

A Code of Practice for the Production of Human-derived Therapeutic Products

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1 The purpose of the Code of Practice

This Code of Practice applies to organisations that supply products that use material of human origin to the health service for therapeutic purposes. In order to provide safe Human-derived Therapeutic Products of reliable quality, good practice standards need to be observed in the selection of donors, retrieval of tissues, testing, processing, storage and delivery; this code addresses these issues¹.

The Code of Practice brings together professional expectations on this subject and has been prepared by the Medical Devices Agency of the Department of Health in consultation with the Medicines Control Agency, interested professional organisations, commercial producers and specialised hospital units.

¹ This Code of Practice is complementary to and expands upon the Code of Practice for Tissue Banks (2001) and Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (2000).

2 Introduction

2.1 What the Code covers

This Code of Practice outlines the principles for assuring the safety and quality of therapeutic products which use material of human origin and which may be produced using tissue engineering practices.

Many recent collaborative research and development programmes have involved scientists, engineers and physicians in integrating engineering technology with the life sciences. This has resulted in the combination of cell culture and biomaterial technologies to enable the production and use of numerous therapeutic products, many of which incorporate material of human origin. The application of these specialist technologies has been extremely rapid and further developments are anticipated in this area.

Illustrative examples of these new kinds of therapeutic products include:

- medical devices (e.g. hip prostheses, bone substitutes, wound dressings), modified by the application of human-derived growth factors, bone morphogenic proteins or cell signalling biomolecules to enhance their expected clinical benefit;
- products that use non-viable material of human origin such as:
 - collagen as a microtubule for nerve regeneration;
 - growth factors and extra-cellular matrix proteins in skin substitutes;
 - granular or demineralized bone matrix as an orthopaedic bone substitute;
 - collagen as a corneal shield dressing;
- viable allogeneic cells (e.g. keratinocytes and/or fibroblasts) in a biodegradable scaffold used as a bioengineered skin substitute;
- viable autologous cells (e.g. chondrocytes) with or without a matrix, used for the repair of cartilage lesions.

For the purposes of this document, these are collectively referred to as Human-derived Therapeutic Products.

Human-derived Therapeutic Products are products that use material of human origin, and which are used for therapeutic purposes. These may include products such as bioengineered skin systems, cartilage repair systems, and novel bone substitutes that may use scaffold matrices with autologous or allogeneic human cells.

While it is clearly important that human tissues are obtained in an ethical and lawful manner, these aspects are beyond the scope of this document. This Code of Practice specifies the scientific principles underlying the production, quality assurance and safety assessment of products that use material of human origin. It is relevant to producers, specialised hospital

units/departments and other organisations that supply the health service in the United Kingdom.

This document is not intended for use in classifying products according to the scope of existing regulations or establishing the safety, quality or compliance of healthcare products covered by existing European Regulations, such as the Medicinal Products Directive (2001/83/EC) or the general Medical Devices Directive (93/42/EEC). Similarly, products that are subject to existing national controls, such as the Department of Health Accreditation Scheme for Tissue Banks, are excluded. Also blood and blood or plasma derived products, human tissue for research purposes, cells and cell lines for gene therapy or for vaccine manufacture, embryos produced *in vitro* and mature gametes, vascularised organs and tissues stored in genomic banks are excluded. Products manufactured from non-viable animal materials are included within the scope of the Medical Devices Directive (93/42/EEC). Products that incorporate viable animal tissues or cells (or use these during production) are excluded from that Directive and producers of such products should seek guidance from the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). Regulatory guidance should be obtained from the medicinal authorities on cell lines/tissues arising from stem cell technologies that lead to therapeutic products or other treatments.

2.2 Regulatory Controls and Guidance

European regulations for medical devices (93/42/EEC) and medicinal products (2001/83/EC) provide a mechanism for ensuring the safety and quality of many healthcare products used in the health service. Many products, however, fall outside the scope of such statutory regulations, although the provisions of the Consumer Protection Act (1987) and the General Product Safety Regulations (1994) still apply.

Irrespective of the operation or nature of regulatory controls, commonly held expectations for safety and quality, based on firmly established scientific principles, apply to all therapeutic products and a number of documents have been developed recently and used in the implementation of non-statutory mechanisms of safety assurance.

The Department of Health Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (2000) is primarily aimed at activities within the Health Service. It highlights the fact that the highest standards need to be maintained when choosing donors, and when collecting, testing, processing, storing, transporting and transplanting organs, tissues or cells. It recognises that maintaining a recognised quality management programme, such as BS EN ISO 9001:2000 and BS EN ISO 13485:2001, will contribute significantly to safety and quality, and that the principles of microbiological safety apply to human cells cultured in a laboratory and to manufactured products or services that use human cells or tissues.

Tissue banking within the NHS is regulated by a voluntary accreditation scheme, centred upon compliance with a Department of Health Code of Practice for Tissue Banks (2001), which applies to finished tissues that are

banked by non-commercial organisations. However, the Code of Practice recognised that there was no specific guidance in the area of tissue engineering, and noted that the following additional principles applied:

- *“ if allogeneic cells are greatly expanded in number and intended for use in multiple recipients, the degree of microbiological testing beyond the mandatory testing², 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.”*

This document expands on the above principles to form a comprehensive series of requirements and expectations applicable to Human-derived Therapeutic Products.

2.3 Using this Code

This document can be used by producers (e.g. commercial organisations, specialised hospital units/departments and universities), certification organisations or regulatory agencies as a basis for non-statutory schemes for assessing product safety and quality. Compliance with this document is amenable to verification by audit, thus enabling assurance of the safety and quality of Human-derived Therapeutic Products. It is anticipated that such use will be of assistance in the preparation for any future statutory controls for products containing human tissues within the European Union. Most importantly, the diligent application and verification of the principles and expectations contained in the following pages will provide purchasers, clinicians and patients alike with the confidence and reassurance necessary for the safe and reliable application of new technologies.

² Minimum serological testing requirements are specified in 'Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation' Department of Health (2000).

