A code of practice for tissue banks : providing tissues of human origin for therapeutic purposes / Department of Health.

A Code of Practice for Tissue Banks

providing tissues of human origin for therapeutic purposes

DH Department of Health

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This Code of Practice will be reviewed not later than June 2005.
Comments should be sent to:
Secretary to the Advisory Committee on the Microbiological Safety of Blood and Tissue for Transplantation, Department of Health, Wellington House, Waterloo Road, London SE1 8UG

Front cover illustration by Paul Stork

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1 The purpose of the Code of Practice

This Code of Practice applies to tissue banks in the public sector supplying human tissues for therapeutic purposes to the health service. It forms the basis of the Department of Health accreditation scheme for these tissue banks in the United Kingdom. In order to provide safe tissue of reliable quality, current good practice standards must be observed in the selection of donors, retrieval of tissues, testing, processing, storage and delivery of finished tissues: this Code addresses these issues.

The Code of Practice brings together current professional guidelines on tissue banking and has been prepared by the Department of Health in consultation with Royal Colleges and relevant professional organisations.

2 Introduction

2.1 What the Code covers

The Code of Practice specifies the requirements for the activities of tissue banks that store and/or process human tissues for therapeutic use within the health service in the United Kingdom.

The scope of this Code includes all human tissues used for therapeutic purposes including those used in clinical trials. Examples of these are: cardiovascular tissues (e.g. valves, vessels); musculoskeletal tissues (e.g. bone, cartilage, osteochondral tissues, ligaments, tendons); skin; ocular tissues (e.g. corneas and sclera); immature gametes; fetal tissues (e.g. neuronal cells and stem cells); haemopoietic progenitor cells (e.g. bone marrow, peripheral blood, cord/placental blood); donor leucocytes/granulocytes; autologous cell systems.

The scope of the Code excludes a number of categories which are covered by existing regulations or guidance:

- blood and blood products subject to other national requirements
- human tissues used for research purposes other than for clinical trials
- cells and cell lines used for gene therapy
- commercially manufactured therapeutic products utilising human tissues (including cells and cell lines)
- embryos produced *in vitro* and mature gametes
- vascularised organs.

This Code of Practice is not intended to limit the development of new concepts or new technologies which have been validated and which provide a level of quality assurance at least equivalent to those set out in this Code. New processes that involve, for example, tissue engineering and the culture of cells, may develop and lead to tissues being provided by tissue banks in the United Kingdom. As such processes develop they will be covered by this Code of Practice.

Tissue banks may be required to provide access to confidential data to demonstrate compliance with this Code but they are not required to provide copies for retention.

2.2 Using this Code

The Code of Practice is based on a quality system approach. It forms the basis of good practice in all tissue banks and will be used when the tissue bank is inspected as part of the Department of Health accreditation scheme.

2.3 Related documents and structure

The framework and content of this Code are based on Quality Management Systems (ISO 9000 series) and principles of good manufacturing practice as set out in *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* (Department of Health, 1997). It emphasises the need for compliance with an integrated quality assurance programme. The Code of Practice takes into account the guidance set out in other documents (see *References and bibliography*).

Tissue banks must also adhere to the principles set out in *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation* (Department of Health, 2000). Relevant professional standards must be considered at all stages of the selection and testing of donors, retrieval of tissues, testing, processing, storage and delivery of tissues.

Tissue banks also have a general duty and responsibility to comply with other statutory legislation, such as the Health and Safety at Work Act 1974 and COSHH Regulations 1999.

Tissue banks must ensure that proper consent has been obtained for the retrieval of tissue, as addressed by the Human Tissue Act 1961, the Human Fertilisation and Embryology Act 1990, the Human Fertilisation and Embryology (disclosure of information) Act 1992 and professional guidelines.

For dated legislation and references, the subsequent amendments or revisions of these are relevant. Any new legislation related to the activities of tissue banks will be applicable.

3 Quality systems

3.1 What is a quality system?

A quality system defines and documents a series of systematic processes that are to be followed by all those working within an organisation. These processes are designed to ensure that quality is evident in every part of the organisation. The objective is to avoid mistakes. However, if a mistake does happen, the cause should be identified and the process amended so that it is not repeated.

The quality systems described in this Code of Practice cover the tissue bank buildings and premises, environmental controls, managerial responsibilities, donor selection and testing, written agreements or contracts with third parties, testing of tissues to specifications, standards for the processing and storage of tissue, documentation and record keeping and transport of tissues.

3.2 Why use a quality system?

The aim of using a quality system in tissue banks is to ensure the safety and quality of the tissues and services provided.

3.3 Who is responsible for the quality system?

The director of the tissue bank has overall responsibility for the policy, implementation and operation of the quality system. This must be relevant to the tissue bank's goals and the needs of the organisations it supplies. All members of staff must be familiar with the quality system and responsible for the quality of their work.

