NATIONAL PHARMACEUTICAL CONTROL BUREAU

MINISTRY OF HEALTH MALAYSIA

GOOD TISSUE PRACTICE GUIDELINE

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INTRODUCTION

The quality of the tissues and cells provided from Cell and Tissue establishments is important to the quality of the final product for human applications. Cells and Tissues by their very nature, inherently, pose potential risk to recipients than conventional medicines that may have a sterilisation process included in their manufacture.

This guide establishes principles and objectives that must be achieved and sets out benchmark practices that should be followed to meet the principles and objectives. Good Tissue Practice (GTP) requirements include requirements for facilities, environmental control, equipment, supplies & reagents, recovery, processing and process controls, labelling controls, storage, receipt and distribution and donor eligibility determinations, donor screening and donor testing.

The aim of GTP is to prevent cell and tissues products with infectious disease agents, and to ensure that these cells and tissues maintain their integrity and function. This guide only focuses on cell and tissue establishments. Reference on detailed methods such as cleanroom classification and monitoring, qualification, validation and quality risk management should be made to other documents such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products Part I and its Annexes. In certain cases, other national regulations or standards may be applicable for cell and tissue establishment whereby it may provide technical requirements for the donation, procurement and testing stages. Cell and tissue establishment shall be responsible to adhere to these requirements (if any) and it must be done in accordance with an appropriate quality system.

CHAPTER 1: QUALITY MANAGEMENT

1.1 A quality system should be established, documented, implemented and maintained to ensure that finished products are safe, are of appropriate quality, and meet regulatory requirements. The quality system should take into account the appropriate elements outlined in the guide and incorporate risk management principles.

1.2 The quality system should involve all activities that determine the quality policy, objectives, and responsibilities and implement them by such measures as quality planning, quality control, quality assurance and quality improvement.

1.3 The quality system should provide a structured and organised approach for quality to be achieved. There should be resources at all levels to enable objectives to be met effectively.

1.4 The organisation's quality policy should be defined and management should take measures to ensure that the quality policy is understood, implemented and maintained at all levels of the organisation.

1.5 The system of Quality Assurance appropriate for the manufacture of cell and tissue should ensure that:

i. products are designed and developed in a way that takes account of the requirements of Good Tissue Practice ;

ii. production and control operations are clearly specified

iii. managerial responsibilities are clearly specified

iv. arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

v. all necessary controls on intermediate products, and any other in process controls and validations are carried out;

vi. the finished product is correctly processed and checked, according to the defined procedures;

vii. medicinal products are not sold or supplied before an authorised person has certified that each production batch has been produced and controlled in accordance with the requirements and any other regulations relevant to the production, control and release of medicinal products;

viii. satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

ix. there is a procedure for self inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the quality assurance system

1.6 Documented procedures to ensure that deviations from the quality system, test procedures and manufacturing procedures are recorded, investigated and approved should be established maintained and implemented.

1.7 The corrective and preventive action system should ensure that existing product nonconformity or quality problems are corrected and that recurrence of the problem is prevented.

1.8 A formal change control system should be in place to evaluate and document all changes that may affect the collection, preparation, storage, dispatch, quality control and quality assurance of cell and tissue products.

1.9 The potential impact of the proposed change on the quality of the product should be evaluated. Scientific judgement should determine what additional testing and validation studies are needed to justify a change in a validated process.

1.10 A system for self-inspection should exist. Self-inspections should be performed under the responsibility of the quality assurance unit by qualified persons to verify compliance with the principles of GTP/GMP and any regulatory requirements.

1.11 Self-inspection should comprise all parts of the operations, be performed regularly and be documented. Corrective actions should be documented and completed in a timely and effective manner.