3 Quality Assurance Systems

Organisations that produce Human-derived Therapeutic Products need to implement and maintain a Quality System that effectively controls the design, processing and supply of the product. The approach listed below provides a sound basis for product characterisation and safety assessment. As with other healthcare products such as medical devices or medicinal products, the acceptability for marketing a Human-derived Therapeutic Product is a function of adequate and effective quality assurance. This comprises:

- a detailed specification of the critical design characteristics of the product;
- a comprehensive risk analysis and assessment;
- development and verification of production and quality control systems that deliver the design specification, including a quantitative assay of activity for viable preparations and, where possible, a correlation with clinical effectiveness;
- demonstration that the systems and product meet the state of the art and deliver the expected benefits to the patient.

Demonstration of the state of the art should be seen in terms of the adequacy of the characterisation and control measures employed as well as the safety, quality and performance of the product. The quality system specifies all technical criteria relevant to this and ensures that these are complied with in the procurement and processing of biological tissues and the production, packaging, labelling, storage and distribution of products. Producers shall implement a Quality Management System that is consistent with BS EN ISO 9001:2000 as supplemented, for medical devices, by BS EN ISO 13485:2001.

It is important to specify, confirm and monitor the quality of all raw materials and equipment used in the preparation and delivery of Human-derived Therapeutic Products. Special attention should be paid to all raw materials and equipment to which cells are or may be exposed. The quality assurance measures adopted need to take account of the inherent variability of biological systems while ensuring that characteristics which are critical to product quality are reliably identified and that, in respect of these, appropriate quality control measures are clearly specified and implemented.

In particular the Quality System shall cover:

- the quality, suitability and functionality of raw and processing materials, including donor selection and screening;
- infection controls, including sourcing controls and inactivation methods;
- phenotypic and genotypic profiling (e.g. biochemical markers and functional characteristics), where appropriate;
- maintenance of the desired phenotypic expression (e.g. through the influence of growth factors and substrate), where appropriate;
- validation and documentation of procedures for tissue culture (e.g. manipulation, expansion, storage, transport and clinical use);
- control of product design and validation of manufacturing processes to ensure that product meets identified requirements for clinical performance;
- the design and maintenance of buildings, equipment and premises;
- quality control testing and inspection during production and prior to release (e.g. cell viability and characterisation), including control of test equipment, to ensure that batches of product meet specified design requirements;
- the development of, and conformance to, appropriate procedures and/or specifications for labelling, handling, packaging, storage and distribution;
- training of staff and their qualification for specific activities;
- product identification and traceability between raw material and distribution records;
- post-market surveillance, including monitoring of clinical performance and effectiveness (e.g. infection, morphology, function, proliferation, persistence, immunotoxicity, efficacy) and corrective or preventative action;
- the management system, including independent responsibility for production and quality, internal audit and management review of the quality system;
- systems to minimise cross-contamination, including contamination from production staff.

The responsibility for operating the Quality System shall be assigned to a designated qualified individual, independent of operational management. There shall also be a designated deputy who can assume responsibility in the absence of the designated individual. The Quality System shall be reviewed by the Senior Management of the organisation at specified regular and frequent intervals to ensure that it continues to meet the requirements of the Quality System and this Code of Practice. The producer shall ensure that the Quality System is operational, effectively resourced and understood by all relevant staff.

4 Risk Management

Risk management is an integral part of the design, development, production and supply of Human-derived Therapeutic Products and an effective system is required for the management of risks associated with their use. The principles of risk management specified in BS EN ISO 14971:2001 are relevant to these products. Risk is estimated on the basis of the probability of harm occurring and the consequences of that harm. The assessment of risk is complicated by the fact that different parties, such as patients, clinicians, producers, regulators and the general public, may well express differing levels of concern over the possibility of particular harmful outcomes occurring on exposure to a hazard. The acceptability of a risk is dependent primarily on the risk estimate, considered in relationship to the degree of benefit expected from the use of the product. Acceptability needs to be judged in the light of the generally recognised state of the art, which takes into account a wide variety of factors, including the regulation applied to comparable types of products (e.g. devices, pharmaceuticals), the clinical and technological state of the art and the public perception of the benefits and risks of such products.

Factors affecting the perception of risks include the scientific background of the different parties and the actual and perceived state of health of the patient. The decision to use a Human-derived Therapeutic Product involves a clinical judgement whereby the residual risks inherent in the product are balanced against the anticipated clinical benefits of the procedure. It is therefore necessary for products to be assessed in relation to commonly understood standards of safety, quality and effectiveness, so that clinicians may make judgements on the basis of meaningful information on residual risks.

At all stages in the product cycle, the producer needs to make judgements relating to the safety of a Human-derived Therapeutic Product. This should include the acceptability of risks, taking into account the generally accepted state of the art, in order to verify the suitability of a Human-derived Therapeutic Product for its intended use and purpose. The producer shall establish and maintain a systematic process for:

- specifying the product characteristics and identifying the potential hazards (hazard identification);
- estimating and evaluating the associated risks (risk analysis);
- controlling these risks to ensure they are negligible or reduced to a level as low as reasonably practicable (risk control);
- judging the acceptability of residual risks (risk assessment);
- monitoring the effectiveness of risk control measures, for example through post-market surveillance.

The producer shall define a policy for determining acceptable risk and regularly review all risk management activities to ensure the continuing suitability and effectiveness of the risk management process. For each Human-derived Therapeutic Product, the records and results of all the risk

management activities shall be recorded and maintained in a risk management file.

Risk analyses conforming to BS EN ISO 14971:2001³ shall be carried out prior to the first human use of any product and before placing it on the market. The intended use and purpose of the product shall be fully described with a comprehensive list of the qualitative and quantitative characteristics that could affect the safety of the product, with defined limits where possible. The risk analysis can identify the process stages and materials in the preparation of a Human-derived Therapeutic Product that represent a potential risk to patients. Risks associated with any critical reagents that might be subject to significant variation shall be analysed. In particular this applies to raw materials of biological origin or other complex compounds or mixtures of compounds as the properties may vary without significant change in the Certificate(s) of Analysis (see Section 5.2). Where feasible such risks should be eliminated by the selection of alternative raw materials, equipment or processes. Where risks cannot be eliminated, they should be reduced to as low a level as is practicable, in line with the requirements of BS EN ISO 14971:2001 and BS EN 12442:2000.

Risk analysis reports shall be prepared prior to the first human use of any product and before placing it on the market, to provide verification that all foreseeable hazards have been analysed and the resulting risk evaluated, that control measures have been implemented and that residual risks have been estimated. Residual risks identified and estimated during risk analysis shall be weighed against the clinical benefits anticipated from the use of the product, to ensure that they have been reduced to an acceptable level, taking into account the generally recognised state of the art.