The responsibility for operating the quality system must be assigned to an appropriately qualified named individual who must be independent of operational management. There must also be a designated deputy who can take on this responsibility in the absence of the first named individual. Other key personnel should include those responsible for medical advice, microbiology, quality assurance and processing.

Key personnel must review the quality system at regular intervals to ensure that it continues to meet the needs of this Code and be relevant to the work of the tissue bank.

3.4 How is the quality system put into effect?

A quality system depends on effective and adequate documentation. The tissue bank must establish and maintain all relevant documents relating to all aspects and stages of the tissue bank's work. This will include standard operating procedures (SOPs) and associated documents for all activities which affect the safety or quality of tissues.

The tissue bank must define and document how the requirements for quality will be met. Documents and data must be reviewed and approved by authorised personnel before they are issued. Current documents must be readily identifiable to ensure that invalid or obsolete documents are not used.

The responsibilities and reporting relationships of all key personnel must be defined and documented. The quality system shall be reviewed at appropriate intervals by the tissue bank management to ensure its suitability and effectiveness.

3.5 Resources for a quality system

Adequate resources must be provided at all levels to ensure effective and efficient delivery of the tissue bank's quality system. The tissue bank must identify and provide adequate resources, including the assignment of trained personnel, for management, performance of work, verification activities and internal audits.

4 Tissue bank facilities

4.1 Buildings and premises

Buildings and premises should be located, designed, constructed and used with the aim of protecting the quality of tissues. Buildings, whether they are newly constructed or modified, should be designed to be fit for their intended purpose. Efficient cleaning and maintenance procedures should be implemented. All tissue processing facilities, equipment and storage areas must be designed to avoid contamination of tissues.

4.2 Environmental controls

There are four main sources of potential contamination of tissue after it has entered the tissue bank:

- processing areas
- personnel
- ancillary materials
- cross-contamination from tissues of different donors.

4.2.1 Processing areas

The tissue bank must establish and document requirements for the environment to which tissue is exposed. The quality of air must be defined for each type of processing area and this will depend on the nature of the process, the tissue and the degree of handling and exposure of the tissue.

Certain features and practices are common requirements in processing areas. These include:

- floors, walls and ceilings of non-porous smooth surfaces that can be cleaned easily
- changing area and washing facilities adjacent to the processing area
- procedures for gowning, hygiene and cleaning
- control and monitoring of the environmental conditions (particles and microbial contamination)
- passage of materials and persons controlled at all times.

The rationale for the design, specification and monitoring programme of environmental controls to minimise microbial and particulate contamination, and the operational and working practices, must be justified and documented. Controlled environments or laminar flow cabinets are effective in minimising levels of contamination.

Critical work areas are those where tissue is manipulated openly, either following a disinfection or sterilisation step or in those cases where tissue has been procured aseptically and will not be further disinfected or sterilised. Critical work areas in which sterile containers or closures, aseptically procured tissue or disinfected tissue is exposed to the environment, must have an air quality of grade A and should have a grade B background as defined in Table 1. This requires a HEPA filtered air supply at a positive pressure with respect to surrounding area.

Work areas in which tissue, materials and containers are prepared prior to disinfection or sterilisation must have an environment with air quality of at least grade C or better.

Table 1: Air classification system for the processing of tissue				
Grade	Maximum permitted number of particles per m^3 equal to or above the size specified			
	At rest		In operation	
	0.5µm	5µm	0.5µm	5µm
A	3,500	0	3,500	0
B	3,500	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

(Adapted from: Rules and Guidance for Pharmaceutical Manufacturers and Distributors, 1997)

Critical work areas must be monitored according to a documented procedure. Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, air and surface sampling. Results from environmental microbiological monitoring programmes should be reviewed as part of the tissue release stage. The recommended limits for microbiological monitoring of critical work areas in operation are given in Table 2.

Table 2: Microbiological monitoring of critical work areas				
Grade	Air sample cfu/m^3	Settle plates cfu/4 hrs	Contact plates cfu/plate	Glove print cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(Adapted from: Rules and Guidance for Pharmaceutical Manufacturers and Distributors, 1997)

The routine monitoring programme for microbiological and particulate contamination shall be performed according to a defined method and plan, with specified alert and action limits. Compliance with the specified requirements shall be verified and results shall be documented to monitor the operational state of critical work areas or laminar flow cabinets.

4.2.2 Personnel

Hygiene programmes must be established and documented. They should include procedures related to health, hygiene practices and the clothing of personnel. These procedures should be understood and followed by all staff, particularly those with duties within processing or controlled environments. Instructions should be issued to personnel ensuring that health conditions of relevance to the quality of the tissues are reported to the person(s) responsible for quality assurance.

