

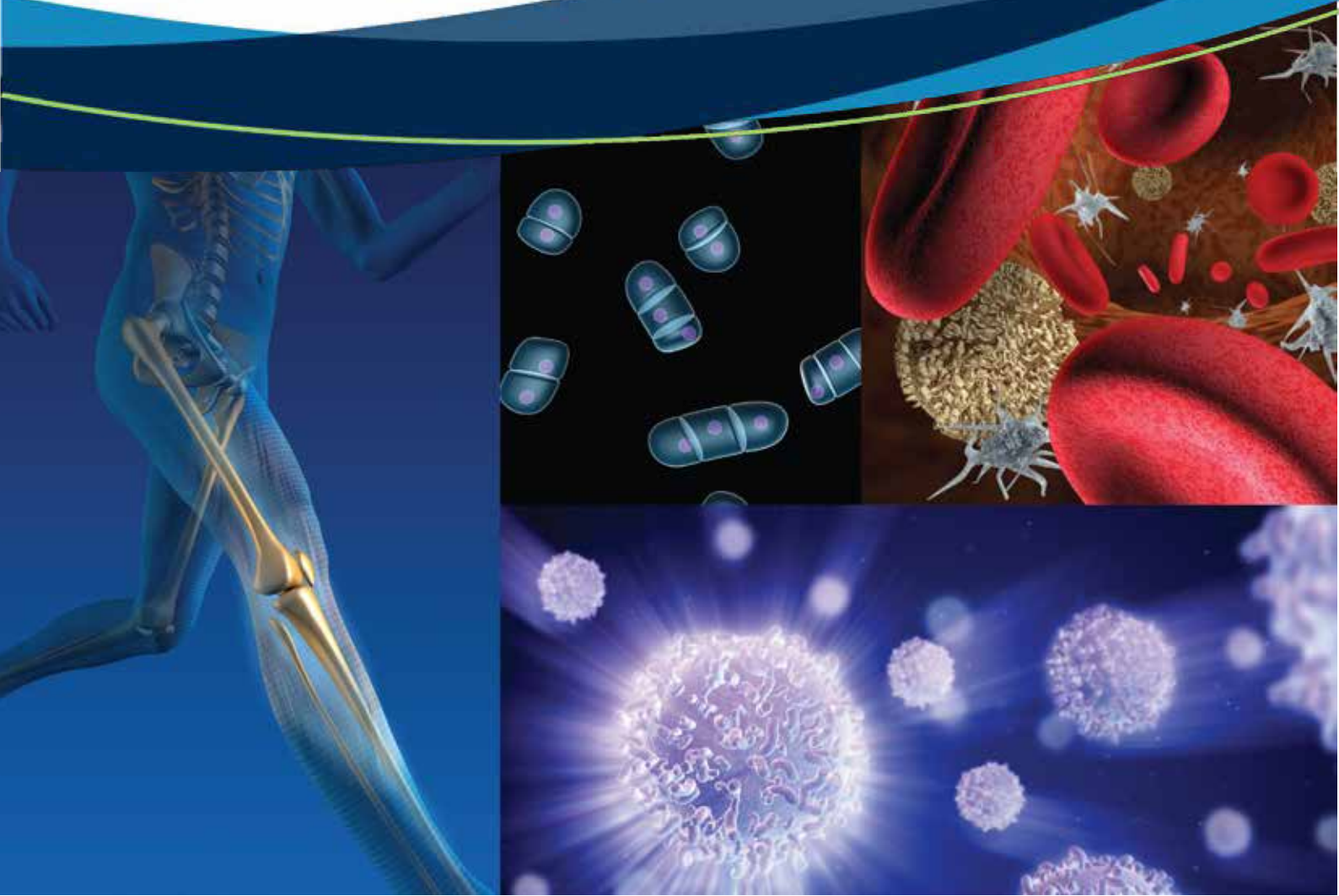


**Australian Government**  
**Department of Health and Ageing**  
Therapeutic Goods Administration

# Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products

Version 1.0 April 2013

**TGA** Health Safety  
Regulation



## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <[www.tga.gov.au](http://www.tga.gov.au)>.