1.12 Regular periodic quality reviews of all products should be conducted with the objective of verifying the consistency of processes and the appropriateness of current specifications for both starting materials and finished product. Quality reviews may be grouped by product type where scientifically justified. Trends should be highlighted to identify necessary product and process improvements. Reviews should be conducted and documented annually, taking into account previous reviews, and should include, as applicable:

i. A review of material used for the product, especially those from new sources;

ii. A review of critical in-process controls and finished product results;

iii. A review of all products that failed to meet established specification(s) and their investigation

iv. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;

v. A review of all changes carried out to the processes or analytical methods;

vi. If applicable, a review of the results of the stability monitoring program and any adverse trends;

vii. A review of all quality-related returns, complaints and recalls and the investigations performed at the time;

viii. A review of adequacy of any other previous product process or equipment corrective actions;

ix. The qualification status of relevant equipment and utilities, e.g. HVAC, water, gases, temperature controlled equipment;

x. A review of Contractual Agreements to ensure that they are up to date

1.13 An effective Quality Risk Management (QRM) approach can ensure the quality of a product by providing proactive means to identify and control potential quality issues. The QRM system should ensure that:

i. the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
ii. the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Examples of the processes and applications of quality risk management can be found in Annex 20 of PIC/S Guide to Medicinal Product.

CHAPTER 2: PERSONNEL

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

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

2.3 Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the authorised person(s) designated for the purpose. The heads of Production and Quality Control must be independent from each other.

2.4 The quality and production heads should have a relevant tertiary level qualification, (e.g. in medicine, science, biological science, medical laboratory science, nursing, pharmacy), and have had practical experience, at management level, in the manufacture of therapeutic products

2.5 The head of the Production Department generally has the following responsibilities:

i. to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

ii. to approve the procedures relating to production operations and to ensure their strict implementation;

iii. to ensure that the production records are evaluated and signed before they are sent to the Quality Control Department;

iv. to ensure that facilities and equipment are maintained;

v. to ensure that the appropriate validations are done;

vi. to ensure that the required initial and continuing training of production personnel is carried out.

2.6 The head of the Quality Control Department generally has the following responsibilities:

i. to approve or reject, as appropriate, materials and products;

ii. to evaluate process/batch records;

iii. to ensure that all necessary testing is carried out;

iv. to approve specifications, sampling instructions, test methods and other quality procedures;

v. to approve and monitor any contract analysts, subcontractors and suppliers (where applicable);

vi. to ensure the maintenance of the quality department premises and equipment;

vii. to ensure that the appropriate validations are done;

viii. to ensure that the required initial and continuing training of the quality personnel is carried out.

2.7 The manufacturer should provide training for all personnel whose duties take them into processing areas or into laboratories, and for other personnel whose activities could affect the quality of the product.

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

i. relevant principles of biological medicine, cell and tissue banking;

ii. GMP;

iii. relevant knowledge in microbiology and hygiene.

2.9 Training should be documented and training records should be retained to demonstrate compliance to training requirements. The effectiveness of the training should be regularly assessed.

2.10 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

2.11 Visitors or untrained personnel should, preferably, not be taken into the production and Quality Control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.12 Detailed hygiene programmes should be established and adapted to the different needs within the manufacturer. They should include procedures relating to the health, hygiene practices and clothing of personnel.

2.13 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

CHAPTER 3: PREMISES AND EQUIPMENT

3.1 Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

3.2 In order to minimise the risk of microbiological and particulate contamination, the manufacture of sterile products, or products required to have a low bio burden, should be subject to special environmental controls (e.g. Clean rooms, biological safety cabinets). Clauses in Annex 1 of the PIC/S GMP Guide for Medicinal Product should apply when applicable.

3.3 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.4 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.5 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.6 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.7 Steps should be taken in order to prevent the entry of unauthorised people. Precautions should be taken to check visitors to the premises, including external maintenance people and contractors, and to provide an appropriate level of access and supervision for their activities.

3.8 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.9 Donor interview facilities should enable interviews to be conducted in private.

Processing Areas

3.10 Materials of construction should not pose a source of contamination to the product. Critical surfaces in processing areas should be non-porous, smooth, and easily cleanable.

3.11 Where environmental conditions (e.g. temperature, humidity, air quality) could have an adverse effect on product quality, appropriate conditions should be defined, implemented and monitored.

3.12 For products requiring control of microbiological bioburden, the manufacturer should establish and document the environmental requirements to which product is exposed during processing.

3.13 Environmentally controlled processing areas should be maintained to an appropriate cleanliness standard and supplied with air, which has passed through filters of an appropriate efficiency. The suitability of the manufacturing environment should be verified by a documented monitoring program. The frequency of environmental monitoring should be based on the assessment of risk to the product. Related records should be kept.