Every person entering processing areas must wear protective clothing appropriate to the operations being carried out. All personnel must use hand washing facilities. The following practices must be prohibited in the processing areas: eating, drinking, smoking, chewing, and the storage of food, drink, smoking materials or personal medication.

4.2.3 Ancillary materials

Any components (e.g. equipment used for processing) and materials (e.g. saline, disinfectant) that are in contact with tissue during processing operations should be specified and controlled to minimise contamination and ensure that the tissue specification is met. Any components previously in contact with other donors should be decontaminated according to the relevant guidelines.

4.2.4 Cross-contamination from tissues of different donors

Systems designed to prevent cross-contamination from tissues from different donors must be in place.

4.3 Equipment

Documented procedures must be established to maintain all equipment that can affect quality. Inspection equipment and measuring and test equipment must be calibrated to appropriate standards. All equipment must be used in a manner which ensures that the measuring uncertainty is known and is consistent with the required measurement capability.

The tissue bank must:

- identify all equipment that can affect tissue quality
- specify details of the equipment type, unique identification, location, frequency of checks, check method, acceptance criteria, and the action to be taken when results are unsatisfactory
- maintain calibration records for inspection equipment and measuring and test equipment
- identify the calibration status of test equipment
- ensure that the handling and storage of inspection equipment and measuring and test equipment is such that the accuracy and fitness for use are maintained.

5 Responsibilities of personnel and training

5.1 Responsibilities of personnel

It is essential that in all cases the quality related functions are separate from the processing functions.

The director of the tissue bank must identify personnel with responsibility for key functions including the medical advisor, microbiology advisor and personnel with responsibility for quality assurance and for processing. In smaller tissue banks some responsibilities may be shared or external contracts held to carry out these key functions.

The following responsibilities are associated with these functions.

The **director's responsibilities** include:

- responsibility for all personnel and implementation of the Code of Practice
- keeping up-to-date with new developments, professional guidelines and related research
- ensuring that donor selection criteria are in line with current United Kingdom guidelines
- ensuring that agreements or contracts for services with third parties are in line with this Code of Practice
- regular meetings with quality assurance and processing managers to review quality
- reviewing clinical efficacy, continuity of the audit trail and advising third parties of their responsibilities
- ensuring corrective and preventative actions are completed.

The **medical advisor's responsibilities** include:

- development of policies on donor suitability and care
- authorisation of the documents related to donor selection
- providing advice on action to be taken for late notification of donor infection risk and recalls
- establishing and maintaining systems for clinical feedback
- authorisation of limited release in exceptional circumstances (see section 8.3).

The **microbiology advisor's responsibilities** include:

- commissioning and monitoring of effective sterilisation/disinfection procedures, facilities and services
- contributing to the development of donor testing strategies
- authorising the investigation of microbial contamination of tissues and advising appropriate action
- developing and authorising strategies for monitoring and recording of environmental contamination at an appropriate frequency, isolating and identifying contaminants and attempting to identify their sources
- authorising strategies for the microbiological control of ancillary materials for processing activities
- developing strategies for the specification and routine monitoring of air conditioning and filtration equipment
- authorising strategies for the monitoring of hygiene and cleaning practices.

The **quality assurance responsibilities** include:

- regular input to the review of the quality system
- approval or rejection of retrieved, intermediate and finished tissue

- evaluating batch processing records
- reviewing process procedures at regular intervals
- performing inspection testing, approving specifications and sampling instructions
- preparing and monitoring agreements of services with third parties
- checking maintenance of premises, equipment and calibration
- ensuring that process validations are completed
- performing and acting on internal audit programmes
- ensuring compliance with training programmes.

The **processing responsibilities** include:

- regular input to the review of the quality system
- ensuring that tissues are retrieved, processed and stored according to the documented procedures
- approving instructions relating to process operations and to ensure implementation
- ensuring that process records are evaluated and authorised
- checking the maintenance of premises and equipment
- ensuring that process validations are completed
- ensuring compliance with training programmes.

Quality assurance and processing also have some joint responsibilities which include:

- authorisation of standard operating procedures and other relevant documents
- monitoring and control of the processing environment
- process qualification and validation of special processes
- designation and monitoring of storage and quarantine practices for materials and tissues
- retention of records
- identification, investigation and monitoring of factors which may affect safety and quality.

5.2 Training

Procedures must be established and maintained for identifying training needs and providing training for all personnel who perform activities affecting quality. Personnel who carry out specific tasks must have appropriate education, training and/or experience. Training records must be maintained and evaluated regularly.

All personnel who are required to work under special environmental conditions, or who perform special processes or functions, must be appropriately trained or supervised by a trained person. Personnel who occasionally work in processing areas must also be appropriately trained.