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## Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Blood, Tissues and Cellular Therapy Products Group/Office of Manufacturing Quality	31/05/2013

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# Introduction

The Australian Code of Good Manufacturing Practice (GMP) for Blood and Blood Components, Human Tissues and Human Cellular Therapy Products (the Code) applies to Blood, Human Tissues and Human Cellular Therapy Products manufacturers that undertake the collection, processing, testing, storage, release for supply, and quality assurance of Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.

Manufacturing Licensing requirements are set out in Part 3-3 of the *Therapeutic Goods Act 1989* and include requirements to comply with both general and specific conditions of licence. It is a condition of licence that, Blood, Tissue and Cellular Therapy Products manufacturers observe the Manufacturing Principles determined under Section 36 of the Act. The Manufacturing Principles require these manufacturers to demonstrate that manufacturing practices comply with the Australian Code of Good Manufacturing Practice for Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products.

The TGA Manufacturing Regulator in consultation with Medsafe NZ and the Australian and New Zealand Human Blood and Human Tissue manufacturers undertook the revision of the Code. The structure of the document has been changed and is written in a less prescriptive style. It describes the way in which Human Blood and Blood components, Human Tissues and Human Cellular Therapies should be manufactured to ensure that they consistently meet specifications and are safe to use.

Therapeutic Goods Orders (TGOs) are established separately which set out specifications addressing product safety and efficacy. Manufacturers are required to develop dossiers for product groups to demonstrate that these TGOs are met.

This Code does not intend to deal with common or statute law requirements, such as Occupational Health and Safety, or the requirements for building construction.

It is not intended that the Code be used to replace procedures that are already in place, but that it be used to ensure that procedures in place meet the requirements of the Code. The Code sets out all the requirements for good manufacturing practice (GMP), which collectively ensure that the final human blood and blood components, human tissues and human cellular therapy products consistently meet specifications. While the Code describes benchmark practices that should be followed, alternative approaches are permitted provided it could be demonstrated that the intent of the Code is met in a timely and effective manner in order to meet quality objectives.

Although this Code covers all aspects of quality assurance systems and manufacture, it is not intended that any constraint should be placed upon the development or introduction of new concepts or technologies. It is acknowledged that there can be acceptable alternatives conforming to the same basic principles and achieving the same end. The manufacturer bears the ultimate responsibility for the products it manufactures.

To assist in the reading of this Code the following information is included:

- Table of Contents
- References and Recommended Standards and Publications
- A Glossary for Biologicals will be provided separately.

Although one of the objectives of this present revision was to prepare a document that would stand for several years it is recognised that amendments may be necessary to accommodate technological change, to clarify uncertainty or to specifically recognise important alternatives. Comments on the Code are therefore invited at any stage of the life of this edition.

# Quality management

## Principle

100. Quality management is that aspect of the overall management function, which directs and controls an organisation with regard to quality. This should include every aspect of manufacture to ensure that the quality objectives will always be achieved.
- 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 Code and incorporate risk management principles.
  - The fundamental concepts of Quality Assurance, Good Manufacturing Practice and Quality Control are inter-related and are described in the Code to emphasise their interaction and their primary importance to the production and control of therapeutic products.

## General

101. 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.
102. 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.
103. Management should define objectives pertaining to the quality, safety, efficacy, and applicable regulatory and legal requirements. Procedures should be available to detail how these objectives are to be met.
104. The system of Quality Assurance appropriate for the manufacture of products should ensure that:
- therapeutic products are designed and developed in a way that takes account of the requirements of this Code ;
  - production and control operations are clearly specified and Good Manufacturing Practice adopted;
  - managerial responsibilities are clearly specified;
  - arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

- all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
  - the finished product is correctly processed and checked, according to the defined procedures;
  - therapeutic products are not supplied before an authorised person has verified that they have been produced and controlled in accordance with the requirements and any other regulations relevant to the production, control and release of therapeutic products;
  - satisfactory arrangements exist to ensure, as far as possible, that the therapeutic products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life.
105. 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.
106. An authorised person within the quality unit should approve deviations and any action taken.
107. If applicable, corrective or preventive action should be taken to eliminate the cause of nonconformities in order to prevent recurrence or occurrence.

