Appendix 6 Donor milk banking – principles of quality

These are based on two key European Union directives related to the quality assurance processes for human tissue and blood establishments. See details in the Appendix to this document.

1 INTRODUCTION AND GENERAL PRINCIPLES

1.1 Quality system

1.1.1 Quality shall be recognised as being the responsibility of all persons involved in the processes of the donor milk bank with management ensuring a systematic approach towards quality and the implementation and maintenance of a quality system.

1.1.2 The quality system encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, collection, testing and processing, storage, distribution, quality control, batch recall, and external and internal auditing, non-conformance and self-inspection.

1.1.3 The quality system shall ensure that all critical processes are specified in appropriate instructions and are carried out in accordance with the standards and specifications set out in these principles. Management shall review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary.

1.2 Quality assurance

1.2.1 All donor milk banks shall be supported by a quality assurance function, whether internal or related, in fulfilling quality assurance. That function shall be involved in all quality-related matters and review and approve all appropriate quality related documents.

1.2.2 All procedures, premises, and equipment that have an influence on the quality and safety of donor milk shall be validated prior to

introduction and be re-validated at regular intervals determined as a result of these activities.

2 PERSONNEL AND ORGANISATION

2.1.1 A responsible person must be appointed having appropriate qualifications and responsibilities for quality as outlined below.

2.1.2 A donor milk bank must have an organisational structure and operational procedures appropriate to their activities; there must be an organisational chart which clearly defines accountability and reporting relationships.

2.1.3 Every donor milk bank must have access to a nominated medical registered practitioner to advise on and oversee the establishment's medical activities such as donor selection, review of outcomes of recipients or interaction as appropriate with clinical users.

2.1.4 Personnel in donor milk banks shall be available in sufficient numbers to carry out the activities related to the collection, testing, processing, storage and distribution of donor milk and be trained and assessed to be competent to perform their tasks.

2.1.5 All personnel in donor milk banks shall have up to date job descriptions which clearly set out their tasks and responsibilities. Donor milk banks shall assign the responsibility for processing management and quality assurance to different individuals and who function independently.

2.1.6 All personnel in donor milk banks shall receive initial and continued training appropriate to their specific tasks. Training records shall be maintained. Training programmes shall be in place and shall include good practice. The training programme must ensure and document that each individual:

- has demonstrated competence in the performance of their designated tasks;
- has an adequate knowledge and understanding of the scientific/technical processes and principles relevant to their designated tasks;
- understands the organisational framework, quality system and health and safety rules of the establishment in which they work, and
- is adequately informed of the broader ethical, legal and regulatory context of their work.

2.1.7 The contents of training programmes shall be periodically assessed and the competence of personnel evaluated regularly.

2.1.8 There shall be written safety and hygiene instructions in place adapted to the activities to be carried out and are in compliance with local policies.

3 PREMISES

3.1 General

3.1.1 Premises, including any designated collection facilities, shall be adapted and maintained to suit the activities to be carried out. They shall enable the work to proceed in a logical sequence so as to minimise the risk of errors, and shall allow for effective cleaning and maintenance in order to minimise the risk of contamination.

3.2 Donor milk bank

3.2.1 There shall be an area for confidential personal interviews with and assessment of individuals to assess their eligibility to donate. This area shall be separated from all processing areas.

3.3 Donor milk testing and processing areas

3.3.1 There shall be a dedicated laboratory area for testing that is separate from the donor milk processing area with access restricted to authorised personnel.

3.4 Storage area

3.4.1 Storage areas shall provide for properly secure and segregated storage of different categories of donor milk including quarantine and released materials.

3.4.2 Provisions shall be in place in the event of equipment or power failure in the main storage facility.

3.5 Waste disposal area

3.5.1 An area shall be designated for the safe disposal of waste, disposable items used during the collection, testing, and processing and for rejected donor milk.

4 EQUIPMENT AND MATERIALS

4.1.1 All equipment shall be validated, calibrated and maintained to suit its intended purpose. Operating instructions shall be available and appropriate records kept.

4.1.2 Equipment shall be selected to minimise any hazard to donors, personnel, or donor milk.

4.1.3 All critical equipment and technical devices must be identified and validated, regularly inspected and preventively maintained in accordance with the manufacturers' instructions. Where equipment or materials affect critical processing or storage parameters (e.g. temperature, microbial contamination levels), they must be identified and must be the subject of appropriate monitoring, alerts, alarms and corrective action, as required, to detect malfunctions and defects and to ensure that the critical parameters are maintained within acceptable limits at all times. All equipment with a critical measuring function must be calibrated against a traceable standard if available.

4.1.4 New and repaired equipment must be tested when installed and must be validated before use. Test results must be documented.

4.1.5 Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment must be performed regularly and recorded accordingly.

4.1.6 Procedures for the operation of each piece of critical equipment, detailing the action to be taken in the event of malfunctions or failure, must be available.