Information gained during the clinical use of the Human-derived Therapeutic Product, after it has been placed on the market shall be reviewed for its impact on the risk assessment (see Section 8.3).

These stages of the risk assessment shall be carried out in compliance with BS EN ISO 14971:2001.

³ Risk analysis is also covered by ISO 14971 (Part 1) and BS EN 1441 (1998).

5 Quality Control of Materials

5.1 Material Specifications

For all primary raw materials, processing materials, reagents and culture media, including cell cultures, the producer shall establish a specification identifying the critical physical, chemical and biological characteristics required. Account shall be taken of any relevant Pharmacopoeia monographs (British Pharmacopoeia / European Pharmacopoeia), protocols and CEN, ISO or other technical standards. This also applies to equipment when there is a direct or indirect influence on the quality or safety of the product.

Producers shall establish or verify appropriate measures and/or systems adopted by suppliers to ensure the safety and quality of raw materials. Material suppliers should operate to a relevant quality standard audited by a recognised independent qualified body. Full documentation is required to demonstrate that the quality of the materials and the equipment meets the specifications set by the producer in respect of any supplier not certified in this way.

5.2 Certificates of Analysis and Source of Materials

The conformity of each material shall be documented by certificates of analysis archived as verification of compliance with the specification. In cases where there is a need to address specific safety issues, such as materials of animal origin, verification of source and preparation of the material is required. Documentation shall be obtained that demonstrates the application of appropriate quality assurance measures by suppliers of biological material, including origins and veterinary certificates for the animals used in the preparation of the material (e.g. bovine serum albumin). Producers should also refer to the Medical Devices Directive (93/42/EEC) for products that use non-viable materials of animal origin.

5.3 Media and Reagents

Culture media, reagents and processing materials derived from animals shall be evaluated for the risk of contamination with micro-organisms, particularly viruses and agents of transmissible spongiform encephalopathies, (BS EN 12442:2000 or EMEA/410/01 rev 1, (2001)). Verification shall be obtained that all primary raw materials of animal origin originated from animals that had been subject to veterinary inspection, certification, an effective surveillance system and comprehensive sourcing controls. Such selection shall be supported by audit trails for collection, pooling, shipping and final formulation by the third party supplier.

The evaluation of information on raw materials, culture media, reagents and processing materials by the European Department on Quality of Medicines (EDQM), to minimise the risks of infection from transmissible spongiform encephalopathies, is recognised as a route for demonstrating the application of expected standards and state of the art.

Reagents, such as trypsin and collagenase, used for cell disaggregation and passage are potential vectors for microbial contamination and shall be

obtained from a source with full documentation of supplementary information. Microbiological testing of such reagents shall be performed.

Polyclonal and monoclonal antibodies⁴ or other animal cell derived molecules (e.g. transferrin, growth factors, cell signalling molecules) may represent a potential risk of exposure to the patient, for example if mixed intimately with the cells. If no practical non-animal recombinant alternative is available, the source and derivation of the antibody or molecule shall be comprehensively traceable and appropriate testing for adventitious agents applied.

Reagents that are subject to inter-batch variation in quality and/or performance and that are significant to the characteristics or performance of final product shall undergo verification before being used. There shall be a standard operating procedure for testing and authorisation for use. Such authorisation shall be documented in the batch preparation record.

5.4 Scaffolds

Scaffolds have a number of roles in the finished Human-derived Therapeutic Product, these may include facilitating localisation and delivery of human cells, defining and maintaining a three-dimensional structure and/or guiding the development of new tissue. There is a wide range of scaffold materials that fulfil these and other functions. These materials may be natural or synthetic in origin and in many cases are degradable. The choice and specification of the scaffold must therefore be part of the product specification and subject to validation.

The scaffold material should be biocompatible and this should be verified. Relevant aspects of biological evaluation are covered in BS EN ISO 10993:1998 (see Section 8.1.2). Non-viable animal tissues may also be used as scaffolds and their safety and quality shall be verified in line with the Medical Devices Directive (93/42/EEC) and BS EN 12442:2000. The scaffold material shall also be evaluated for compatibility with any cells used in the Human-derived Therapeutic Product (BS EN 30993-4:1994).

Stability when in contact with body surfaces and fluids, and the absorption profile following degradation or hydrolysis shall be evaluated where appropriate. Structural strength shall also be evaluated where this property is essential to the performance of the finished product.

Scaffolds are typically processed as a sterile component and the choice of sterilization process shall be documented and justified.

⁴ Guidance on antibodies may be found in Guidelines on the production and quality control of monoclonal antibodies of murine origin intended for use in man (EC-Commission. Notes to applicants for marketing authorizations) Tibtech (January 1988), Vol 6, p65-68 and Points to Consider in the Manufacture and testing of Monoclonal Antibody Products for Human Use, August 2, 1994, CBER (FDA), USA.

6 Microbiological Safety of Donations

Donations may be allogeneic (the donor and recipient being different people) or autologous (the donor and recipient being the same person). Donations shall adhere to the principles set out in the Code of Practice for Tissue Banks (2001) and in the Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (2000). Relevant professional standards also need to be considered at all stages of the selection and testing of donors, retrieval of tissues, testing, processing, storage and delivery of donations.

A comprehensive programme for the microbiological safety of the procured tissue or cells contributes significantly to the overall safety and quality of the Human-derived Therapeutic Product. Documented procedures and specifications, with anonymised traceability systems linking the donor information to the product shall be established within the quality system. Section 5 of the Code of Practice for Tissue Banks (2001) specifies the responsibilities and training requirements of personnel involved in procuring and processing donations, and this should be referred to for guidance.

6.1 Donor Selection

A plan shall be documented and justified for donations, specifying requirements for medical and behavioural history and mandatory donor screening.

6.1.1 Medical and Behavioural History

Appropriately trained personnel shall obtain a medical and behavioural history of the donor either by direct interview (living donors) or with family members or friends most likely to know the required history (cadaveric donors). Additional sources of medical information shall also be consulted and they may include the family doctor, hospital records, or an autopsy report (when available). The medical and behavioural history shall be reviewed for the possibility of serious disease, or behaviour indicative of serious infectious disease that would be likely to result in a significantly higher risk of disease transmission, or that would render the tissue less safe or efficacious in other ways. These are considered a contraindication to donation. A policy specifying acceptance and rejection criteria shall be documented. All medical and behavioural history details shall be recorded and maintained in the quality records.