3.14. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses, manipulations during the manufacture of cell and tissue therapies) measures should be put in place, including engineering and environmental controls on the basis of QRM principles. These QRM principles should take into account the principles and requirements from the appropriate sections of Annex 1 PIC/S GMP Guide for Medicinal Product when selecting environmental classification cascades and associated controls.

3.15 Personnel should be instructed to use the hand-washing facilities. Dedicated hand-washing facilities should be provided, and where appropriate.

3.16 All persons entering processing areas should wear protective garments appropriate to the operations carried out.

Storage Areas

3.17 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access should be restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.19 Segregated areas should be provided for the storage of quarantined, rejected, recalled or returned materials or products.

Equipment

3.20 Manufacturing equipment should be designed, located and maintained to suit its intended purpose. Equipment should not present any risk to the products. The parts of the equipment that come into contact with the product should be compatible with the product.

3.21 There should be protocols, which address installation (IQ) and operational (OQ) qualification of equipment and performance qualification (PQ). These protocols should be approved and include the predefined acceptance criteria and the

development of procedures for operation, calibration, maintenance, and cleaning. Qualification should be recorded, reviewed and approved prior to use of the equipment.

3.22 Repair and maintenance operations should not present any hazard to the quality of the products.

3.23 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned and sterilised (if applicable) according to detailed and written procedures and stored only in a clean and dry condition.

3.24 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.25 Equipment should be uniquely identifiable. This identification should be traceable to all records pertaining to the equipment.

3.26 There should be contingency plans in place for instances where routine equipment cannot be used. In such instances, the contingency plan equipment should meet the same acceptance criteria as for routine.

3.27 Defective equipment should, if possible, be removed from processing and quality control areas, or at least be clearly labelled as defective.

3.28 Fixed pipe-work for gases and liquids should be labelled to indicate the contents and the direction of flow.

3.29 Where controlled temperature conditions (including during transport, where appropriate) are required, the environment should be monitored as follows:

i. there should be temperature recording devices, and records are kept and reviewed;

ii. there should be an alarm to indicate that a temperature control system has failed. The system should permit resetting only by authorised personnel, and should be checked at regular defined intervals.

3.30 Distilled, deionized and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

Maintenance and Cleaning

3.31 Documented cleaning procedures for premises and equipment should be established, implemented and maintained. The following should be included:

i. the cleaning frequency;

ii. the materials and equipment to be used;

iii. records of cleaning should be maintained;

iv. the use of only appropriate specified disinfectants;

v. the specific requirements for different equipment and surfaces; and

vi. the dilution and the date of expiry of cleaning agents.

3.32 Cleaning agents should be selected on the basis of their suitability for intended use.

3.33 Washing and cleaning of equipment should be chosen and used in order not to be a source of contamination. Cleaning equipment, which generates contamination such as particles, dust or aerosols should be avoided.

3.34 Where the removal of traces of material or product is important to minimise risk, cleaning methods should be validated.

3.35 Equipment designed or designated to be portable should be used in accordance with the manufacturer's instructions and should have the necessary operational checks carried out before each period of use.

3.36 Preventive maintenance should be carried out on premises, facilities and equipment at defined regular intervals.

3.37 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. The accuracy of calibration equipment should be assured. Adequate records of calibration and checks should be maintained.

CHAPTER 4: DOCUMENTATION

4.1 All processes and associated activities in the manufacture of product should be documented and the documentation is controlled.

4.2 Documentation should be legible, accurate, readily identifiable and retrievable.

4.3 All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place.

4.4 Documents should not be handwritten; although, where documents require the entry of data, these entries should be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

4.5 Documents should be approved, signed and dated by appropriate and authorised persons.

4.6 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.7 Any alteration made to the entry on a document should be signed and dated in permanent ink; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.8 The manufacturer should establish, implement and maintain a procedure for controlling documents. The procedure should ensure that:

i. documents are authorised;

ii. documents are reviewed at regular intervals to ensure that they are up-to-date;

iii. multiple copies are controlled with a distribution list;

iv. obsolete documents are removed from all points of issue and use, and controlled to prevent further use;

v. the version of a document should be uniquely identified.

4.9 A system should be in place to ensure that records containing confidential information are secured from unauthorised access.