4.1.7 Inventory records shall be retained for a period acceptable to and agreed with the competent authority.

4.1.8 When computerised systems are used, software, hardware and back-up procedures must be checked regularly to ensure reliability, be validated before use, and be maintained in a validated state. Hardware and software shall be protected against unauthorised use or unauthorised changes. The back-up procedure shall prevent loss of or damage to data at expected and unexpected down times or function failures.

5 DOCUMENTATION

5.1.1 Documents setting out specifications, procedures and records covering each activity performed by the donor milk bank shall be in place and kept up to date.

5.1.2 A document control procedure must be established to provide for the history of document reviews and changes and to ensure that only current versions of documents are in use.

5.1.3 Records shall be legible and may be handwritten, transferred to another medium such as microfilm or documented in a computerised system.

5.1.4 All records, including raw data, which are critical to the safety and quality of the donor milk shall be kept so as to ensure access to these data for at least 10 years after expiry date, use or disposal.

5.1.5 All significant changes to documents shall be acted upon promptly and shall be reviewed, dated and signed by a person authorised to perform this task.

6 DONOR MILK COLLECTION, TESTING AND PROCESSING

6.1 Donor eligibility

6.1.1 Procedures for safe donor identification, suitability interview and eligibility assessment shall be implemented and maintained. They shall take place before each donation and comply with the requirements set out in the NICE guidelines.

6.1.2 The donor interview shall be conducted in such a way as to ensure confidentiality.

6.1.3 The donor suitability records and final assessment shall be signed by a qualified health professional.

6.2 Collection of donor milk

6.2.1 The donor milk collection procedure shall be designed to ensure that the identity of the donor is verified and securely recorded and that the link between the donor and the donated milk is clearly established.

6.2.2 The containers used for the collection of donor milk and their processing shall be CE-marked. The batch number of the donor milk shall be traceable.

6.2.3 Donor milk handling procedures shall minimise the risk of microbial contamination.

6.2.4 Laboratory samples shall be taken at the time of donation and appropriately stored prior to testing.

6.2.5 The procedure used for the labelling of records, donor milk samples and batches, and laboratory samples with donation numbers shall be designed to avoid any risk of identification error and mix-up.

6.2.6 After milk collection, the containers shall be handled in a way that maintains the quality of the donor milk and at a storage and transport temperature appropriate to further processing requirements.

6.2.7 There shall be a system in place to ensure that each donation can be linked to the collection and processing system into which it was collected and/or processed.

6.3 Laboratory testing

6.3.1 All laboratory testing procedures shall be validated before use.

6.3.2 Each donation shall be tested in conformity with the requirements laid down in the NICE guidelines on the operation of donor milk banks.

6.3.3 There shall be clearly defined procedures to resolve discrepant results and ensure that donor milk samples from donors who have a repeatedly reactive result in a serological screening test for infection with the viruses mentioned in the NICE guidelines shall be excluded from therapeutic use and be disposed of. Appropriate confirmatory serological testing shall take place. In case of confirmed positive results, appropriate donor management shall take place including the provision of information to the donor and follow-up procedures.

6.3.4 There shall be data confirming the suitability of any laboratory reagents used in the testing of donor blood samples.

6.3.5 The quality of the laboratory testing shall be regularly assessed by the participation in a formal system of proficiency testing, such as an external quality assurance programme.

6.3.6 Blood group serology testing shall include procedures for testing specific groups of donors (e.g. those assessed as being at a higher risk).

6.4 Processing and validation

6.4.1 All equipment and technical devices shall be used in accordance with validated procedures.

6.4.2 The processing of donor milk shall be carried out using appropriate and validated procedures including measures to avoid the risk of contamination and microbial growth in the prepared batches.

6.5 Labelling

6.5.1 At all stages, all containers shall be labelled with relevant information of their identity. In the absence of a validated computerised system for status control, the labelling shall clearly distinguish released from non-released batches of donor milk.

6.5.2 The labelling system for the collected donor milk, intermediate and finished batches must unmistakably identify the type of content, and comply with the labelling and traceability requirements defined in the NICE guidelines.

6.6 Release of donor milk

6.6.1 There shall be a safe and secure system to prevent each batch of donor milk from being released until all mandatory requirements set out in the NICE guidelines have been fulfilled. Each donor milk bank shall be able to demonstrate that each batch has been formally released by an authorised person. Records shall demonstrate that before a batch of donor milk is released, all current declaration forms, relevant medical records and test results meet all acceptance criteria.

6.6.2 Before release, donor milk shall be kept administratively and physically segregated from released donor milk. In the absence of a validated computerised system for status control the label of either the sample or batch shall identify the release status in accordance with 6.5.1.

6.6.3 In the event that the final batch fails release due to a confirmed positive infection test result, in conformity with the requirements set out in Section 6.3.2 and 6.3.3, a check shall be made to ensure that other samples from the same donation and batches prepared from

previous donations given by the donor are identified. There shall be an immediate update of the donor record.

7 STORAGE AND DISTRIBUTION

7.1 General

7.1.1 The quality system of the donor milk bank shall ensure that storage and distribution requirements shall comply with the NICE guidelines.