6.1.2 Mandatory Donor Screening

Blood samples shall be tested for specific infections that might be transmitted with the donation, in line with a documented policy. Tests required for certain mandatory infectious agents, in compliance with current United Kingdom guidelines⁵, shall be performed by accredited testing laboratories.

⁵ Mandatory serological tests for infectious agents are specified in the Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (2000) and in the Guidelines for Blood Transfusion Services in the United Kingdom (2000).

A policy shall be documented, detailing the requirements or specifications in respect of the following:

- quality and validity of samples;
- resampling and retesting of live donors (a second blood sample shall be taken at least 180 days after donation and tested for the mandatory markers);
- timing of sampling in relation to the donation of the tissue;
- testing of post-mortem samples;
- criteria for identification of positive samples;
- testing of mothers of donors less than 18 months of age;
- archiving of samples;
- action in respect of repeat reactive samples;
- criteria for acceptance or rejection of donations.

Protocols shall be established for retesting (if appropriate), confirmatory testing, and counselling of donors and contacts.

6.2 Donor Types

Donations may be of tissues or cells and both shall be subject to the requirements for medical and behavioural history, and mandatory donor screening set out in Section 6.1.

6.2.1 Tissue Donors

Tissue donors are donors of tissues that are processed and used as a tissue matrix for direct implantation, or used as a scaffold for the seeding of human cells to produce a composite product. Most commonly, tissue donors are allogeneic i.e. the tissue donor and product recipient are different people. The provisions of the Code of Practice for Tissue Banks (2001) applies directly to tissue donors.

6.2.2 Cell Donors

Cell donors are donors of living human cells. The cells may be used directly or subjected to an expansion phase in culture to increase the cell number; they may be implanted with or without seeding onto scaffolds prior to implantation.

Allogeneic cell donors

Where the cells are expanded in culture prior to therapeutic use, the number of recipients is potentially orders of magnitude higher than for tissue matrices and there is the possibility of contamination by infectious agents during cell culture. Procedures applied shall reflect the potential for generating very high titres of infectious agents during the culture period and hence greater risks of cross-infection between different cell lines.

Autologous cell donors

Although autologous cells are destined for re-implantation in the original donor, there is a need for a thorough medical and behavioural history and microbiological testing regime. This is because there is the potential for the amplification of infectious agents and inadvertent microbiological contamination during the cell culturing period. Additionally, there is the potential for cross-infection between cell cultures from different donors.

A policy shall be established that identifies circumstances in which the cell culturing can or cannot continue. The policy shall specify any special culturing conditions or additional tests that are required, for example if the donor is positive for specific infectious agents. The procedures, technical equipment and containment facilities shall be specified in such cases.

6.3 Donation Release

No donation shall be released from quarantine until all the activities specified in the documented procedures, including mandatory donor screening, have been satisfactorily completed and the associated data and documentation are available and authorised.

Cell donations shall be subject to tests for authenticity and lack of contamination of cells. Where cells are greatly expanded in number, and/or intended for allogeneic use in multiple recipients, a more stringent and wider screening programme, than is mandatory shall be implemented. This should cover donors of primary cell cultures, and working cell lines arising from the master cell bank. Justification for the testing programme shall be included in the risk management file. Processing may commence while donations are held in quarantine.

Donations shall be held in quarantine until released by person(s) responsible for quality assurance. Records shall identify the inspection authority responsible for release of the donation.

6.4 Traceability

Traceability is essential to effective post-market evaluation (see Section 8.3.2) therefore traceability of human tissues/cells between the donor, the finished product and the customer is necessary. The receiving organisation is responsible for maintaining internal records that ensure the continuity of the two-way audit trail.

Procedures shall be established, documented and maintained to define the extent of traceability required and facilitate corrective action. Traceability shall include all components, materials used, and records of environmental conditions (see Section 7.2).

7 Production and Processing Practices

7.1 Cell Culture

The cell culture preparation process shall be validated for inactivation or removal of viruses whenever this is technically possible and/or the product tested for adventitious agents. (CPMP/ICH/295/95, 1997). The genetic and phenotypic stability of cell cultures shall be evaluated and characterised where possible. The risk represented by potentially oncogenic DNA and transforming proteins shall be estimated and documented. Where cell culturing techniques use cell lines that are not of human origin, for example murine fibroblasts used for co-culture, guidance should be sought from the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA).

Batch preparation records for cultured cells shall be prepared and authorised for all aspects of dispatch, harvesting and preparation for use. These records shall identify cell origin and include certificates of origin and the results of quality control tests performed on all materials and reagents used. All equipment shall be maintained and sterilized between batches to ensure correct and reproducible operation and freedom from contamination. Sterilization, cleaning and maintenance records shall be authorised and retained for all reusable equipment (e.g. tubing, filters and containers) used in direct contact with cells.

Primary Cells

In the preparation of products using primary cells of human origin an audit trail shall demonstrate for each batch of cells:

- the authenticity of the strain;
- appropriate microbiological screening of the donor;
- records of tissue/cell removal, cell harvesting and preparation.

Processing techniques for primary cells shall be chosen to minimise exposure to sources of contamination and culture passages that may lead to an alteration in the characteristics of the cell(s).

Cells from different donors should not be pooled or otherwise combined for use in a Human-derived Therapeutic Product. However, in exceptional circumstances, pooling or co-culture of cells from different donors may be deemed necessary to achieve clinical effectiveness. In such cases cells from different donors shall only be combined when it can be justified on the basis of a risk-benefit assessment specific to that product and the target patient population.

Cell Lines

The origin and passage history of continuous and finite cell lines shall be documented. Evidence of quality control and authentication tests performed by the supplier shall be obtained. Evidence of the use and suitability of the cell line in other medical applications shall be investigated, evaluated and recorded.

Master and working cell banks shall be established and appropriate testing performed as recommended in the relevant guidelines for cell substrates (CPMP/ICH/294/95, 1997). A risk assessment based on the tissue of origin and the history and nature of the cell line shall be used to determine further testing requirements.