Training and retraining must be in accordance with documented programmes. All processes applied to tissues that may affect quality should be carried out by personnel trained in accordance with the documented procedures.

6 Donor selection

Tissue banks must adhere to the principles set out in *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation* (Department of Health, 2000).

Policies and specified requirements for donor selection must be documented. This must include medical and behavioural history, microbiological testing, exclusion factors, consent and blood sample testing. Tissue banks must adhere to the principles set out in *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation* (Department of Health, 2000). All procedures must also cover donors donating tissue for autologous and/or directed allogeneic use.

6.1 Medical and behavioural history

For dated legislation and references, the subsequent amendments or revisions to these are relevant. Any new legislation related to the activities of tissue banks will be applicable.

Initial assessment and selection of donors is essential to minimise the transmission of disease. For guidance on microbiological disease transmission, tissue banks must adhere to the principles set out in the current Department of Health *Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation* (Department of Health, 2000). For guidance on other conditions that may affect the eligibility of the donor, current professional guidance must be considered.

Donor selection procedures and conditions that contraindicate the use of tissues for therapeutic purposes must be documented. Trained personnel should obtain this information through donor interview and review of medical and behavioural history according to a specified procedure. A policy must be in place documenting the procedure that needs to be followed where a donor cannot be interviewed.

6.2 Microbiological screening

There must be a documented policy on testing blood samples for specific infections that might be transmitted with the graft. The tests must be performed for certain mandatory infectious agents by accredited testing laboratories, in line with current United Kingdom guidelines.

The documented policy must consider:

- quality and validity of samples
- retesting in the case of live donors
- timing of samples in relation to the donation of the tissue
- testing of post-mortem samples
- positive sample identification
- testing of mothers of donors less than 18 months of age
- archiving of samples.

The tissue bank must have a documented policy for donors with repeat reactive samples. There should be protocols for retesting if appropriate, confirmatory testing, counselling of donors and contacts, and acceptance or rejection of donations.

7 Control of tissues, services and materials

7.1 When are written agreements or contracts required?

Written agreements or contracts are required to define and document the relationships between the tissue bank and any third party. The requirements for written agreements or contracts, with regular review, apply in the following circumstances.

Where a third party takes responsibility for any aspect of tissue donor selection, tissue retrieval or tissue processing on behalf of the tissue bank
For example, where a transplant co-ordinator interviews a donor family on behalf of a tissue bank; where a centre retrieves corneas on behalf of an eye bank; or where a commercial sterilisation facility sterilises tissues on behalf of a tissue bank.

Where a third party provides goods or services that may affect tissue quality or safety
For example, where companies hold equipment maintenance or calibration contracts with tissue banks; where companies supply tissue packaging and labelling to a tissue bank; where a contracted microbiologist provides testing and consultant services to a tissue bank; or where a cleaning contractor is employed.

Where a tissue bank provides services to another tissue bank
For example, where a tissue bank receives, processes and returns tissue to another bank or stores tissue for supply to users on behalf of another bank.

Where a tissue bank provides finished tissue to a user
Before accepting a request from a user, the tissue bank must ensure that the requirements are adequately defined and documented and that the tissue bank has the capability to meet those requirements.

7.2 Management of written agreements and contracts

The tissue bank must establish and maintain documented procedures for the review of agreements and contracts.

The details of the agreement or contract, including responsibilities, must be clearly specified, documented and agreed between the parties. The agreement or contract must include an option for audit of procedures carried out by a third party. The tissue bank must identify and document how an amendment to an agreement or contract is made. Records of reviews of agreements and contracts must be maintained.

The tissue bank must:

- evaluate and select third parties on the basis of their ability to meet the required standards, including quality systems and any specific quality assurance requirements
- define the type and extent of control exercised by the tissue bank over third parties. This will depend on the type of product or service provided, on the impact of the third party product or service on the quality of finished tissue and, where applicable, on the quality audit reports and/or quality records maintained by the third party
- establish and maintain documented procedures for the control, verification, storage and maintenance provided for processing and/or storage by other banks
- specify the required procedures before it will accept tissue for processing by another bank
- establish and maintain quality records of acceptable third parties, where appropriate.

7.3 Inspection of tissues on receipt at the tissue bank

The tissue bank must ensure that tissue, from within the United Kingdom or

outside, is quarantined until the tissue and its associated documentation have been inspected or otherwise verified as conforming to the tissue bank's requirements, including those relating to donor selection and testing. Verification of conformity to the requirements must be in accordance with documented procedures. The tissue bank must establish and maintain records which provide clear evidence that the tissue (or its packaging) and associated documentation have been inspected on receipt.