## Measurement and monitoring

108. The quality system should be reviewed to ensure ongoing effectiveness and to identify any improvements needed.
109. A program for self-inspection should be established, documented and implemented to periodically assess the effectiveness of the quality system.
110. Selection of auditors and conduct of self-inspections should ensure objectivity and impartiality. Auditors should not audit their own work.
111. Self-inspections should be recorded. Reports should include observations made during the inspections and, where applicable, proposals for corrective measures. Records of the subsequent actions should be maintained.
112. There should be procedures for the ongoing management and review of the corrective actions to ensure timely and effective implementation.
113. 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. Such reviews should be conducted and documented annually, taking into account previous reviews, and should include, as applicable:
- A review of material used for the product, especially those from new sources;
  - A review of critical in-process controls and finished product results;
  - A review of all products that failed to meet established specification(s) and their investigation;



- A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
  - A review of all changes carried out to the processes or analytical methods;
  - If applicable, a review of the results of the stability monitoring program and any adverse trends;
  - A review of all quality-related returns, complaints and recalls and the investigations performed at the time;
  - A review of adequacy of any other previous product process or equipment corrective actions;
  - The qualification status of relevant equipment and utilities, e.g. HVAC, water, gases, temperature controlled equipment;
  - A review of Contractual Agreements to ensure that they are up to date.
114. The manufacturer should evaluate the results of the product review and an assessment should be made whether corrective and preventive action or any revalidation should be undertaken.
115. The quality system should be reviewed by management at appropriate and defined regular intervals, to ensure the continuing suitability, adequacy and effectiveness of the quality system. Records should be maintained.

Management reviews should include:

- results of self-inspections;
  - complaints and recalls;
  - results from product reviews;
  - status of preventive and corrective actions;
  - deviations and any trends;
  - follow-up actions from previous management reviews;
  - the need for improvement to ensure the effectiveness of the quality system.
116. A formal change control system should be in place to evaluate and document all changes that may affect the collection, processing, storage, dispatch, quality control and quality assurance of product.
117. The potential impact of the proposed change on the quality of the product should be evaluated and should be approved by the quality manager, or delegate, before implementation.

# Personnel and training

## Principle

200. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of therapeutic products relies upon people. For this reason there should be sufficient competent personnel to carry out all the tasks in accordance with documented procedures. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training relevant to their needs.

## General

201. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
202. The manufacturer should have an organisation chart. Key personnel should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to suitably qualified designated deputies. There should be no gaps or unexplained overlaps in the responsibilities of personnel.

## Key personnel

### Quality and production nominees

203. The responsibility for quality and production should be allocated to persons specified on the manufacturing licence.
204. The nominees should be different persons, neither responsible to the other. They should have the authority to ensure that quality measures are employed in the manufacture (including testing) of product.
205. The quality and production nominees 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.
206. The Production nominee generally has the following responsibilities:
- to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
  - to approve the procedures relating to production operations and to ensure their strict implementation;
  - to ensure that facilities and equipment are maintained;
  - to ensure that the appropriate validations are done;

- to ensure that the required initial and continuing training of production personnel is carried out.
207. The Quality nominee generally has the following responsibilities:
- to approve or reject, as appropriate, materials and therapeutic products;
  - to evaluate process records;
  - to ensure that all necessary testing is carried out;
  - to approve specifications, sampling instructions, test methods and other quality procedures;
  - to approve and monitor any subcontractors and suppliers;
  - to ensure the maintenance of the quality department premises and equipment;
  - to ensure that the appropriate validations are done;
  - to ensure that the required initial and continuing training of the quality personnel is carried out.

## Training

208. 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.
209. Beside the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.
210. Personnel working in areas where contamination is a hazard, (e.g. clean areas or areas where infectious materials are handled), should be given specific training.
211. Visitors or untrained personnel should not be taken into the processing and Quality Control areas. If this is unavoidable, they should be given appropriate information in advance and they should be closely supervised.

## Records

212. Records should demonstrate that each staff member is trained and competent for the work practices they are authorised to perform.
213. Personnel should not be permitted to sign or initial a document unless they have been trained and assessed as competent in the work practices associated with the signature, and in the significance of the signature.
214. A register of staff signatures and initials should be established and kept up to date.

# Premises and equipment

## Principle

300. Premises, facilities and equipment should be located, designed, constructed, adapted, maintained, and suitable for its intended purpose. Their layout and design should aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, build up of dirt and, in general, any adverse effect on the quality of products.
- In order to minimise the risk of microbiological and particulate contamination, the manufacture of sterile products, or products required to have a low bioburden, should be subject to special environmental controls (e.g. Clean rooms, biological safety cabinets). Where required, applicable code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products should apply.
  - Premises, facilities and equipment which, is critical to the control of processing should be formally qualified.

