Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Code of Good Manufacturing Practice

Human Blood and Tissues

24 August 2000

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

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PREFACE

Under the *Therapeutic Goods Act 1989* (the Act), a single national licensing scheme was introduced for manufacture of therapeutic goods. In February 1991, it was determined that any blood collection centre supplying plasma to a fractionation centre for further manufacture was required to be licensed.

The Australian Code of Good Manufacturing Practice (GMP) for Blood and Blood Products was published in July 1992, and audits commenced. This Code was based on the UK 1989 "Guidelines for the Blood Transfusion Services in the United Kingdom", which served as the foundation for the development of this first edition. A second edition Australian Code of GMP for Blood and Blood Components was published in December 1995.

For human tissues there was a delay to the process. Although human tissue was determined under the Act to be a therapeutic good, there was no appropriate Code of GMP for human tissue manufacture. In September 1995 the Australian Code of GMP for Human Tissues was published, and audits commenced in January 1996.

Although the regulation of product for blood banks has been limited only to plasma product for further fractionation, the regulations have now been extended to include all fresh blood products, and the TGA is the regulation agency. Recently the regulations for human tissues have been extended to include moderately and highly manipulated products, and a new Code of GMP was required to manage these changes.

For this reason, the human blood and tissue GMP licensing requirements required review to ensure that there would be a Code of GMP which would encompass all products within the blood and tissue groups. As the two Codes of GMP for both blood and tissue are similar for most of the quality system requirements, this new Code of GMP combines Human Blood and Tissues into one generic Code of GMP.

INTRODUCTION

Licensing standards are provided for in Section 36, Part 4 of the *Therapeutic Goods Act 1989*. These have been amended many times since being first determined in 1991. To meet the requirements of the Act, the blood and tissue banks must meet the requirements of the Manufacturing Principles, which reference the Australian Code of GMP for Human Blood and Tissues (the Code).

The current Code continues to include the elements of quality systems from the ISO 9000 series of standards and applies these principles to blood and tissue banking. It has been undertaken by the TGA in collaboration with the individual licensed sites. Many clauses were re-written to take into account changing national and international requirements and standards. Some prescriptive information has been removed, as it is intended that appendices and/or master file specifications will be written for specific product groups, and will be applied as additional requirements to this generic Code of GMP.

As with the previous Codes, which are being replaced, there will be some clauses that will not apply to the step in the manufacture of a product for which a particular site is licensed, and therefore the Code should be applied accordingly.

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. However, interaction with the GMP Audit and Licensing Section is strongly recommended before any major changes such as building reconstruction or the introduction of a computer system are made.

It is not intended that the Code be used to replace procedures and specifications that are already in place, but that it be used to ensure that procedures and specifications in place meet the regulatory standards established by the new Code. The Code establishes principles and objectives that must be achieved, and sets out benchmark practices that should be followed to meet the principles and objectives. Unless the practice in question is mandatory, (that is, the practice in question "**must**" be adopted under the Code), these practices may only be adopted or used in lieu of the benchmark practices if at audit the TGA finds that the alternative practice meets the objectives of the Code. In some circumstances, written approval of the secretary may be required.

Although this Code covers all aspects of quality assurance systems and manufacture, it is not intended that any restraint 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.

The Code has been written in a style intended to be readable rather than regulatory so that it may be used for both regulatory inspection and self-audit.

Most clauses in the Code specifying the practices that are to be adopted to achieve the stated principles and objectives are written using the term "should", which indicates that the particular requirement must be followed unless approval for alternative practices has been given. Where an alternative to the benchmark practices has been chosen, the manufacturer must demonstrate at audit that an equivalent level of quality assurance to meet the stated principles or objectives has been met. Where "**must**" is used, which is shown in bold type, an alternative practice is not acceptable, or permitted.

To assist in the reading of this Code the following information is included:
* Table of Contents
* Index
* Key Interpretations (from the Therapeutic Goods Act);
* References and Recommended Standards and Publications; and
* Glossary.

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.

KEY INTERPRETATIONS FROM THE THERAPEUTIC GOODS ACT 1989

The Act and Regulations should always be consulted for the exact wording and context.

"**manufacture**", in relation to therapeutic goods, means:

a) to produce the goods; or
b) to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

"**manufacturing premises**" means premises (including premises that comprise 2 or more sites):

a) that are for use in the manufacture of a particular kind of therapeutic goods; and
b) at which the same persons have control of the management of the production of the goods and the procedures for quality control.

"**manufacturing principles**" means the principles for the time being having effect under section 36 of the Act;

"**State law**" means a law of a State, of the Australian Capital Territory or of the Northern Territory.