Tissues must be correctly identified at all times. Each delivery or batch of tissues must be allocated an identifying code which can be related to the tissue and be traceable to the donor through processing and storage.

7.4 Inspection of materials on receipt at the tissue bank

Purchased materials that may affect the quality of finished tissues must similarly be quarantined until inspection has confirmed that they comply with agreed specifications.

7.5 Microbiological controls

There must be documented procedures for the policy and practice of the microbiological test programmes for the screening of tissues, the processing environment and the potential sources of contamination. All aspects of processing that contribute to the microbiological safety and quality of the tissues must be controlled. Contamination must be minimised by all practical means.

7.6 Storage

Designated storage areas or stock rooms must be used in order to prevent damage and minimise deterioration of tissue prior to its despatch for clinical use. Appropriate methods for authorised receipt to, and despatch from, such areas must be specified in the documented procedures.

Conditions of storage and transport must not compromise the quality of the tissue. Equipment for the storage and transport of tissue must be suitable for the intended use. Procedures for monitoring must be validated so that tissue meets the specified requirements. If special storage conditions are required at any stage, these must be controlled and monitored.

Retrieved and finished tissue must be stored and issued according to documented procedures. Records must be maintained for stock reconciliation. Materials that have been rejected, recalled or returned must be accepted by the person responsible for quality assurance who will ensure that they are identified, recorded and placed in separate quarantine areas.

Any tissue returned to the tissue bank must be treated as nonconforming tissue until it has satisfied a documented acceptance procedure.

7.7 Traceability

Documented procedures must be established and maintained for identifying the tissue from receipt and during all stages of processing and delivery, as well as unique identification of individual tissue or batches. These data must be recorded.

Procedures for traceability must be established, documented and maintained. These procedures must define the extent of traceability and facilitate corrective action. Traceability must include all components, materials used, and records of the environmental conditions.

There must be an effective system that enables the traceability of human tissues between the donor, the finished tissue and the identification of the recipient. The receiving hospital should maintain internal records on the finished tissue that ensures the continuity of a two-way audit trail.

8 Process control

8.1 General

The tissue bank must identify and plan the processes that directly affect quality and must ensure that these processes are carried out under controlled conditions. Controlled conditions must include:

- use of suitable processes, equipment, and a suitable working environment
- compliance with reference standards/codes, quality plans and/or documented procedures
- monitoring and control of suitable process parameters and tissue characteristics
- approval of processes and equipment, as appropriate
- proper servicing and maintenance of equipment.

The requirements for any process operations, including associated equipment and personnel must be specified and records maintained. Each time a process is carried out, conformity with the documented procedure should be confirmed by using work sheets to note the performance of each critical step or data collection. Any deviation from the documented procedures should be specified and formally reviewed for possible effects on quality.

8.2 Validation of special processes

Protocols for the development or significant modification of tissue processing operations or special processes must be documented and authorised by appropriate persons. The protocol should include provision for verification that the process meets the process specification and is compatible with the tissue specification. Each critical step that may affect tissue quality should be qualified and validated.

The tissue bank must subject tissue to effective validated processes (e.g. disinfection, sterilisation or controlled rate freezing). All the control parameters of the process must be recorded. These validation data must be recorded and a re-evaluation made of any changes to the process. Details of the physical control parameters must form part of the batch processing records for any method of disinfection/sterilisation. For ethylene oxide the results of the biological indicators must be included in the batch history records. Procedures used should determine ethylene oxide residual levels. Equipment for sterilisation must be provided with recording equipment or indicators.

Where the results of processes cannot be fully verified by subsequent inspection and testing of the tissue, the processes must be continuously monitored to ensure that the specified requirements are met.

Quality records of special processes must identify the work instruction used, the date the special process was performed and the identity of the operator.

Before processes are implemented they must be validated to demonstrate that the process will consistently produce tissue in accordance with the specification. Documented procedures must identify the specific equipment used in processing (e.g. sterilisation, refrigeration, freezing, culturing). Processes should undergo a regular critical appraisal to ensure that they remain capable of achieving the intended results. Where validation is not performed, the rationale and authorisation must be recorded. Similar procedures should be followed where any significant change in processing occurs involving new or modified equipment, major overhauls or change of location.

Where pooling of human tissues from donors is practised, this will require a fully documented risk analysis with a rationale and justification.

8.3 Tissue release

Finished tissue must be held in quarantine until released by the person(s) responsible for quality assurance. Tissue must not be released from quarantine until all the activities in the documented procedures have been satisfactorily completed and the associated data and documentation are available and authorised.

The batch processing record must be verified and authorised, and include a statement of whether the tissue has been approved for release or been rejected. No tissue shall be released for distribution until all the necessary procedures, including microbiological procedures, have been satisfactorily completed. Records must identify the inspection authority responsible for the release of tissue.