## Premises

### General

301. The manufacture of products should be carried out under appropriate and specified conditions, and each area, including mobile sites, should be designed and maintained to suit the operation(s) to be performed.
302. Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
303. Steps should be taken in order to prevent the entry of unauthorised personnel to premises and restricted access areas. 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.
304. Where appropriate, contingency plans for breakdowns in critical services or equipment should be developed and regularly reviewed. For example, in the event of power failure, where necessary there should be access to a power source to allow the maintenance of critical services and equipment to permit the safe conclusion of activities in progress.
305. Lighting, temperature, humidity, air quality and ventilation should be appropriate and such that they do not adversely affect either the products during their manufacture and storage, or the correct functioning of equipment.
306. Premises for the manufacture of products should be specifically designed and used so as to avoid mix-ups or contamination.
307. Donor interview facilities should enable interviews to be conducted in private.

**Processing areas**

308. 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.
309. 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.
310. For products requiring control of microbiological bioburden, the manufacturer should establish and document the environmental requirements to which product is exposed during processing.
  - 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. Records of environmental monitoring should be kept.
311. Dedicated hand-washing facilities should be provided, and where appropriate, near working areas.
312. All persons entering processing areas should wear protective garments appropriate to the operations carried out.
313. Eating, drinking and smoking should be prohibited in processing areas.

**Storage areas**

314. Storage areas should provide adequate space, suitable lighting, and be arranged and equipped to allow dry, clean and orderly placement of stored material under monitored environmental conditions (e.g. temperature, light, humidity).
315. Storage areas should provide for suitable and effective segregation of quarantined, rejected and released material.
316. If despatch areas are physically different locations from the storage areas, there should be provision for appropriate storage while awaiting transport.
317. Storage facilities should be secured to ensure that quarantined or released product could not be tampered with or removed by unauthorised persons. Product storage facilities should not be used for any other purpose, where this poses a risk to the product.

**Equipment**

318. 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.
319. 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.
320. Repair and maintenance operations should not present any hazard to the quality of the products.
  321. 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 under appropriate conditions.
  322. Equipment should be uniquely identifiable. This identification should be traceable to all records pertaining to the equipment.
  323. Processing equipment should be used according to documented procedures.
  324. 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.
  325. Defective equipment should, if possible, be removed from production and quality control areas, or at least be labelled as defective.
  326. Actions to be taken when equipment does not meet specified parameters should be documented.
  327. Fixed pipe-work for gases and liquids should be labelled to indicate the contents and the direction of flow.
  328. Where controlled temperature conditions (including during transport, where appropriate) are required, the environment should be monitored as follows:
    - there should be temperature recording devices, and records kept and reviewed;
    - 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.
  329. Water systems used in the manufacturing should be sanitised according to written procedures. The quality of water should be monitored to ensure that it meets specification for its intended purpose.

## **Maintenance and cleaning**

330. Documented cleaning procedures for premises and equipment should be established, implemented and maintained. The following should be included:
  - the cleaning frequency;
  - the materials and equipment to be used;
  - records of cleaning should be maintained;
  - the use of only appropriate specified disinfectants;
  - the specific requirements for different equipment and surfaces; and
  - the dilution and the date of expiry of cleaning agents.
331. Cleaning agents should be selected on the basis of their suitability for intended use.

332. 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.
333. Where the removal of traces of material or product is important to minimise risk, cleaning methods should be validated.
334. Equipment already in use, which has been moved to another location, taken out of service, modified or undergone major repairs should be re-qualified before re-entry into service.
335. 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.
336. Preventive maintenance should be carried out on premises, facilities and equipment at defined regular intervals.
337. 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.

## Documentation

### Principle

400. The objectives of good documentation are to define the system of information and control, to minimise the risk of misinterpretation and error inherent in oral or casually written communication, and to provide unambiguous procedures to be followed.
  - Records should document the outcome of the activities carried out, and parameters measured. The system should provide a means of collating information, confirmation of performance and traceability.