7.1.2 Maximum storage time must be specified for each type of storage condition. The selected period must reflect among others possible deterioration of the donor milk and its component properties.

7.1.3 Critical transport conditions, such as temperature and time limit must be defined to maintain the required properties.

7.1.4 The container/package must be secure and ensure that the donor milk is maintained in the specified conditions. All containers and packages need to be validated as fit for purpose.

7.1.5 Where distribution is carried out by a contracted third party, a documented agreement must be in place to ensure that the required conditions are maintained.

7.1.6 Procedures for storage and distribution shall be validated to ensure donor milk quality during the entire storage period and to exclude mix-ups of milk from different donors. All transportation and storage actions, including receipt and distribution, shall be defined by written procedures and specifications.

7.1.7 Appropriate records of inventory and distribution shall be kept.

7.1.8 Packaging shall maintain the integrity and storage temperature of donor milk during distribution and transportation.

7.2 Final labelling for distribution

7.2.1 The primary donor milk container must provide:

- type of donor milk (if appropriate), identification number or code of the sample, and lot or batch number where applicable;
- identification of the donor milk bank;
- expiry date;
- when donor milk is known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD.

If any of the information above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.

7.2.2 The following information must be provided either on the label or in accompanying documentation:

- date of distribution of the donor milk;
- biological determinations carried out on the donor and results;
- storage recommendations;
- instructions for opening the container, package, and any required manipulation/reconstitution;
- expiry dates after opening/manipulation;
- instructions for reporting serious adverse reactions and/or events as set out above.

7.3 External labelling of the shipping container

7.3.1 For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

- identification of the originating donor milk bank, including an address and phone number;

- identification of the receiving organisation, including address and phone number;
- a statement that the package contains human donor milk and HANDLE WITH CARE;
- recommended transport conditions (e.g. keep cool, in upright position, etc.);
- safety instructions/method of cooling (when applicable).

8 CONTRACT MANAGEMENT

8.1.1 Tasks that are performed externally shall be defined in a specific written contract.

9 NON-CONFORMANCE

9.1 Deviations

9.1.1 Donor milk deviating from required standards set out in the NICE guidelines shall be released for use only in exceptional circumstances and with the recorded agreement of the prescribing physician and the donor milk bank manager.

9.2 Complaints

9.2.1 All complaints and other information, including serious adverse reactions and serious adverse events, which may suggest that defective donor milk batches have been issued, shall be documented, carefully investigated for causative factors of the defect and, where necessary, followed by recall and the implementation of corrective actions to prevent recurrence. Procedures shall be in place to ensure that the competent authorities are notified as appropriate of serious adverse reactions or serious adverse events in accordance with regulatory requirements.

9.3 Recall

9.3.1 There shall be personnel authorised within the donor milk bank to assess the need for batch recall and to initiate and coordinate the necessary actions.

9.3.2 An effective recall procedure shall be in place, including a description of the responsibilities and actions to be taken. This shall include notification to the competent authority.

9.3.3 Actions shall be taken within pre-defined periods of time and shall include tracing all relevant batches and, where applicable, shall include trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the recipient reaction and to retrieve available samples or batches from that donor, as well as to notify consignees and recipients of milk collected from the same donor in the event that they might have been put at risk.

9.4 Corrective and preventive actions

9.4.1 A system to ensure corrective and preventive actions on donor milk non-conformity and quality problems shall be in place.

9.4.2 Data shall be routinely analysed to identify quality problems that may require corrective action or to identify unfavourable trends that may require preventive action.

9.4.3 All errors and accidents shall be documented and investigated in order to identify system problems for correction.

10 SELF-INSPECTION, AUDITS AND IMPROVEMENTS

10.1.1 Self-inspection or audit systems shall be in place for all parts of the operations to verify compliance with the standards set out in the NICE guidelines. They shall be carried out regularly by trained and competent persons in an independent way according to approved procedures.

10.1.2 All results shall be documented and appropriate corrective and preventive actions shall be taken.

Appendix

10.2 Directive 2006/86/EC of 24 October 2006 'implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells'. OJ, 25.10.2006

ANNEX I

Requirements for accreditation, designation, authorisation or licensing of tissue establishments as referred to in Article 3

A. ORGANISATION AND MANAGEMENT

1. A responsible person must be appointed having qualifications and responsibilities as provided in Article 17 of Directive 2004/23/EC.

2. A tissue establishment must have an organisational structure and operational procedures appropriate to the activities for which accreditation/designation/authorisation/licensing is sought; there must be an organisational chart which clearly defines accountability and reporting relationships.

3. Every tissue establishment must have access to a nominated medical registered practitioner to advise on and oversee the establishment’s medical activities such as donor selection, review of clinical outcomes of applied tissues and cells or interaction as appropriate with clinical users.

4. There must be a documented quality management system applied to the activities for which accreditation/designation/authorisation or licensing is sought, in accordance with the standards laid down in this Directive.