4.10 If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked.

4.11 Records electronically stored should be protected by back up. It is particularly important that the data are readily available throughout the period of retention.

4.12 Records should be maintained to demonstrate that the quality system has operated effectively and that the specified requirements have been met.

4.13 Records should be completed at the time each action is taken and in such a way that all significant activities concerning the manufacture and disposition of products are traceable.

4.14 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Processing Formula (where applicable) and Processing Instructions, and should contain the following information:

i. The name and batch number of the product;

ii. Dates and times of commencement, of significant intermediate stages and of completion of processing;

iii. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

iv. The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

v. Any relevant processing operation or event and major equipment used;

vi. A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

vii. The product yield obtained at different and pertinent stages of processing;

viii. Notes on special problems including details, with signed authorisation for any deviation;

ix. Approval by the person responsible for the processing operations

4.15 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions. The batch packaging record should contain the following information:

i. The name and batch number of the product;

ii. The date(s) and times of the packaging operations;

iii. Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

iv. Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;

v. Details of the packaging operations carried out, including references to equipment and the packaging lines used;

vi. Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

vii. Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

viii. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information;

ix. Approval by the person responsible for the packaging operations.

4.16 Access to registers and data must be restricted to persons authorised. Records must be kept for a minimum of 30 years after clinical use.

CHAPTER 5: COLLECTION AND PROCESSING

5.1 Collection and processing should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, collection, processing, packaging and distribution should be done in accordance with written procedures and, where necessary, recorded.

Collection

5.3 The selection of donors and relevant screening tests including those for infectious agents should ensure that the manufactured products are suitable for their intended purpose.

5.4 Donors should be selected according to documented procedures defining the selection criteria, infectious disease screening tests and any other relevant tests.

5.5 A procedure should be established, implemented and maintained for obtaining medical and other required statutory information prior to donation.

5.6 For Tissue Collections, there should be a documented procedure for defining the medical assessment requirements for live and deceased donors, including the acceptable timeframe for assessment, if it is not be able to be done on the day of donation. For a live donor, the donor selection records, including consent and medical history, signed by the donor should be witnessed and signed by an authorised person.

5.7 For Tissue collections, in the case of the deceased donation, the medical assessment records examined should be documented and there must be a statement of acceptability of the donor signed by a nominated authorised person. The medical assessment should be made as close as possible to collection.

5.8 Donor selection records, including informed consent and final assessment, should be reviewed and recorded by an authorised person to ensure the suitability of the donor.

5.9 Procedures for donation should be established, implemented and maintained.

5.10 At donation, any information, which may affect product quality, should be recorded.

5.11 The donor identification and any critical materials used should be traceable to the donation and associated records.

5.12 Collection areas should be organised to avoid any potential errors with donor records or labels.

5.13 The donation number or a unique identifier to the donor should be written / printed on all product and sample containers, and on donor records. This should be inspected and the inspection is recorded. Donation numbers should not be repeated, unless after a reasonable timeframe.

5.14 Procedures for the identification labelling of donations should be established, implemented and maintained. The procedures should be designed to avoid any risk of identification error or mix-up. They should require that labels be reconciled and any discrepancy is investigated.

5.15 Collection of Cells and Tissues should be performed aseptically and carried out under controlled conditions. Equipment used should be sterile. Retrieved tissue and cellular therapy products should be packaged using sterile containers and in a manner which will minimise contamination.

5.16 Collection documentation and records should include:

i. The donor identity;

ii. The date, time and place of the procedure;

iii. The identity of the person(s) performing the collection;

iv. The Cells collected, Donor and cell selection information, details of the physical examination of the donor prior to collection, where applicable;

v. The Tissue(s) collected, Donor and Tissue selection information, details of the physical examination of the donor prior to collection, where applicable.

5.17 Documented procedures for the transport of donations should be established, implemented and maintained. The procedures should ensure that the integrity of donations is protected and traceability is maintained.

Processing

5.18 Tissue and cellular therapy products should be processed in an environment and manner, which will prevent contact or cross contamination with tissues or cellular therapy products from other donors.

5.19 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any materials/component or documents not required for the current operation. Records should be maintained.

5.20 There should be documentation, which defines the material, procedures and controls used in the processing of product.