### General

401. All processes and associated activities in the manufacture of product should be documented and the documentation controlled.
402. Documentation should be legible, accurate, readily identifiable and retrievable.
403. Documentation should not include superfluous data and should be written in the imperative (i.e. as instructions rather than statements of what is desired or should happen).
404. 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.
405. Documents should be approved, signed and dated by appropriate and authorised persons.

406. 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.
407. 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.
408. The manufacturer should establish, implement and maintain a procedure for controlling documents. The procedure should ensure that:
- documents are authorised;
  - documents are reviewed at regular intervals to ensure that they are current ;
  - multiple copies are controlled with a distribution list;
  - obsolete documents are removed from all points of issue and use, and controlled to prevent further use;
  - the version of a document should be uniquely identified.
409. The retention period and storage conditions for all documents should be defined and comply with legislation.
410. A system should be in place to ensure that records containing confidential information are secured from unauthorised access.
411. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.
412. 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.
413. Records electronically stored should be protected by back up. It is particularly important that the data are readily available throughout the period of retention.
414. Records should be maintained to demonstrate that the quality system has operated effectively and that the specified requirements have been met.
415. 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.



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# Control of material

## Principle

500. All materials, which may affect product quality and safety, should be controlled and meet defined specifications. The level of control of each material should reflect its use and potential risk to the product.

## General

501. 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.
502. 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.
503. 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 the following information:
- description of the materials;
  - instructions for sampling and testing or reference to procedures;
  - qualitative and quantitative requirements with acceptance limits, including the key physical, chemical or biological properties and the criteria for test and limits.
504. Incoming materials should be quarantined and assessed to ensure that they meet approved specifications, before being released for use.
505. Where appropriate, the maximum period of storage before re-assessment should be determined.
506. 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.
507. When not under the direct control of an authorised person, all labels for critical material should be secured in a locked storage area accessible only to authorised personnel.
508. Material, which does not conform to specifications, should be prevented from unintended use and its disposition recorded.
509. Any defect or problem associated with a material used in processing should be notified to the supplier and, if applicable, to the national therapeutic goods authority.
510. 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.

511. Reagents should be of appropriate quality and suitable for intended use.
512. Products returned from the customer and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory. They may be considered for re-supply only after they have been critically assessed by the Quality Manager or delegate in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-supply. Any action taken should be appropriately recorded.

## **Subcontracting**

### **Principle**

600. 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.

### **General**

601. 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 GMP or supervised whilst on the licensed premises. Records should be maintained.
602. The contract acceptor must not subcontract any work without written authorisation from the contract giver.

## **Complaints and recalls**

### **Principle**

700. 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 products known or suspected to be defective, from the market.

## Complaints

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

## Recalls

702. 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.
703. The national therapeutic goods regulatory authority should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.
704. 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.

# Collection and processing

## Principle

800. Collection and processing activities should follow clearly defined procedures; they should comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with regulatory requirements.
- Collection and processing should be conducted in a manner that minimises errors and the risk of particulate and microbial contamination.

## General

801. Collection and processing should be performed and supervised by competent people.
802. 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.

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## Collection

803. 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.
804. Donors should be selected according to documented procedures defining the selection criteria, infectious disease screening tests and any other relevant tests.
805. A procedure should be established, implemented and maintained for obtaining medical and other required statutory information prior to donation.
806. 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 not 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.
807. 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.
808. For Blood, Blood Components and Cellular Therapy Products, there should be a documented procedure for defining the medical assessment requirements including the acceptable timeframe for assessment, if not able to be done on the day of collection. The donor selection records, including informed consent, and final assessment, should be reviewed and recorded by an authorised person.
809. 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.
810. Where State/Federal requirements require consent for the collection of tissue or cells, the consent must be obtained. In exceptional circumstances where consent cannot be obtained at collection, the consent should be obtained before tissue or cellular therapy products can be released.
811. Procedures for donation should be established, implemented and maintained.
812. For Blood donations, the procedures should include requirements that donor selection interview and donor assessment should take place immediately before each donation and donor identification be confirmed before venepuncture.
813. At donation, any information, which may affect product quality, should be recorded.
814. The donor identification and any critical materials used should be traceable to the donation and associated records.
815. Collection areas should be organised to avoid any potential errors with donor records or labels.
816. The donation number or a unique identifier to the donor should be on all product and sample containers, and on donor records. This should be checked and the check recorded. Donation numbers should not be repeated, unless after a reasonable timeframe.
817. 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 investigated.
818. 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.
819. Collection documentation and records should include:
- The donor identity;
  - The date, time and place of the procedure;
  - The identity of the person(s) performing the collection;
  - For Cellular Therapy Products; : the Cells collected, Donor and cell selection information, details of the physical examination of the donor prior to collection;
  - For Tissues: the Tissue(s) collected, Donor and Tissue selection information, details of the physical examination of the donor prior to collection.
- § Confidentiality of the donor should be maintained.
820. If applicable, 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