5. It must be ensured that the risks inherent in the use and handling of biological material are identified and minimised, consistent with maintaining adequate quality and safety for the intended purpose of the tissues and cells. The risks include those relating in particular to the procedures, environment, staff health status specific to the tissue establishment.

6. Agreements between tissue establishments and third parties must comply with Article 24 of Directive 2004/23/EC. Third party agreements must specify the terms of the relationship and responsibilities as well as the protocols to be followed to meet the required performance specification.

7. There must be a documented system in place, supervised by the responsible person, for ratifying that tissues and/or cells meet appropriate specifications for safety and quality for release and for their distribution.

8. In the event of termination of activities the agreements concluded and the procedures adopted in accordance with Article 21(5) of Directive 2004/23/EC shall include traceability data and material concerning the quality and safety of cells and tissues.

9. There must be a documented system in place that ensures the identification of every unit of tissue or cells at all stages of the activities for which accreditation/designation/authorisation/licensing is sought.

B. PERSONNEL

1. The personnel in tissue establishments must be available in sufficient number and be qualified for the tasks they perform. The competency of the personnel must be evaluated at appropriate intervals specified in the quality system.

2. All personnel should have clear, documented and up-to-date job descriptions. Their tasks, responsibilities and accountability must be clearly documented and understood.

3. Personnel must be provided with initial/basic training, updated training as required when procedures change or scientific knowledge develops and

adequate opportunities for relevant professional development. The training programme must ensure and document that each individual:

(a) has demonstrated competence in the performance of their designated tasks;

(b) has an adequate knowledge and understanding of the scientific/technical processes and principles relevant to their designated tasks;

(c) understands the organisational framework, quality system and health and safety rules of the establishment in which they work, and

(d) is adequately informed of the broader ethical, legal and regulatory context of their work.

C. EQUIPMENT AND MATERIALS

1. All equipment and material must be designed and maintained to suit its intended purpose and must minimise any hazard to recipients and/or staff.

2. All critical equipment and technical devices must be identified and validated, regularly inspected and preventively maintained in accordance with the manufacturers' instructions. Where equipment or materials affect critical processing or storage parameters (e.g. temperature, pressure, particle counts, microbial contamination levels), they must be identified and must be the subject of appropriate monitoring, alerts, alarms and corrective action, as required, to detect malfunctions and defects and to ensure that the critical parameters are maintained within acceptable limits at all times. All equipment with a critical measuring function must be calibrated against a traceable standard if available.

3. New and repaired equipment must be tested when installed and must be validated before use. Test results must be documented.

4. Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment must be performed regularly and recorded accordingly.

5. Procedures for the operation of each piece of critical equipment, detailing the action to be taken in the event of malfunctions or failure, must be available.

6. The procedures for the activities for which accreditation/designation/authorisation/licensing is sought, must detail the specifications for all critical materials and reagents. In particular, specifications for additives (e.g. solutions) and packaging materials must be defined. Critical reagents and materials must meet documented requirements and specifications and when applicable the requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [1] and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices [2].

D. FACILITIES/PREMISES

1. A tissue establishment must have suitable facilities to carry out the activities for which accreditation/designation/authorisation or licensing is sought, in accordance with the standards laid down in this Directive.

2. When these activities include processing of tissues and cells while exposed to the environment, this must take place in an environment with specified air quality and cleanliness in order to minimise the risk of contamination, including cross-contamination between donations. The effectiveness of these measures must be validated and monitored.

3. Unless otherwise specified in point 4, where tissues or cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned but at least equivalent to GMP Grade D in terms of particles and microbial counts.

4. A less stringent environment than specified in point 3 may be acceptable where:

(a) a validated microbial inactivation or validated terminal sterilisation process is applied;

(b) or, where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned;

(c) or, where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation;

(d) or, where it is not technically possible to carry out the required process in a Grade A environment (for example, due to requirements for specific equipment in the processing area that is not fully compatible with Grade A).

5. In point 4(a), (b), (c) and (d), an environment must be specified. It must be demonstrated and documented that the chosen environment achieves the quality and safety required, at least taking into account the intended purpose, mode of application and immune status of the recipient. Appropriate garments and equipment for personal protection and hygiene must be provided in each relevant department of the tissue establishment along with written hygiene and gowning instructions.

6. When the activities for which accreditation/designation/authorisation or licensing is sought involve storage of tissues and cells, the storage conditions necessary to maintain the required tissue and cell properties, including relevant parameters such as temperature, humidity or air quality must be defined.

7. Critical parameters (e.g. temperature, humidity, air quality) must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.

8. Storage facilities must be provided that clearly separate and distinguish tissues and cells prior to release/in quarantine from those that are released and from those that are rejected, in order to prevent mix-up and cross-

contamination between them. Physically separate areas or storage devices or secured segregation within the device must be allocated in both quarantine and released storage locations for holding certain tissue and cells collected in compliance with special criteria.

9. The tissue establishment must have written policies and procedures for controlled access, cleaning and maintenance, waste disposal and for the re-provision of services in an emergency situation.