5.21 There should be procedures in place for all specific processing steps such as: antibiotic treatment, enzymatic digestion, the use of cell selection devices, and addition of additives or growth factors.

5.22 Records of processing should provide traceability and should be reviewed.

5.23 Tissues and cells should be correctly identified at all times. Each batch of tissues or cells shall be assigned by a unique identification number/batch number.

Treatment by Radiation

5.24 The exposure time, load configuration and radiation source, should be set to ensure that all products receive the specified minimum dose, with no part receiving more than the maximum specified dose.

5.25 Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour indicators should also be used to differentiate between products, which have been subjected to irradiation, and those, which have not.

Freeze Drying

5.26 Freeze drying records should be maintained including time, temperature and vacuum pressure at each step in the cycle.

Cryopreservation

5.27 Cryopreservation records should be maintained includes the time and temperature of the process.

Storage and Dispatch

5.28 Storage and dispatch processes should take place according to documented procedures to assure product quality during the storage period and to avoid mix-ups of products.

5.29 There should be a system in place to maintain and control the storage of products during their shelf life, including any transportation that may be required.

Control of Material

5.30 All handling of materials, such as receipt and quarantine, sampling, release, storage, and labelling should be performed in accordance with written procedures and, where necessary, recorded.

5.31 There should be a record of the receipt of material, which should include the description, date of receipt, quantity, supplier, and as applicable, lot or batch number, or a unique identifying number.

5.32 There should be approved quality control specifications for any material, which may have a direct effect on the quality of the product. As applicable, the specifications should include information such as description of the materials, instructions for sampling and testing or reference to procedures and qualitative and quantitative requirements with acceptance limits, including the key physical, chemical or biological properties and the criteria for test and limits.

5.33 Incoming materials should be quarantined and assessed to ensure that they meet approved specifications, before being released for use.

5.34 All materials should be stored under appropriate conditions. The status of any material should be evident from the visual appearance of its status label or by alternate equivalent systems.

5.35 Material, which does not conform to specifications, should be prevented from unintended use and its disposition recorded.

5.36 Materials should only be obtained from suppliers that have been evaluated and approved to ensure their ability to supply material meeting requirements. Records should be maintained.

Validation

5.37 Facilities, systems and equipment to be used should be qualified and quality control testing methods should be validated.

5.38 Facilities, systems equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

5.39 A validation study should be performed to show the effectiveness of the processing procedures. Generally, it is considered as acceptable that three consecutive processes within the finally agreed parameters would constitute a validation of the process. Refer to Annex 15 of PIC/S GMP Guide for Medicinal Product for further details on the approaches of validation.

CHAPTER 6: QUALITY CONTROL

6.1 Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released until their quality has been determined to be satisfactory. Quality Control is not confined to laboratory operations, but should be involved in all decisions, which may concern the quality of the product.

6.2 Samples for laboratory testing should be taken in a manner so as to avoid risk of microbial contamination of the product and mix-up of samples.

6.3 Documented procedures for quality control should be established, implemented and maintained. The procedures should ensure that the product meets specifications.

6.4 Solutions, which are in direct contact with the product during manufacture, should be sterile. If prepared in-house, they should be prepared in an appropriate environment and should comply with the requirements of the test for sterility.

Testing

6.5 Screening tests for donor suitability should be carried out by a competent laboratory. Where required by legislation the laboratory should be licensed or accredited accordingly.

6.6 Screening tests should be conducted according to documented procedures and should include (or refer to) the acceptance criteria for individual tests.

6.7 Tests should be performed using qualified equipment and methodology, which has been appropriately validated.

6.8 Testing of samples should take into account any factors (including pooling of samples), which may cause dilution sufficient to alter test results.

6.9 The quality of the laboratory testing should be regularly assessed by the participation in a formal system of proficiency testing, such as an external quality assurance program.

6.10 Test records should include at least the following data:

i. reference to the donation;

ii. details of equipment and materials used;

iii. references to the relevant specifications and testing procedures;

iv. test results, including observations and calculations;

v. date(s) of testing;

vi. identification of the person(s) who performed the testing;

vii. identification of the person(s) who reviewed the results, including a check of calculations, where applicable.