"**therapeutic goods**" means goods:

a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:

    i) for therapeutic use; or
    ii) for use as an ingredient or component in the manufacture of therapeutic goods; or
    iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii); or

b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a)(ii)or(iii);

and includes goods declared to be therapeutic goods under an order in force under section 7 of the Act, but does not include:

c) goods declared not to be therapeutic goods under an order in force under section 7 of the act; or
d) goods in respect of which such an order is in force, being an order that declares the goods not to be therapeutic goods when used, advertised, or presented for supply in the way specified in the order where the goods are used, advertised, or presented for supply in that way; or
e) foods.

Section 1

QUALITY SYSTEM

Rationale

100 A quality system is the organisational structure, responsibilities, procedures, instructions, processes and resources for implementing quality management. The quality system should take into account the appropriate elements outlined in the Code.

The quality system should operate to ensure that all materiel, intermediate or finished product, or samples from any materiel or product relevant to product quality are tested to determine their release or rejection on the basis of their quality, and that facilities are chosen, personnel are competent, and procedures are in place, to ensure this quality.

General

101 Quality management is that aspect of the overall management function which determines and implements quality policy. There should be involvement in every aspect of manufacture to ensure that the quality criteria will always be achieved.

102 The quality system should provide a structured and organised approach for quality to be achieved, to ensure that each member of staff is responsible for the quality of their work.

103 There should be an organisational quality policy in place. Management should take measures to ensure that the quality policy is understood, implemented and maintained at all levels of the organisation.

Quality objectives

104 From the organisational quality policy, management should define objectives pertaining to the quality and safety of product, and to meet regulatory and legal requirements. Procedures should be available to detail how these objectives are to be met.

Organisational Structure

General

105 The responsibility, authority and reporting structures **must** be clearly documented.

106 The level and scope of responsibility should be formally defined for each group or for individual members of staff. The degree of authority to evaluate quality problems and to initiate, recommend and provide effective corrective actions should be determined and should be commensurate with the responsibility.

Director

107 It is ultimately the responsibility of the Director to manage the quality system and its implementation, and in conjunction with staff with specialised skills, to develop, compile and record the policy for the organisation.

Quality Assurance and Production Nominees

108 The responsibility for quality assurance and production **must** be allocated to a person(s) as required by the manufacturing licence. Those nominated for these responsibilities should be different persons, neither responsible to the other, unless other arrangements acceptable to the TGA are made.

The licensed site **must** be able to demonstrate supervisory control over any manufacturing step(s) carried out at another site.

109 The quality assurance nominee (manager) **must** have the necessary independence and authority to ensure that quality measures are employed in the manufacture (including testing) of product. This person should report to the Director.

110 The production nominee (manager) **must** have the necessary authority to control the manufacture of product.

111 The quality assurance and production nominees should usually have a relevant tertiary level qualification, (eg. in medicine, science, medical laboratory science, nursing), and have had practical experience, at management level and under professional guidance, in the manufacture of blood and/or tissue products, in accordance with GMP requirements.

112 Where operational events and quality policy conflict, the Director (or nominee), **must** have the authority to make a decision to resolve the conflict. The circumstances and the decision taken should be recorded.

Resources and Personnel

113 There should be sufficient resources at all levels to enable objectives to be met effectively and efficiently.

Quality system requirements

Documentation

114 Documented procedures of the quality system **must** be available to enable the effective implementation of the quality objectives.

115 There **must** be a document or documentation defining the overall quality system and quality objectives.

Change control

116 A system **must** be established and maintained to identify, document, review and approve all process and product changes. The results of the review **must** be recorded and any changes or modifications approved by the quality assurance manager, or nominee, before implementation.

Monitoring systems

General

117 There should be a system(s) in place to monitor and improve the quality system. Documented procedures should define any monitoring systems required to facilitate continuous improvement.

Internal audit

118 A program for internal audits **must** be developed to periodically review the operation and effectiveness of the quality system, including all manufacturing steps.

119 The procedure for internal audits **must** include the frequency and requirements for conducting audits, and recording and reporting of results, including the scope of the audit.

120 Audits should be performed by trained personnel who do not have direct responsibilities for the processes being audited. Training requirements for auditors should be defined and documented.

Corrective action

121 There **must** be a system in place which ensures that product which does not conform to specifications is under control and is prevented from unintended use.

122 The system **must** ensure that deviations from the documented quality system, and manufacturing procedures, are recorded, assessed, corrected effectively and if necessary, new procedures implemented.

Management Review

123 The quality system **must** be reviewed by management at appropriate and stated regular intervals, to ensure the continuing suitability, adequacy and effectiveness of the quality system.

124 The review by management should evaluate any changes to the quality system, and should include the monitoring systems in use and any resultant action(s) taken.

125 The management review process **must** be documented and records of the review maintained.

Section 2

PERSONNEL AND TRAINING

Rationale

200 The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of product relies upon people. For this reason there **must** be competent personnel to carry out all tasks in accordance with documented procedures.