E. DOCUMENTATION AND RECORDS

1. There must be a system in place that results in clearly defined and effective documentation, correct records and registers and authorised Standard Operating Procedures (SOPs), for the activities for which accreditation/designation/authorisation/licensing is sought. Documents must be regularly reviewed and must conform to the standards laid down in this Directive. The system must ensure that work performed is standardised, and that all steps are traceable; i.e. coding, donor eligibility, procurement, processing, preservation, storage, transport, distribution or disposal, including aspects relating to quality control and quality assurance.

2. For every critical activity, the materials, equipment and personnel involved must be identified and documented.

3. In the tissue establishments all changes to documents must be reviewed, dated, approved, documented and implemented promptly by authorised personnel.

4. A document control procedure must be established to provide for the history of document reviews and changes and to ensure that only current versions of documents are in use.

5. Records must be shown to be reliable and a true representation of the results.

6. Records must be legible and indelible and may be handwritten or transferred to another validated system, such as a computer or microfilm.

7. Without prejudice to Article 9(2), all records, including raw data, which are critical to the safety and quality of the tissues and cells shall be kept so as to ensure access to these data for at least 10 years after expiry date, clinical use or disposal.

8. Records must meet the confidentiality requirements laid down in Article 14 of Directive 2004/23/EC. Access to registers and data must be restricted to persons authorised by the responsible person, and to the competent authority for the purpose of inspection and control measures.

F. QUALITY REVIEW

1. An audit system must be in place for the activities for which accreditation/designation/authorisation/licensing is sought. Trained and competent persons must conduct the audit in an independent way, at least every two years, in order to verify compliance with the approved protocols and the regulatory requirements. Findings and corrective actions must be documented.

2. Deviations from the required standards of quality and safety must lead to documented investigations, which include a decision on possible corrective and preventive actions. The fate of non-conforming tissues and cells must be decided in accordance with written procedures supervised by the responsible person and recorded. All affected tissues and cells must be identified and accounted for.

3. Corrective actions must be documented, initiated and completed in a timely and effective manner. Preventive and corrective actions should be assessed for effectiveness after implementation.

4. The tissue establishment should have processes in place for review of the performance of the quality management system to ensure continuous and systematic improvement.

ANNEX II

Requirements for the authorisation of tissue and cell preparation processes at the tissue establishments as referred to in Article 4

The competent authority shall authorise each tissue and cell preparation process after evaluation of the donor selection criteria and procurement procedures, the protocols for each step of the process, the quality management criteria, and the final quantitative and qualitative criteria for cells and tissues. This evaluation must comply at least with the requirements set out in this Annex.

A. RECEPTION AT THE TISSUE ESTABLISHMENT

Upon reception of procured tissues and cells at the tissue establishment, the tissues and cells must comply with the requirements defined in Directive 2006/17/EC.

B. PROCESSING

When the activities for which the accreditation/designation/authorisation/licensing is sought include processing of tissues and cells, the tissue establishment procedures must comply with the following criteria:

1. The critical processing procedures must be validated and must not render the tissues or cells clinically ineffective or harmful to the recipient. This validation may be based on studies performed by the establishment itself, or on data from published studies or, for well established processing procedures, by retrospective evaluation of the clinical results for tissues supplied by the establishment.

2. It has to be demonstrated that the validated process can be carried out consistently and effectively in the tissue establishment environment by the staff.

3. The procedures must be documented in SOPs which must conform to the validated method and to the standards laid down in this Directive, accordingly with Annex I(E), points 1 to 4.

4. It must be ensured that all processes are conducted in accordance with the approved SOPs.

5. Where a microbial inactivation procedure is applied to the tissue or cells, it must be specified, documented, and validated.

6. Before implementing any significant change in processing, the modified process must be validated and documented.

7. The processing procedures must undergo regular critical evaluation to ensure that they continue to achieve the intended results.

8. Procedures for discarding tissue and cells must prevent the contamination of other donations and products, the processing environment or personnel. These procedures must comply with national regulations.

C. STORAGE AND RELEASE OF PRODUCTS

When the activities for which the accreditation/designation/authorisation/licensing is sought include storage and release of tissues and cells, the authorised tissue establishment procedures must comply with the following criteria:

1. Maximum storage time must be specified for each type of storage condition. The selected period must reflect among others possible deterioration of the required tissue and cell properties.

2. There must be a system of inventory hold for tissues and/or cells to ensure that they cannot be released until all requirements laid down in this Directive have been satisfied. There must be a standard operating procedure that details the circumstances, responsibilities and procedures for the release of tissues and cells for distribution.

3. A system for identification of tissues and cells throughout any phase of processing in the tissue establishment must clearly distinguish released from non-released (quarantined) and discarded products.

4. Records must demonstrate that before tissues and cells are released all appropriate specifications are met, in particular all current declaration forms, relevant medical records, processing records and test results have been verified according to a written procedure by a person authorised for this task

by the responsible person as specified in Article 17 of Directive 2004/23/EC. If a computer is used to release results from the laboratory, an audit trail should indicate who was responsible for their release.