The composition of the batch processing record must be defined and may include the quantity of raw materials, components and intermediate products, their batch/control number, the quantity of tissue processed, the number of finished tissues, results of in-process controls, microbiological test results, identity of personnel, details of any nonconformity to processing specifications, copies of labels and final identification numbers, and where relevant, processing/sterilisation records.

In exceptional clinical circumstances the limited release of nonconforming tissue may be authorised. Where such tissue is released, the rationale and conditions must be agreed by the tissue bank's medical advisor and the clinician treating the intended recipient and documented in accordance with a written procedure. In these circumstances, records must be maintained and be subject to regular review.

8.4 Discard of tissue

Special provisions must be made by the tissue bank for the handling of tissue to be discarded in order to prevent contamination of other tissue, the processing environment or personnel. These provisions must conform to the local policy for discard of human tissue and the relevant guidance on the discard of clinical waste.

8.5 Monitoring systems

8.5.1 Audits

Documented procedures must be established and maintained for planning and implementing internal quality audits to monitor the implementation of quality activities and results. Audits should include examination of processing records.

Internal quality audits should be conducted against a predefined schedule by a person independent of the area being audited and who has been trained to a defined level.

Audit reports must be recorded and maintained. They should contain all the observations made during the inspection and, where applicable, proposals for corrective measures. Statements about the action that is subsequently taken should also be recorded.

The type and frequency of adverse incidents, complaints and the effectiveness of corrective and preventive action must be reviewed by the tissue bank management to ensure that the quality system is effective and suitable.

8.5.2 Corrective and preventive action

Where appropriate, corrective action should be followed by preventive action to include a review of the causes of the nonconformance and the implementation of appropriate changes to procedures to prevent recurrence.

Documented procedures must be established and maintained for implementing corrective and preventive action.

Any changes to the documented procedures resulting from corrective and preventive action must be implemented and recorded.

The procedures for corrective action must cover:

- the effective handling of reported adverse incidents and reports of other nonconformities
- the investigation of the cause of nonconformities relating to tissue, process and the quality system
- reviewing and recording the results of the investigation
- specification of the corrective action to eliminate the cause of the nonconformities
- application of controls to ensure that corrective action is taken and that it is effective.

8.5.3 Nonconforming tissue

Documented procedures must be established and monitored to ensure that the unintended use of nonconforming tissue is avoided. These must provide for identification, documentation, evaluation, segregation, disposal of nonconforming tissue, and for notification to the persons responsible for quality assurance and processing in the tissue bank.

Responsibility for the review and authority for the distribution of nonconforming tissue must be defined and reviewed in accordance with documented procedures. Nonconforming tissue may be:

- accepted with or without reprocessing
- regraded for alternative applications
- rejected or disposed of as clinical waste, or
- reprocessed to meet the specified requirements.

The reprocessing of nonconforming tissue should be exceptional. It should only be allowed if the final quality is not affected, if specifications are met and if it is done in accordance with the authorised procedure, after a risk assessment. Records must be kept of the reprocessing.

8.5.4 Complaints

All feedback information, including reported complaints and returned tissue must be documented, investigated, analysed, collated and communicated in accordance with defined procedures by a designated person. If any complaint is not followed by corrective action, the reason must be recorded. When the investigation determines that activities at other premises or third parties played a part in the complaint, a summary of the original complaint and copy of the outcome report must be sent to those premises. Consideration should be given to amending the agreement or contract as necessary.

8.5.5 Recalls

Procedures must be established, documented and maintained for advisory and recall notices. These procedures should cover the:

- system to prevent distribution of affected batches (or donations from the same affected donor)
- method of communicating recall and advisory notices to all relevant parties, including other tissue banks that may have processed and stored tissue from the same affected donor

- records to be maintained
- reconciliation of returned tissues
- storage and quarantine of recalled tissue
- regulatory authorities to be informed.

The implementation of the recall procedure must be co-ordinated by the designated person. A recall may be instigated as a result of a complaint, an adverse incident, or as a result of late information received that the donor did not meet the inclusion and exclusion criteria. A person must be nominated to initiate and co-ordinate the procedures. Recalled tissues must be identified, stored and quarantined whilst awaiting a decision. The recall process must be recorded and a final report issued, including a reconciliation between the number of finished tissues originally delivered and subsequently recovered.

9 Packaging, labelling and transport

9.1 Packaging and labelling

Packing, packaging and marking processes (including materials used) must conform to the specified requirements.

Procedures must be established and maintained to ensure that:

- the tissue is presented in a container designed to maintain quality and prevent contamination
- the tissue is capable of being presented in an aseptic manner, if its use so requires
- the package clearly reveals whether it has been opened
- the tissue bank records the identity of persons who perform the final labelling operation
- the suitability of packaging and labels for transport and storage have been validated.