Full passage records shall be kept to enable calculation of population doublings for cell banks and final products. Cells cryopreserved for use in Human-derived Therapeutic Products shall be traceable to the original working bank stocks and the testing performed on these banks. Extended passage experiments shall be performed to establish the stability of extended cell banks. These banks shall then be retested for safety and stability of the cells.

7.1.1 Altered Growth Conditions

All cell cultures are subject to cell turnover and cell death and this may be influenced under certain conditions. The response to an alteration in culture conditions or cell treatment may not be obvious from microscopic examinations. For example, subjecting cell cultures to serum-free or protein-free media may increase the rate of cell death and/or alter the cell characteristics. Where cells have been adapted to such media, cell banks shall be established and re-tested to exclude the activation of endogenous agents, and to assure the intended performance and the absence of increased levels of toxicity factors.

Culture of more than one cell type, where the cells are in direct physical contact or where the supernatant of one culture is in contact with other cells, may alter cell characteristics including susceptibility to infection. This possibility shall be evaluated as part of the risk analysis and appropriate testing and verification procedures applied to control the risk.

Cells may have the potential for tumorigenicity and this should be determined and measures taken to minimise risk. Cell lines of low stability or tumorigenic origin should be avoided, but where they are selected they shall be subject to a comprehensive risk/benefit assessment.

7.2 Environment

An assessment shall be performed to identify critical points where cells may be exposed to contamination during the preparation of the product. These critical points shall be closely controlled, and strict regimes and protocols shall be developed and adopted in order to prevent contamination throughout processing. The Code of Practice for Tissue Banks (2001) provides guidance for environmental conditions that are also relevant for this Code of Practice.

All staff involved in production shall be fully trained and undergo periodic assessment and re-training. Standard operating procedures (SOPs) shall be implemented to control movement of production materials and ensure that staff adhere to hygiene protocols. A documented programme of cleaning and disinfection/fumigation routines shall be developed and be in operation.

Air quality shall be maintained to a standard appropriate to the type of product being produced. Air quality shall be monitored, ideally during processing, to assure the air quality of the production facility⁶.

Whenever cells or tissue are manipulated openly in work areas (e.g. aliquoting) they shall be handled under local Grade A conditions and should have a Grade B background⁶. Biological materials shall be handled under strictly controlled conditions to minimise the possibility of cross-contamination by other cells or tissues and by contamination from the operator or processing environment. Where cells or tissues are not exposed (i.e. closed procedures), processes may be operated under less stringent environmental conditions.

7.3 Processing

The production process shall take into account the microbiological status of the final product. For products containing non-viable, highly processed tissue a validated terminal sterilization step shall be employed whenever possible. Sourcing and screening procedures, control of biological raw materials and the use of one or more process steps capable of removing or inactivating viruses (CPMP/ICH/295/95, 1997) shall be applied to reduce the risk of disease transmission.

Products containing viable cells, and those for which the use of terminal sterilization and virus removal/inactivation steps are not technically possible, shall be produced under aseptic conditions. The process adopted for such products shall be based upon a combination of approaches, to minimise the risk of disease-causing agents, including sourcing and screening of donor tissue, testing of tissue for the presence of adventitious agents, repeated screening of cell cultures, control of biological raw materials, and final testing of the product.

All operators shall be trained in aseptic processing techniques. There shall be periodic re-validation of aseptic processes to ensure that they are capable of excluding microbial contamination.

7.3.1 Preservation and Storage

When isolated cells or cells seeded into the scaffold matrix are preserved *in situ*, the levels of post-preservation cell injury shall be determined and procedures adopted to remove the toxic by-products of cell death where necessary. Evaluation of the toxicity of the preservation process shall be performed to establish the optimum conditions for preservation and cell survival. The selection of the preservation process shall also be based on the degree of stability of the cells/Human-derived Therapeutic Product under the defined storage and transport conditions. The storage and preservation process shall be validated before its implementation.

Cryopreserved cells shall be protected from general microbial contamination that may accumulate over time in liquid nitrogen vessels or those that may be introduced by cross-contamination by other patient material (Guidance Notes on the Processing, Storage and Issue of Bone Marrow and Blood Stem Cells, 1997).

⁶ See Rules and Guidance for Pharmaceutical Manufacturers and Distributors incorporating Guide to Good Manufacturing Practice for Medicinal Products (1997).

7.4 In-process Testing

The producer shall implement in-process tests to confirm that the processing operations are proceeding correctly and that the biological material, cell culture and part-processed Human-derived Therapeutic Product meet defined criteria consistent with the production of an acceptable finished product. These controls shall include tests for microbiological quality, cell culture attributes, composition, physical and chemical properties as necessitated by the type of product.

The degree of microbiological testing beyond the mandatory testing should reflect the process applied to the cells used in the product and the increased size of the population at risk of any disease. Where cells are cryopreserved as cell banks or bulk harvests, samples shall be tested post-thaw. Further testing of these cell lines should be directed by the risk assessment and subject to validation.

Examples of in-process testing:

Test	Example	Test Point	Test Item
Microbiology	Sterility Endotoxin Mycoplasma Viral markers	Appropriate points in process including cell banks and final product	Cell culture medium Bulk human tissue or cell concentrate Purified cell products/processed tissue
Cell culture	Morphology Viability Yield	At each passage and post preservation	Cells
Composition	Assay of critical component	After addition of critical component (e.g. human protein)	Human-derived Therapeutic Product

7.5 Discard of Material of Human Origin

Provisions shall be established and documented for the discard of materials of human origin, including products themselves in order to prevent contamination of other materials, the processing environment or personnel. These provisions shall conform to the local policy for discard of human tissue and relevant guidance on the discard of clinical waste.

7.6 Final Inspection and Testing

The producer shall define a finished product specification adequate to control the quality and performance of the product. Specification limits shall be based on experience of the capability of the production process and also reflect the ranges of results seen in safety and clinical tests. Limits shall be

reviewed on an ongoing basis in the light of production experience and information from post-marketing surveillance.

Each batch of finished product shall be tested against the finished product specification prior to its release to the market. There shall be a full review of the production documentation to ensure that all raw materials and reagents met their required quality specifications and there have been no processing or environmental excursions that could compromise the quality or safety of the batch.