5. A documented risk assessment approved by the responsible person as defined in Article 17 of Directive 2004/23/EC must be undertaken to determine the fate of all stored tissues and cells following the introduction of any new donor selection or testing criterion or any significantly modified processing step that enhances safety or quality.

D. DISTRIBUTION AND RECALL

When the activities for which the accreditation/designation/authorisation/licensing is sought include distribution of tissues and cells, the authorised tissue establishment procedures must comply with the following criteria:

1. Critical transport conditions, such as temperature and time limit must be defined to maintain the required tissue and cell properties.

2. The container/package must be secure and ensure that the tissue and cells are maintained in the specified conditions. All containers and packages need to be validated as fit for purpose.

3. Where distribution is carried out by a contracted third party, a documented agreement must be in place to ensure that the required conditions are maintained.

4. There must be personnel authorised within the tissue establishment to assess the need for recall and to initiate and coordinate the necessary actions.

5. An effective recall procedure must be in place, including a description of the responsibilities and actions to be taken. This must include notification to the competent authority.

6. Actions must be taken within pre-defined periods of time and must include tracing all relevant tissues and cells and, where applicable, must include

trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the reaction in the recipient and to retrieve available tissues and cells from that donor, as well as to notify consignees and recipients of tissues and cells procured from the same donor in the event that they might have been put at risk.

7. Procedures must be in place for the handling of requests for tissues and cells. The rules for allocation of tissues and cells to certain patients or health care institutions must be documented and made available to these parties upon request.

8. A documented system must be in place for the handling of returned products including criteria for their acceptance into the inventory, if applicable.

E. FINAL LABELLING FOR DISTRIBUTION

1. The primary tissue/cell container must provide:

(a) type of tissues and cells, identification number or code of the tissue/cells, and lot or batch number where applicable;

(b) identification of the tissue establishment;

(c) expiry date;

(d) in the case of autologous donation, this has to be specified (for autologous use only) and the donor/recipient has to be identified;

(e) in the case of directed donations - the label must identify the intended recipient;

(f) when tissues and cells are known to be positive for a relevant infectious disease marker, it must be marked as: BIOLOGICAL HAZARD.

If any of the information under points (d) and (e) above cannot be included on the primary container label, it must be provided on a separate sheet accompanying the primary container. This sheet must be packaged with the primary container in a manner that ensures that they remain together.

2. The following information must be provided either on the label or in accompanying documentation:

(a) description (definition) and, if relevant, dimensions of the tissue or cell product;

(b) morphology and functional data where relevant;

(c) date of distribution of the tissue/cells;

(d) biological determinations carried out on the donor and results;

(e) storage recommendations;

(f) instructions for opening the container, package, and any required manipulation/reconstitution;

(g) expiry dates after opening/manipulation;

(h) instructions for reporting serious adverse reactions and/or events as set out in Articles 5 to 6;

(i) presence of potential harmful residues (e.g. antibiotics, ethylene oxide etc).

F. EXTERNAL LABELLING OF THE SHIPPING CONTAINER

For transport, the primary container must be placed in a shipping container that must be labelled with at least the following information:

(a) identification of the originating tissue establishment, including an address and phone number;

(b) identification of the organisation responsible for human application of destination, including address and phone number;

(c) a statement that the package contains human tissue/cells and HANDLE WITH CARE;

(d) where living cells are required for the function of the graft, such as stem cells gametes and embryos, the following must be added: "DO NOT IRRADIATE";

(e) recommended transport conditions (e.g. keep cool, in upright position, etc.);

(f) safety instructions/method of cooling (when applicable).

10.3 COMMISSION DIRECTIVE 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments

1. INTRODUCTION AND GENERAL PRINCIPLES

1.1. Quality system

1 Quality shall be recognised as being the responsibility of all persons involved in the processes of the blood establishment with management ensuring a systematic approach towards quality and the implementation and maintenance of a quality system.

2 The quality system encompasses quality management, quality assurance, continuous quality improvement, personnel, premises and equipment, documentation, collection, testing and processing, storage, distribution, quality control, blood component recall, and external and internal auditing, contract management, non-conformance and self-inspection.

3 The quality system shall ensure that all critical processes are specified in appropriate instructions and are carried out in accordance with the standards and specifications set out in this Annex. Management shall review the system at regular intervals to verify its effectiveness and introduce corrective measures if deemed necessary.

1.2. Quality assurance

1 All blood establishments and hospital blood banks shall be supported by a quality assurance function, whether internal or related, in fulfilling quality assurance. That function shall be involved in all quality-related matters and review and approve all appropriate quality related documents.

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

introduction and be re-validated at regular intervals determined as a result of these activities.

2. PERSONNEL AND ORGANISATION

1 Personnel in blood establishments shall be available in sufficient numbers to carry out the activities related to the collection, testing, processing, storage and distribution of blood and blood components and be trained and assessed to be competent to perform their tasks.