Unit labels and/or package inserts must be labelled with:

- a description of the contents, including size, number or volume, where relevant
- the full name of the tissue bank
- a batch/lot/serial number
- the date of donation
- advice on handling and any hazards that might occur in use
- directions for opening and aseptic presentation where necessary
- an expiry date for tissues that have a determined shelf life
- a statement that each package is for single patient use only
- any necessary instructions for storage.

Where it is impractical to label the unit container with this information it should be included in the package insert. However, all unit labels must at least include a description of the contents, (including size, number or volume, where relevant), the full name of the tissue bank, a batch/lot/serial number and an expiry date for finished tissues that have a determined shelf life.

9.2 Transport and delivery

The tissue bank must arrange for the protection of the quality of tissue after the final inspection and test. Where contractually specified, this must be extended to include delivery to the destination. The name and address of the shipping package consignee must be included in the quality records.

The tissue bank must document its policy for the acceptance or rejection of unused tissue returned to the tissue bank. Users should be clearly informed of this policy.

The tissue bank must require that any recognised intermediary maintains records of distribution and that such records are available for inspection.

10 Documentation

10.1 General

A quality system must be established, documented and maintained as a means of ensuring that tissue conforms to specified requirements. The tissue bank must prepare:

- standard operating procedures
- specifications, such as graft specification, donor referral standard
- records, such as donor records.

Documentation must be reviewed and approved by authorised personnel prior to issue. This must ensure that:

- the relevant issues of appropriate documents are available at all locations where operations essential to the effective functioning of the quality system are performed
- invalid or obsolete documents are removed from all points of issue or use, to prevent unintended use
- any obsolete documents retained for knowledge preservation or legal purposes are suitably identified and stored.

There must be documented procedures for the maintenance of records. These must include: identification, collection, indexing, batch processing records, access, filing, storage, maintenance and disposition of quality records. These must be maintained to conform with the specified requirements of the quality system. Where specified by agreement or contract, the relevant quality records from third parties or service providers must be maintained.

Donor records relating to medical and behavioural history and tissue retrieval details must be maintained. These records must show that the donated tissue has been rejected or released by a designated person. Confidential records should be held in restricted areas accessed only by authorised personnel.

Tissue release records must be established and maintained for each batch of tissues to provide traceability at least to the extent required by this Code. Records must identify the quantity manufactured and quantity released for distribution.

The tissue bank must maintain comprehensive records of all user complaint investigations and the issue of advisory notices and recalls. The tissue bank must ensure that records include the description of tissue, any control number used, the name of the complainant, the nature of the complaint, the corrective or preventive action implemented and the reply to the complainant.

10.2 Changes to documentation

Changes to documentation must be reviewed and approved by the same functions or organisations that performed the previous review and approval, unless specifically designated otherwise. Pertinent background information must be accessible for the process of review and approval.

10.3 Storage and retention

The minimum periods of retention for all categories of documents must be specified and justified. Documents must be stored and retained so they are retrievable in facilities that provide a suitable environment to prevent damage, deterioration or loss. The tissue bank must define the period for which at least one copy of obsolete documents must be retained.

10.4 Computer records

The introduction of computerised systems into processing practices, including storage, distribution and quality control does not alter the need to comply with the requirements of this Code of Practice. The same criteria and standards apply as to other records.

A schematic plan or flow diagram for software should be available to evaluate the capability of the system to meet the specified requirements. Qualification and validation is part of the life cycle of a computer system. A description of the system, its function and specified requirements must be documented. The system should record the identity of persons entering or confirming critical data. Alterations to the system or program should only be made in accordance with defined procedures. When the release of finished batches for storage or issue is conducted by computerised systems it must identify and record the person(s) releasing the batches.

Alternative management systems should be available to cope with failures in computerised systems.

11 Special considerations

Professional bodies and specialist societies have, in many instances, prepared standards or guidelines relating to specific tissues. This Code of Practice acts as a framework for developing and supporting pre-existing standards and guidelines. Directors and medical advisors of tissue banks should ensure that the standards or guidelines from such organisations are observed and incorporated into the quality assurance systems based on this Code of Practice. Specific standards and guidelines are referred to in the References and bibliography section.

Tissue engineering

An area where there is currently no specific guidance is the area of tissue engineering. Where therapeutic products that include substrates or cells of human origin are banked by non-commercial organisations, this Code of Practice applies. In addition the following principles apply.

- If allogeneic cells are greatly expanded in number and intended for use in multiple recipients, the degree of microbiological testing beyond the mandatory testing, should reflect the increased size of the population at risk of any disease.
- If cells are cultured *in vitro* prior to implantation, the procedures must be validated or monitored, e.g. to demonstrate lack of malignant transformation, and maintenance of relevant biological properties.

