjork G, Blombäck M, Akerblom O. Improvement of plasma quality as raw material for factor VIII:C concentrates. Storage of whole blood and plasma and interindividual plasma levels of fibrinopeptide A. *Vox Sanguinis*, 1983, 45:233.
16. Nilsson L et al. Shelf-life of bank blood and stored plasma with special reference to coagulation factors. *Transfusion*, 1983, 23:377.
17. Pietersz RN et al. Storage of whole blood for up to 24 hours at ambient temperature prior to component preparation. *Vox Sanguinis*, 1989, 56:145.
18. Kotitschke R et al. Stability of fresh frozen plasma: results of 36-month storage at -20°C, -25°C, -30°C and -40°C. *Infusionstherapie und Transfusionsmedizin*, 2000, 27:174.
19. Klein HG. Pathogen inactivation technology: cleansing the blood supply. *Journal of Internal Medicine*, 2005, 257:224–237.
20. Bryant BJ, Klein HG. Pathogen inactivation: the definitive safeguard for the blood supply. *Archives of pathology & laboratory medicine*, 2007, 131:719–733.
21. WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929, Annex 4).