2 All personnel in blood establishments shall have up to date job descriptions which clearly set out their tasks and responsibilities. Blood establishments shall assign the responsibility for processing management and quality assurance to different individuals and who function independently.

3 All personnel in blood establishments shall receive initial and continued training appropriate to their specific tasks. Training records shall be maintained. Training programmes shall be in place and shall include good practice.

4 The contents of training programmes shall be periodically assessed and the competence of personnel evaluated regularly.

5 There shall be written safety and hygiene instructions in place adapted to the activities to be carried out and are in compliance with Council Directive 89/391/EEC ([1]) and Directive 2000/54/EC of the European Parliament and of the Council ([2]).

3. PREMISES

3.1. General

Premises including mobile sites shall be adapted and maintained to suit the activities to be carried out. They shall enable the work to proceed in a logical sequence so as to minimise the risk of errors, and shall allow for effective cleaning and maintenance in order to minimise the risk of contamination.

3.2. Blood donor area

There shall be an area for confidential personal interviews with and assessment of individuals to assess their eligibility to donate. This area shall be separated from all processing areas.

3.3. Blood collection area

Blood collection shall be carried out in an area intended for the safe withdrawal of blood from donors, appropriately equipped for the initial treatment of donors experiencing adverse reactions or injuries from events associated with blood donation, and organised in such a way as to ensure the safety of both donors and personnel as well as to avoid errors in the collection procedure.

3.4. Blood testing and processing areas

There shall be a dedicated laboratory area for testing that is separate from the blood donor and blood component processing area with access restricted to authorised personnel.

3.5. Storage area

1 Storage areas shall provide for properly secure and segregated storage of different categories of blood and blood components and materials including quarantine and released materials and units of blood or blood components collected under special criteria (e.g. autologous donation).

2 Provisions shall be in place in the event of equipment or power failure in the main storage facility.

3.6. Waste disposal area

An area shall be designated for the safe disposal of waste, disposable items used during the collection, testing, and processing and for rejected blood or blood components.

4. EQUIPMENT AND MATERIALS

1 All equipment shall be validated, calibrated and maintained to suit its intended purpose. Operating instructions shall be available and appropriate records kept.

2 Equipment shall be selected to minimise any hazard to donors, personnel, or blood components.

3 Only reagents and materials from approved suppliers that meet the documented requirements and specifications shall be used. Critical materials shall be released by a person qualified to perform this task. Where relevant, materials, reagents and equipment shall meet the requirements of Council Directive 93/42/EEC ([1]) for medical devices and Directive 98/79/EC of the European Parliament and of the Council ([2]) for in vitro diagnostic medical devices or comply with equivalent standards in the case of collection in third countries.

4 Inventory records shall be retained for a period acceptable to and agreed with the competent authority.

5 When computerised systems are used, software, hardware and back-up procedures must be checked regularly to ensure reliability, be validated before use, and be maintained in a validated state. Hardware and software shall be protected against unauthorised use or unauthorised changes. The back-up procedure shall prevent loss of or damage to data at expected and unexpected down times or function failures.

5. DOCUMENTATION

1 Documents setting out specifications, procedures and records covering each activity performed by the blood establishment shall be in place and kept up to date.

2 Records shall be legible and may be handwritten, transferred to another medium such as microfilm or documented in a computerised system.

3 All significant changes to documents shall be acted upon promptly and shall be reviewed, dated and signed by a person authorised to perform this task.

6. BLOOD COLLECTION, TESTING AND PROCESSING

6.1. Donor eligibility

1 Procedures for safe donor identification, suitability interview and eligibility assessment shall be implemented and maintained. They shall take place before each donation and comply with the requirements set out in Annex II and Annex III to Directive 2004/33/EC.

2 The donor interview shall be conducted in such a way as to ensure confidentiality.

3 The donor suitability records and final assessment shall be signed by a qualified health professional.

6.2. Collection of blood and blood components

1 The blood collection procedure shall be designed to ensure that the identity of the donor is verified and securely recorded and that the link between the donor and the blood, blood components and blood samples is clearly established.

2 The sterile blood bag systems used for the collection of blood and blood components and their processing shall be CE-marked or comply with equivalent standards if the blood and blood components are collected in third countries. The batch number of the blood bag shall be traceable for each blood component.

3 Blood collection procedures shall minimise the risk of microbial contamination.

4 Laboratory samples shall be taken at the time of donation and appropriately stored prior to testing.

5 The procedure used for the labelling of records, blood bags and laboratory samples with donation numbers shall be designed to avoid any risk of identification error and mix-up.

6 After blood collection, the blood bags shall be handled in a way that maintains the quality of the blood and at a storage and transport temperature appropriate to further processing requirements.

There shall be a system in place to ensure that each donation can be linked to the collection and processing system into which it was collected and/or processed.