Tests shall include the following, as appropriate:

- composition;
- physical attributes;
- microbiological quality;
- assay of specific biological components;
- cellular activity or other markers for clinical performance.

The above procedure may not be appropriate for individually produced products such as autologous implants or tissue constructs, when the shelf life of the product is limited to a few days. In such instances the producer shall implement a system for unequivocally assuring that the finished product is derived from the original tissues of the intended recipient.

7.7 Packaging and Labelling

Packing, packaging and marking processes (including materials used) shall conform to the specified requirements. Procedures shall be established and maintained to ensure that:

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

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

- a description of the contents, including size, number or volume, where relevant;
- the full name of the producer;
- a batch/lot/serial number;
- advice on handling and any hazards that might occur in use;
- directions for opening and aseptic presentation where necessary;
- an expiry date for products that have a determined shelf life;
- a statement that each package is for single patient use only;
- any necessary instructions for storage;
- an indication of sterility or microbiological status;
- the name of the intended recipient for autologous products.

Where it is impractical to label the unit container with these details, the relevant information should be included in the package insert.

7.8 Product Release

Finished product shall be held in quarantine until released by the person(s) responsible for quality assurance. Products shall not be released from quarantine until all the activities required by the documented procedures, including microbiological testing, have been satisfactorily completed and the associated data and documentation are available and authorised.

The batch processing records shall be verified and authorised, and include a statement indicating whether the product has been approved for release or been rejected. Records shall identify the inspection authority responsible for the release of product.

The composition of the batch processing record shall be defined and shall include as a minimum:

- the quantity and batch/control number of components, raw materials, processing materials, and intermediate tissues;
- verification of donation release;
- the number of finished products;
- results of in-process controls;
- microbiological test results;
- identity of personnel performing and authorising work;
- details of any nonconformity to processing specifications;
- copies of labels and final identification numbers;
- processing/sterilization records.

7.9 Storage

Designated storage areas shall be used to prevent damage and minimise deterioration of the product prior to its despatch for clinical use. Conditions of storage and transport shall not compromise the quality of the product and equipment shall be suitable for the intended use. If special storage conditions are required at any stage, these must be controlled and monitored. Procedures for monitoring shall be validated to provide assurance that the product meets the specified requirements.

Finished products 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 they are identified, recorded and placed in separate quarantine areas.

7.10 Transport and Delivery

The producer shall provide systems for the protection of the quality of the product after the final inspection and testing. Where contractually specified, this shall be extended to include delivery to the destination. The name and address of the shipping package consignee shall be included in the quality records.

The producer shall require any recognised intermediary to maintain a record of distribution and ensure that such records are available for inspection. The producer shall document a policy for acceptance or rejection of returned unused product and inform users of this policy.

8 Product Performance

The use of material of human origin has the potential for improved results in the treatment of a number of important medical conditions but also the potential for associated adverse events. Therefore it is essential to demonstrate the safety and clinical effectiveness of Human-derived Therapeutic Products by implementing a phased programme of pre-clinical and clinical evaluation before making them available to the market.

The physical and biological characteristics of the product shall be investigated through the review of relevant existing information and by carrying out appropriate pre-clinical studies. A clinical evaluation to verify functionality and safety and obtain experience in the use of the product shall follow a risk assessment based on the pre-clinical data. The decision to market the product shall be taken on the basis of a risk assessment that takes into account all the relevant pre-clinical and clinical data. Demonstration of clinical acceptability shall be established by well-controlled clinical trials, if possible randomised against the current best alternative in clinical practice for the condition in question.

Comprehensive post-market clinical studies shall be undertaken to build further confidence in the safety of the product and its effectiveness in the intended use or identify unsatisfactory performance. All information obtained during the clinical use of the product shall be documented and assessed to ensure that the product continues to meet defined expectations for safety and clinical effectiveness and that appropriate remedial action is taken promptly to mitigate risks due to significant unanticipated events.

8.1 Pre-clinical Studies

The general principles of biological safety, inherent in medical device and medicinal product Directives and other relevant legislation or guidance, provide a clear indication of the sort of analysis that is appropriate for demonstrating safety and quality. The key to determining acceptability for use lies in a detailed characterisation of functionality, with reference to those functions of the native tissue that the product is intended to replace or restore. An explanation of how the design, composition, structure and function of the product facilitates its intended biological function is required. This principle applies irrespective of whether the materials are synthetic or biological, or whether the intended biological function is active or passive. However, the nature and extent of the characterisation of the material and the comparison with native tissue differs considerably with the nature of the material. The ultimate aim is to be as confident as possible that the state of the art has been achieved. Confidence is gained both by the conscientiousness of the scientific analysis and by the precision of the comparison. An assessment of the pre-clinical studies shall be documented.

8.1.1 Performance Assessment

Where the product is intended to repair and/or replace native tissue, an assessment shall be made of the product performance in relation to the normal native tissue it is replacing and/or the best clinical alternative for treatment. Performance assessments will be dependent on the type of

Human-derived Therapeutic Product and should take into account the final working environment of the product. Examples of performance evaluations that should be carried out include:

- assessment of morphology and type of replacement/repair tissue;
- time for formation of repair;
- product/cellular activities, including excretion of molecules.

Where recombinant molecules have been used, their action, binding and release in the product should be assessed. The degradation dynamics of degradable scaffolds should be assessed, and the effect on product performance ascertained.

8.1.2 Biological Safety Assessment

Biomaterials

The chemical nature and physical form of the biomaterial are selected to provide the necessary physical and biological properties over the functional lifetime of the Human-derived Therapeutic Product. The influence of the demanding biological environment in which it has to operate is a significant factor in the safety assessment. While the principles of biological safety evaluation described in Part 1 of BS EN ISO 10993:1998 are relevant for all biomaterials, the standard does not specifically address the requirements of tissue engineering. The usual approach to the biological safety assessment of medical devices is directed primarily towards the evaluation of toxicological risks. However for Human-derived Therapeutic Products there is a need to demonstrate and assure the promotion of a desired tissue response rather than simply an absence of toxicity.

There are complex interactions between a material and the cellular and biochemical processes that may lead either to biocompatibility or to an undesirable reaction. The assessment of the suitability of the biological response therefore requires a detailed characterisation of relevant materials properties and a mechanistic analysis of critical biological endpoints.