6.11 The retention time, storage conditions, quantity and expiry of donor test samples retained for retesting, should be determined on a risk basis and take regulatory requirements should be taken into account.

6.12 In order to ensure both the reliability of the manufacturing process and the quality of the final product, there should be a routine microbial contamination testing being carried out. In case of contamination is demonstrated, records should show the corrective action taken.

Product Release

6.13 There should be a system of quarantine for all products to ensure that they are not released for supply until they have met all defined acceptance criteria, including regulatory requirements. There should be a documented procedure, which defines the requirements for release of product for supply. Records of product release should be maintained.

6.14 The manufacturer should ensure that where cell and tissue products that do not meet the product specifications, a review of the product should be undertaken. Only when a risk based approach and/or regulatory requirements have been met can such products to be released.

6.15 Traceability must be ensured from donor to recipient (or until the removal of tissues or cells concerned) and vice versa. The traceability of the donor up to distribution is the responsibility of the manufacturer, while traceability from reception of the tissue or cells up to its use is the responsibility of the institution that receives it.

6.16 There should be a documented procedure, which defines the disposal requirements for product not suitable for use. Product, which is to be discarded, should be labelled to reflect its status, stored in a dedicated and secure area, and disposed of. There should be a record of discarded product, including the reason for discard.

CHAPTER 7: SUBCONTRACTING

7.1 Subcontracting should be correctly defined, agreed and controlled in order to avoid misunderstandings, which could result in a product or work of unsatisfactory quality. There should be a written agreement between the manufacturer and the subcontractor, which clearly establishes the duties of each party.

7.2 The subcontractor (e.g. testing, irradiation, pest control, cleaning, calibration, preventive maintenance) should be subject to an initial evaluation and regular review to ensure compliance with the quality system. Subcontracting should be covered by a formal documented agreement specifying the responsibilities of both parties. If applicable, subcontracted personnel should be trained in GTP/GMP or supervised whilst on the licensed premises. Records should be maintained.

7.3 The contract acceptor must not subcontract any work without written authorisation from the contract giver.

CHAPTER 8: COMPLAINTS & RECALLS

8.1 All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to promptly and effectively recall cell and tissue products known or suspected to be defective, from the market.

8.2 There should be a procedure established, implemented and maintained for the investigation of adverse events and product complaints.

8.3 A written procedure for product recall should be established, implemented and maintained. The procedure should specify the actions to be taken for all reasonable contingencies that may be anticipated. It should be capable of being put into operation at any time, and should include emergency and 'out of hours' contacts and telephone numbers. Distribution records should be maintained, to expedite the recall of any product or material whenever necessary.

8.4 The recall of a product should be followed immediately by an investigation of the reasons for the recall. The record of the recall should include all action taken from initial advice to final closeout.

GLOSSARY

Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.

Action limit
Established criteria, requiring immediate follow-up and corrective action if exceeded.

Alert limit
Established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Batch (or lot)
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

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

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

Clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Annex 1 of PIC/S Guide to GMP for Medicinal Products, for the Manufacture of sterile medicinal products.

Deviation
Departure from an approved instruction or established standard.

Distribution
Transportation and delivery of tissues or cells for human applications.

Donor
Every human source, whether living or deceased, of human cells or tissues.

Donation
Donating human tissues or cells intended for human applications.

Finished product
A medicinal product which has undergone all stages of production, including packaging in its final container.

Informed Consent
Written permission for donation of tissues and cells and for the ulterior use of them. The donor, one of his relatives or his legal representative must have understood the nature of the donation and the proposed use and accept any implied risks before giving legal consent.

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

Manufacture
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Manufacturer
May also be an establishment in this context

Processing/Production
All operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.

Qualification
Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Quarantine
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Recipient
The human person on or in which tissues or cells are used.

Release
The provision of tissues or cells by a tissue bank for transplantation/ implantation to a recipient

Return
Sending back to the cell and tissue establishment of a product which may or may not present a quality defect.

Specification
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described.

Starting material
Any substance used in the production of a medicinal products, but excluding packaging materials.

Tissue
All constituent parts of the human body formed by cells.

Traceability
The ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storage the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells.

Validation
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

REFERENCES

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5. FDA Guidance for Industry Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues and Cellular and Tissue-Based Products December 2011
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