821. 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.
822. Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, blood or blood component, tissue or cellular therapy product residues or documents not required for the current operation. Records should be maintained.
823. There should be documentation, which defines the material, procedures and controls used in the processing of product.
824. Records of processing should provide traceability and, as applicable, include:
- the date, time, venue, unique identifying donation number(s);
  - the identity of the person(s) performing and authorising critical steps;
  - the in-process quality control tests performed;
  - the equipment used;
  - all products prepared from each donation.
825. Where a process is applied to Tissue or Cellular Therapy Products from a number of donors at the same time (e.g. bioburden reduction) a unique batch number should be included in the records.
826. Process records should be reviewed and the review recorded.

827. There should be a system in place to maintain and control work in progress Tissue or Cellular Therapy Products, including any transportation required.
828. 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.

## **Treatment by radiation**

829. 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.
830. 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**

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

## **Cryopreservation**

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

## **Storage and despatch**

833. Storage and despatch processes should take place according to documented procedures to assure product quality during the storage period and to avoid mix-ups of products.
834. 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.

## **Validation**

835. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document. Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

836. The manufacturer should identify what validation work is required to demonstrate control of the manufacturing process. A risk assessment approach should be used to determine the scope and the extent of the validation.
837. Significant changes to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or reproducibility of the process, should be validated.
838. When any changes to the manufacturing process are adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.

## Process validation

839. Process validation should normally be completed prior to the release of the therapeutic product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine processing (concurrent validation). Processes in use for some time should also be validated (retrospective validation).
840. Facilities, systems and equipment to be used should be qualified and quality control testing methods should be validated.
841. Facilities, systems equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

# Quality control

## Principle

900. 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.

## General

901. 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.
902. Documented procedures for quality control should be established, implemented and maintained. The procedures should ensure that the product meets specifications.

903. 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.

## Sampling

904. Sampling should be conducted in accordance with approved written procedures that describe:
- the method of sampling;
  - the equipment to be used;
  - the number and quantity of the samples to be taken;
  - the type and condition of the sample container to be used;
  - any special precautions to be observed;
  - the storage conditions for samples;
  - Instructions for the cleaning and storage of sampling equipment.

## Testing

905. Screening tests for donor suitability should be carried out by a competent laboratory. Where required by legislation the laboratory should be licensed by the regulatory authority for therapeutic products.
906. Screening tests should be conducted according to documented procedures and should include (or refer to) the acceptance criteria for individual tests.
907. Tests should be performed using qualified equipment and methodology, which has been appropriately validated.
908. Testing of samples should take into account any factors (including pooling of samples), which may cause dilution sufficient to alter test results.
909. 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.
910. Test records should include at least the following data:
- reference to the donation;
  - details of equipment and materials used;
  - references to the relevant specifications and testing procedures;
  - test results, including observations and calculations;
  - date(s) of testing;
  - identification of the person(s) who performed the testing;
  - identification of the person(s) who reviewed the results, including a check of calculations, where applicable.



911. Laboratory test results, which do not satisfy, specified acceptance criteria should be handled according to documented procedures. The procedures should ensure that products not meeting acceptance criteria are quarantined, the out of specification investigated and if applicable, samples are re-tested.
912. 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 into account.
913. In order to ensure both the reliability of the manufacturing process and the quality of the final product there should be routine microbial contamination testing. Where contamination is demonstrated, records should show the corrective action taken.