Studies investigating the safety and performance of biomaterials shall be carried out to provide assurance in relation to the following:

- confirmation that the properties permit the growth and proper function of the tissue with which it is in contact;
- features (e.g. topography, surface chemistry) critical to the optimisation of viability and cellular growth;
- retention of tissue differentiation and functionality during production and use. This is highly dependent on the local environment and thus on the choice of biomaterials and cell signalling biomolecules (e.g. growth factors);
- compatibility of the biomaterial with the tissues with which it is in contact (e.g. cell adhesion studies, growth studies) to confirm that the system maintains the desired phenotype and genotype;
- the influence of the nature and rate of degradation on the mechanical and structural properties of the product;
- the presence and, if appropriate, biological effects of any leachable chemicals or degradation products.

The optimum characteristics of the chosen biomaterial shall be specified in advance and rigorous controls shall be implemented within the manufacturing quality system, to ensure that these specified requirements are consistently achieved.

Biological components

The biological safety of the biological component and of the complete product should be assessed in a similar manner to that of the biomaterial component. While the process is the same, the parameters to be investigated in the biological components and products are of even greater complexity and indeed, are those addressed throughout this document.

8.2 Pre-market Clinical Studies

A clinical investigation shall be conducted according to recognised standards (ISO/FDIS 14155 parts 1 and 2: 2002). A Clinical Investigation Plan (CIP) shall be designed to optimise the scientific validity and reproducibility of the results of the study in accordance with the current state of the art. The CIP shall include a critical literature review and the summary of pre-clinical studies performed in order to justify and determine the study design. Particular attention shall be paid to:

- the design and objectives of the study;
- the numbers of subjects entered;
- the duration of the study;
- the suitable choice of end points;
- the statistical significance of the results.

8.3 Post-market Evaluation

A systematic procedure shall be in operation for obtaining and reviewing data and experience relating to the clinical use of the product. The data so collected, including those obtained from clinical studies and other sources such as customer complaints, shall be analysed on a continuous basis to monitor the safety and performance of the product (BS EN ISO 14971:2001). The results of such analyses shall be evaluated to identify the need for design changes to be initiated or other appropriate corrective action to be taken. Both proactive and reactive post-market evaluation shall be performed, as specified in the risk management plan.

8.3.1 Proactive Post-market Evaluation

Clinical subjects enrolled in pre-market clinical investigations shall be followed up during the post-market phase to monitor safety, performance and clinical effectiveness. The intended duration or omission of post-market follow-up shall be justified on the basis of the risk analysis and/or ethical considerations, and documented in the risk management plan.

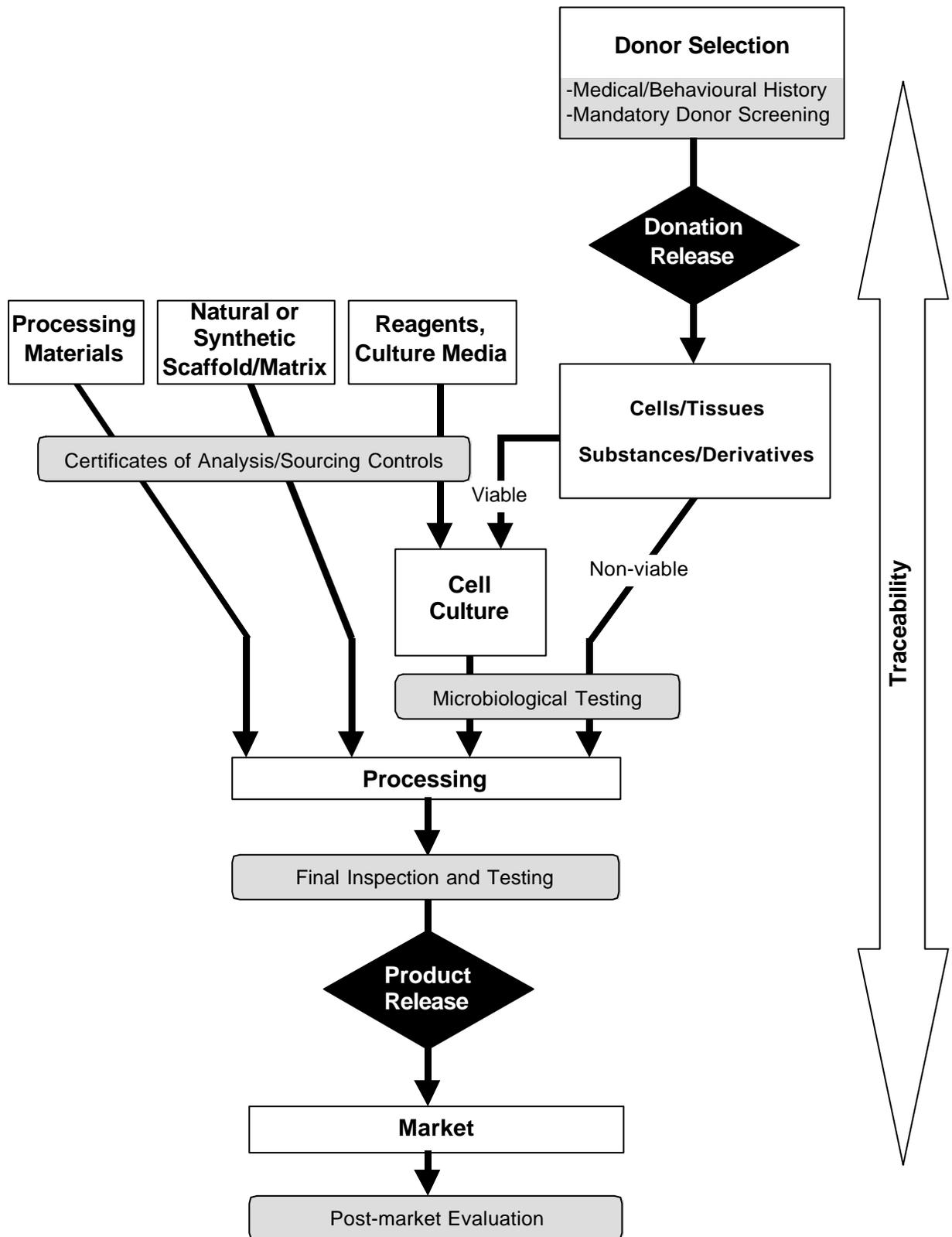
Additional clinical subjects shall be enrolled in post-market studies where indicated by statistical or other considerations. The duration of follow-up shall be determined prior to the decision to market the product and will be dependent on the nature of the product and the expected duration of persistence of biomaterial and biological components (including potential residual genomic material). This process is intended to verify the original assessment of the product and to identify the presence of previously unrecognised hazards, the acceptability of which can then be evaluated.