6.3. Laboratory testing

1 All laboratory testing procedures shall be validated before use.

2 Each donation shall be tested in conformity with the requirements laid down in Annex IV to Directive 2002/98/EC.

3 There shall be clearly defined procedures to resolve discrepant results and ensure that blood and blood components that have a repeatedly reactive result in a serological screening test for infection with the viruses mentioned in Annex IV to Directive 2002/98/EC shall be excluded from therapeutic use and be stored separately in a dedicated environment. Appropriate confirmatory testing shall take place. In case of confirmed positive results, appropriate donor management shall take place including the provision of information to the donor and follow-up procedures.

4 There shall be data confirming the suitability of any laboratory reagents used in the testing of donor samples and blood component samples.

5 The quality of the laboratory testing shall be regularly assessed by the participation in a formal system of proficiency testing, such as an external quality assurance programme.

6 Blood group serology testing shall include procedures for testing specific groups of donors (e.g. first time donors, donors with a history of transfusion).

6.4. Processing and validation

1 All equipment and technical devices shall be used in accordance with validated procedures.

2 The processing of blood components shall be carried out using appropriate and validated procedures including measures to avoid the risk of contamination and microbial growth in the prepared blood components.

6.5. Labelling

1 At all stages, all containers shall be labelled with relevant information of their identity. In the absence of a validated computerised system for status control, the labelling shall clearly distinguish released from non-released units of blood and blood components.

2 The labelling system for the collected blood, intermediate and finished blood components and samples must unmistakably identify the type of content, and comply with the labelling and traceability requirements referred to in Article 14 of Directive 2002/98/EC and Commission Directive 2005/61/EC (1). The label for a final blood component shall comply with the requirements of Annex III to Directive 2002/98/EC.

3 For autologous blood and blood components, the label also shall comply with Article 7 of Directive 2004/33/EC and the additional requirements for autologous donations specified in Annex IV to that Directive.

6.6. Release of blood and blood components

1 There shall be a safe and secure system to prevent each single blood and blood component from being released until all mandatory requirements set out in this Directive have been fulfilled. Each blood establishment shall be able to demonstrate that each blood or blood component has been formally released by an authorised person. Records shall demonstrate that before a blood component is released, all current declaration forms, relevant medical records and test results meet all acceptance criteria.

2 Before release, blood and blood components shall be kept administratively and physically segregated from released blood and blood components. In the

absence of a validated computerised system for status control the label of a unit of blood or blood component shall identify the release status in accordance with 6.5.1.

3 In the event that the final component fails release due to a confirmed positive infection test result, in conformity with the requirements set out in Section 6.3.2 and 6.3.3, a check shall be made to ensure that other components from the same donation and components prepared from previous donations given by the donor are identified. There shall be an immediate update of the donor record.

7. STORAGE AND DISTRIBUTION

1 The quality system of the blood establishment shall ensure that, for blood and blood components intended for the manufacture of medicinal products, the storage and distribution requirements shall comply with Directive 2003/94/EC.

2 Procedures for storage and distribution shall be validated to ensure blood and blood component quality during the entire storage period and to exclude mix-ups of blood components. All transportation and storage actions, including receipt and distribution, shall be defined by written procedures and specifications.

3 Autologous blood and blood components as well as blood components collected and prepared for specific purposes shall be stored separately.

4 Appropriate records of inventory and distribution shall be kept.

5 Packaging shall maintain the integrity and storage temperature of blood or blood components during distribution and transportation.

6 Return of blood and blood components into inventory for subsequent reissue shall only be accepted when all quality requirements and procedures laid down by the blood establishment to ensure blood component integrity are fulfilled.

8. CONTRACT MANAGEMENT

Tasks that are performed externally shall be defined in a specific written contract.

9. NON-CONFORMANCE

9.1. Deviations

Blood components deviating from required standards set out in Annex V to Directive 2004/33/EC shall be released for transfusion only in exceptional circumstances and with the recorded agreement of the prescribing physician and the blood establishment physician.

9.2. Complaints

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

9.3. Recall

1 There shall be personnel authorised within the blood establishment to assess the need for blood and blood component recall and to initiate and coordinate the necessary actions.

2 An effective recall procedure shall be in place, including a description of the responsibilities and actions to be taken. This shall include notification to the competent authority.

3 Actions shall be taken within pre-defined periods of time and shall include tracing all relevant blood components and, where applicable, shall include trace-back. The purpose of the investigation is to identify any donor who might have contributed to causing the transfusion reaction and to retrieve available

blood components from that donor, as well as to notify consignees and recipients of components collected from the same donor in the event that they might have been put at risk.

9.4. Corrective and preventive actions

1 A system to ensure corrective and preventive actions on blood component non-conformity and quality problems shall be in place.

2 Data shall be routinely analysed to identify quality problems that may require corrective action or to identify unfavourable trends that may require preventive action.

3 All errors and accidents shall be documented and investigated in order to identify system problems for correction.

10. SELF-INSPECTION, AUDITS AND IMPROVEMENTS

1 Self-inspection or audit systems shall be in place for all parts of the operations to verify compliance with the standards set out in this Annex. They shall be carried out regularly by trained and competent persons in an independent way according to approved procedures.

2 All results shall be documented and appropriate corrective and preventive actions shall be taken.