Special requirement of Human Fertilisation and Embryology Act (1990)

Storage of ovarian or testicular tissue that contains, or may contain, mature gametes requires a storage licence under the terms of the Human Fertilisation and Embryology Act (1990). Storage without a licence is a criminal offence.

Similarly, therapeutic use of thawed gametes, or handling, or maturation of immature gametes *in vitro* for the purposes of treatment requires a licence from the Human Fertilisation Embryology Authority (HFEA), and may only be undertaken in premises licensed by the HFEA. Posthumous use of such gametes will require appropriate antemortem written consents in accordance with the Human Fertilisation and Embryology Act and the HFEA Code of Practice.

Glossary

For the purposes of this Code of Practice the following definitions apply.

Advisory notice
A notice issued to provide information and/or advice on what action should be taken in the use, modification, disposal or return of a tissue.

Allogeneic use
Cells or tissues transplanted from one person to another.

Ancillary materials
Any item that is in contact with the tissue during processing.

Autologous use
Cells or tissues removed from and transplanted back to the same person.

Batch or Lot
A defined quantity of starting material, packaging material or tissue processed in one series of processes or series of processes.
Note: A batch may be a single finished tissue.

Calibration
The set of operations that establishes under specified conditions the relationship between values indicated by measuring equipment or a measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell culture
The *in vitro* growth of cells.

Cells
Individual cells or collection of cells when not bound by any form of connective tissue.

Complaint
Any written or oral report, of deficiencies related to the identity, quality, durability, reliability, delivery, safety or performance of a tissue.

Confirmatory tests
A series of tests conducted on a repeat reactive sample by a designated reference laboratory to confirm the true or false nature of the repeat reactivity observed in the screening laboratory.

Cord blood
Blood in the placenta and umbilical cord; i.e. blood taken at the time of birth.

Cross-contamination
Contamination of a material or of a tissue with another material or tissue.

Directed allogeneic
A donation made by one individual for transplantation to another specified individual.

Disinfection
Treatment which reduces the numbers of bacteria, fungi and some viruses present.

Donor
A living or a recently deceased person from whom tissues have been removed. Donated tissues may be for allogeneic or autologous use.

Finished tissue
Tissue that has undergone all of the stages of processing, including packaging.

Gamete
A reproductive cell, which has a haploid set of chromosomes and which is able to take part in fertilisation.

Good practice
Practices that meet accepted standards as defined by relevant government or professional organisations.

Haemopoietic progenitor cells
Cells capable of developing into a particular cell lineage. Cells capable of generating white blood cells, red blood cells, and platelets. Haemopoietic stem cells are collected from peripheral blood, cord blood or bone marrow, for therapeutic use.

Implantation
The procedure of inserting a graft (tissue or cells) into the body.

In-process control
Checks performed during processing in order to monitor and if necessary adjust the process to ensure that the tissue conforms to its specification. The control of the environment or equipment may also be part of in-process control.

Intermediate tissue
Partly processed tissue that must undergo further processing steps.

Label
All written, printed or graphic matter (on any of the containers, wrappers or package inserts accompanying a tissue) relating to identification, technical description and use of the tissue, but excluding shipping documents.

Processing
All operations involved in the preparation of the tissue, from receipt of materials, through preparation and packaging, to its completion as a finished tissue.

Quarantine
The status of retrieved tissue or packaging material, or tissue isolated physically or by other effective means whilst awaiting a decision on their release or rejection.

Recall
The requested return of finished tissue known or suspected to be non-compliant to the tissue bank, in accordance with the instructions contained in an advisory notice.

Recipient
The person into whom the finished tissue is grafted/implanted.

Repeat reactive sample
Samples that are initially reactive and show a further reactive result in one or more aliquots taken from the original sample and tested using the same assay.

Reprocessing
The reworking of tissue of unacceptable quality from a defined stage of processing so that its quality may be rendered acceptable by one or more additional operations.

Retrieval
The removal of tissues or cells from a donor.

Stem cells
Cells capable of self-replication, proliferation and differentiation.

Sterile
Condition of a product that is free from viable micro-organisms. For a terminally sterilised product to be labelled as 'sterile' the theoretical probability of there being a viable micro-organism present on the product shall be equal or less than one in 1×10^{6}.

Tissue
Material of human origin, tissue or cells, used for therapeutic purposes.

Tissue bank
The organisation that is responsible for the activities of retrieval, processing, packaging, labelling, storage, and delivery of the finished tissue issued under its name, regardless of whether these operations are carried out by that organisation or on its behalf by a third party.

Verification
Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

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Notes

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