The post-market evaluation shall have appropriate methodology with particular reference to suitable end-points, statistical significance, standards and good clinical practice (BS EN ISO 14971:2001). In addition, the requirements of ISO/FDIS 14155, parts 1 and 2:2002 shall apply to post-market clinical investigations as appropriate.

8.3.2 Reactive Post-market Surveillance

A procedure shall be in place and in operation for the management and evaluation of reported adverse incidents or unexpected effects, user complaints and other information arising from clinical use. The supplier shall investigate whether any such report arose from a malfunction or deterioration in the characteristics and performance of the product and whether any death, injury or deterioration in the health of a patient occurred, or could have occurred. Ensuring traceability of the product (see Section 6.4) will assist these investigations. The results of such investigations shall be analysed to identify unsuspected hazards, adjust risk estimates or form the basis for design changes, field corrective action and warnings to users. A procedure shall be in place that specifies the circumstances under which, and the mechanism by which, incidents leading to or that could have led to, death or serious injury shall be reported to an appropriate United Kingdom regulatory body.

Key Stages in Routine Processing and Quality Assurance



Glossary

For the purposes of this document the following definitions apply:

Adverse incident

An event where death or serious injury or unexpected event occurs.

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.

Biomaterial

Natural or synthetic materials, including polymers, ceramics and collagen matrix, that may be used as a scaffold.

Cell culture

The maintenance of cells *in vitro*.

Cells

Individual cells or collection of cells that are not bound by any form of connective tissue.

Cell expansion

Increasing the quantity of cells by their replication *in vitro*.

Cell line

A well characterised culture that has been demonstrated to be phenotypically and genotypically consistent over a specified number of population doublings.

Clinical effectiveness

The ability to produce a specific clinical result, exert a specific measurable clinical influence or produce a desired beneficial clinical effect in actual use.

Clinical performance

The ability to exhibit a specific property or function in actual use.

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.

Continuous cell lines

A cell line that appears to have the capacity for indefinite replication.

Cross-contamination

Contamination of cells or tissues with other cells or tissues and contamination between production staff and the product.

Disinfection

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

Donor

A living or a recently deceased person from whom tissues or cells have been removed.

Finite cell line

A cell line that can be maintained for a limited number of population doublings and ultimately loses the ability to replicate.

Human-derived Therapeutic Product (HTP)

Products that use material of human origin, which are used for therapeutic purposes for the repair, restoration or regeneration of cells or tissue damaged by injury or disease.

Examples include bioengineered skin systems, cartilage repair systems, and novel bone substitutes that may use biodegradable scaffold matrices with autologous or allogeneic human cells.

Implantation

The procedure of inserting a Human-derived Therapeutic Product into the body.

Intended use/purpose

Use of a product, process or service in accordance with the specifications, instructions and information provided by the producer.

In-process control

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

Morphometry

Methods that measure shape and distribution.

Population doubling

A measured doubling of cell numbers.

Passage

Transfer of cells from one culture environment to another.

Primary cells

Cells derived from an in vivo or ex vivo source.

Processing

All operations from receipt of materials, through preparation and packaging, to the completion of a finished Human-derived Therapeutic Product.

Producer

The organisation responsible for activities such as cell retrieval, cell culturing, processing, packaging, labelling, storage, and delivery of the Human-derived Therapeutic Product issued under its own name, regardless of whether those operations are carried out by that organisation or on its behalf by a third party.

Raw material

Any material or fabricated component used singly, or in conjunction with other raw materials and/or components, in the assembly or fabrication of parts or in the total production of products.

Recipient

The patient for whom the Human-derived Therapeutic Product is intended.

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.

Residual risk

Risk remaining after protective measures have been taken.

Retrieval

The removal of tissues or cells from a donor.

Risk

Combination of the probability of occurrence of harm and the severity of that harm.

Risk management

Systematic application of management policies, procedures and practices to the tasks of analysing, evaluation and controlling risk.

Risk management file

Set of records, not necessarily contiguous, that are produced by a risk management process.

Safety

The freedom from unacceptable risk.

Scaffold

A support, delivery vehicle or matrix for facilitating the migration, binding or transport of cells and/or bioactive molecules.

Sterile

Condition of product that is free from viable micro-organisms. For a terminally sterilized product (or component) 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, used for therapeutic purposes.

Tissue engineering

The development and processing of a product of human cells (including bioactive molecules derived from cells) or tissues that may use scaffolds for repair, restoration or regeneration of cells or tissue damaged by injury and/or disease.

Validation

The establishment of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes.

Verification

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

Viable

Cells capable of propagation or metabolism.

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Membership of the Consultation Group

Mr M Cox (Chair)

Senior Medical Device Specialist, Medical Devices Agency

Ms S Bourne (Secretariat)

Medical Device Specialist, Medical Devices Agency

Mr I Cutler

Consultant, Association of British Healthcare Industries

Dr J Kearney

Head of R&D Tissue Services, National Blood Service

Mr P Newlands

Technical Manager, Ethicon (Association of British Healthcare Industries)

Dr T Phelps

Standards Director, Association British Healthcare Industries

Dr G Schild

Director, National Institute of Biological Standards and Control

Dr G Stacey

Cell Biology, Division of Virology, National Institute of Biological Standards and Control

Mr J Tinkler

Technical Manager, Medical Devices Agency

Dr L Tsang

Head of Biologicals and Biotechnology Unit, Medicines Control Agency

Mrs A Wilson

Regulatory Affairs Manager Tissue Engineering, Smith & Nephew Wound Management

Additional Contributors/Observers

Dr C Cacou

Medical Device Specialist, Medical Devices Agency

Mr M Kreuzer

Association British Healthcare Industries

Dr J Lang

Corporate Product Safety Assurance Manager, Smith and Nephew Group Research Centre

Mr C Powell

Technical and Regulation Manager, Association British Healthcare Industries