## Product release

914. 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.
915. The manufacturer should ensure that where Tissue and Cellular Therapy Products 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.
  - Procedures for the management of products where all requirements have not been fulfilled should be established and maintained. Records including actions taken should be documented and maintained.
916. Products not released should be identifiable from those, which conform to specification and have received their final inspection. Appropriate records should be maintained. In the event that the final product fails release, and where applicable, a check should be made to ensure that other products from the same donation are identified. Products prepared from previous donations (where applicable) by the same donor should also be identified. There should be an immediate update of the donor record to ensure that the donor cannot make a further donation, if appropriate.
917. Where applicable, autologous Human Blood or Human Blood Components, Human Tissue and Human Cellular Therapy Products from donors with repeatedly reactive mandatory screening tests, with the intended purpose of reintroduction into that donor, records should be available to demonstrate the rationale for this use. Where applicable, product should be appropriately labelled. Authority for the release of this product should be documented.
918. 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.

# Computers

## Principle

1000. The introduction of computerised systems does not alter the need to observe the relevant principles given elsewhere in the Code. Where a computerised system is implemented, there should be no adverse affect on product quality and safety, or security and integrity of data.

## General

1001. Where a computer is used in connection with a step in the manufacture of the product, this should meet the same quality systems requirements for those manual functions, which it replaces.

1002. Computer equipment should be located in appropriate conditions where environmental factors cannot interfere with the system.

1003. The development and subsequent modification of manufacturing systems software should follow appropriate development methodology using a quality system approach.

1004. The development, implementation and operation of a computer system should be carefully documented at all stages and each step proven to achieve its written objective.

1005. When a computer system replaces a manual operation, records should demonstrate that the two systems have operated in parallel, and been found equivalent, before the computer system is used for the manual operation it replaces.

1006. The following documentation and records for the computer system should be available:

- a written protocol for the initial verification and prospective validation of the computer system;
- a general description (including diagrams as appropriate) of the system, its components and operating characteristics;
- a list of programs with brief description of each;
- diagrams of hardware layout and interaction, system logic or other schematic forms for manufacturing systems software packages (excluding Operating Systems and similar);
- a review of hardware and software “start up” and “normal run” fault logs during development and subsequent ongoing use of the computer system.
- records of evaluation data to demonstrate that the system is operating as stated (verification stage and ongoing monitoring);
- range of limits for operating variables;
- details of access security levels/controls;
- details of formal change control procedures;

- procedure for ongoing evaluation; and
  - records of operator training.
1007. Any change to an existing computer system should be made in accordance with a documented change control procedure. Records should include the following:
- the purpose and date of implementation of the change; and
  - checks to confirm the changes have been correctly applied; and
  - checks to confirm that the changes do not adversely affect the correct operation of the system.
1008. The following procedures and controls should be adopted for records retained by computer storage:
- records should be regularly and progressively backed up, and the backup retained at a location remote from the active file;
  - data collected directly from equipment and control signals between computers and equipment should be checked by verification circuits/ software to confirm accuracy and reliability;
  - interfaces between computers and equipment should be checked to ensure accuracy and reliability;
  - there should be documented contingency plans and recovery procedures in the event of a breakdown. The recovery procedures should be periodically checked for the return of the system to its previous state; and
  - the system should be able to provide accurate printed copies of relevant data and information stored within. Printed matter produced by computer peripherals should be clearly legible and, in the case of printing onto forms, should be properly aligned onto the forms.
1009. The system should include, where appropriate, built-in checks of the correct entry and processing of data.
1010. The confidentiality of donor information should be maintained.
1011. Data should only be entered or amended by persons authorised to do so. Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation and alteration of authorisation to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.
1012. Critical data entered manually into a computer system should be checked for accuracy by a second person. The persons carrying out the data entry and verification should be identifiable.
1013. The computer system should create an audit trail of any changes to electronic data. The record should include the time of each change, the nature of the change, and the identity of the person involved.
1014. Data should be secured by physical or electronic means against wilful or accidental damage. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.

1015. Critical computer-dependent systems should have alternate systems available in the event of a systems failure.
1016. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency.
1017. When the release of product is carried out using a computerised system, the system should recognise that only an authorised person can release the product and it should clearly identify and record the person releasing the products.

## References

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4. Recommendations on Validation Master Plan, Installation and Operation Qualification, Non-Sterile Process Validation, Cleaning Validation. PI 006-2, 1 July 2004. PIC/S.
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6. Guide to Good Manufacturing Practice for Medicinal Products. PE 009-8 15 15 January, 2009. PIC/S

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