General

201 Areas of responsibility and lines of authority of key personnel should be identifiable on an organisational chart.

202 The names and job descriptions of key personnel **must** be documented.

203 Personnel **must** be shown to be competent in their assigned duties.

204 Key personnel **must** have adequate authority to discharge their responsibilities. Suitable persons should be deputised to carry out the duties and functions of key personnel in their absence.

205 There should be no unexplained or conflicting overlaps in the responsibilities of those concerned with GMP. The responsibilities placed upon any one person should not compromise the effective execution of assigned duties.

206 The key personnel, responsible for managing and supervising manufacture, quality assurance and quality control, must have the necessary competencies to ensure that blood or tissues meet the required standards and specifications consistently**.**

Training

207 Learning and development programs **must** be developed in accordance with identified needs. Programs should be documented and include on-going training and refresher training.

208 Personnel **must** be made aware of the principles of GMP relevant to their duties.

209 There should be a formal mechanism for determining the competency of the workplace trainer and assessor to deliver training and assess the competency of the trainee.

210 For personnel at sites remote from the licensed site, who undertake a step in manufacture, (such as at tissue retrieval), there **must** be documentation to demonstrate that the work practice(s) undertaken are under the control of, and acceptable to, the licensed site.

211 All personnel **must** be shown to have undergone learning and development for the documented procedure relevant to the work practice being performed. There **must** be records to show that all personnel have acknowledged subsequent changes to a procedure(s).

212 Learning and development related to sanitation and personal hygiene should be included in staff learning and development programs.

Records

213 Records **must** demonstrate that each staff member is trained for the work practices they are authorised to perform. The records should include the following:

- the learning and development program set up to meet individual needs;
- the timeframe required to complete the program; and
- assessment and any action taken if expected competence was not achieved.

214 Personnel **must** 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.

215 A register of staff signatures and initials **must** be maintained. Entries should be updated at regular stated intervals and the previous records archived.

Section 3

BUILDINGS AND FACILITIES

Rationale

300 Buildings should be located, designed, constructed, utilised and maintained so as to ensure protection of the product, to minimise the risk of manufacturing error and to permit efficient cleaning and maintenance.

General

301 The manufacture of products should be carried out under appropriate and specified conditions, and each area should be designed to suit the operation(s) to be performed.

302 Buildings, including receiving and despatch areas, should be designed, constructed and maintained so as to protect against the effects of weather or ground seepage and the entry of vermin, birds and pests. Cavities and voids should not be present unless sealed or provided with access for pest control.

303 Buildings **must** be secured against entry of unauthorised personnel. 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, there should be access to an emergency power source to allow the maintenance of critical services and equipment, and in the event of power failure, to permit the safe conclusion of activities in progress.

Environmental control

305 The environment **must** be suitable for the particular operation carried out. Processing steps **must** take place in an appropriately controlled environment.

306 Where critical materiel is being stored, temperatures or other critical parameters **must** be monitored and demonstrated to be in accordance with the manufacturer's instructions.

307 Product manufactured in an "open" system **must** have the environmental conditions and monitoring of the area clearly defined, (such as for a "clean room" or laminar flow cabinet). Where environmental conditions are required to be monitored, records **must** demonstrate that the area is monitored frequently for microbiological contamination and air control.

308 Access to environmental-controlled areas should be from corridors or other manufacturing areas. Where internal doors are a barrier to avoid cross-contamination, they **must** be kept closed when not in use and signposted to that effect.

Floors, walls and fittings

309 Floors and walls in manufacturing areas should be free from cracks and open joints. Floors and walls should be non-porous, smooth, non-slip and resistant to cleaning agents used.

310 Joins between walls and floors should be easy to clean, adequately sealed and, where appropriate, coved to form a smooth curve between floor and wall.

311 Wood should be avoided as a material of construction or support for equipment, especially where it may be wetted. Surfaces (including undersurfaces where appropriate) should be sealed with a coating that is resistant to chipping and is easily cleaned.

Cleaning

312 The documented cleaning procedure for all areas **must** be available to staff or cleaners of those areas. It should detail the following information:

- the authorised contact for the cleaning procedures;
- the areas to be cleaned, the frequency and specific requirements for individual areas;
- the materials and equipment to be used; and
- the methods used to decontaminate cleaning equipment.

313 Cleaning equipment, which generates contamination such as particles, dust or aerosols should be avoided where possible.

314 Documentation describing the correct storage and use of disinfectants should emphasise the following:

- the use of only specified disinfectants and when rotation of disinfectant type should occur;
- the specific requirements for different equipment and surfaces;
- the correct choice of dilution for purpose; and
- the date of expiry.

315 Where the removal of traces of product is critical, evidence should demonstrate that methods are effective.

316 Waste material should be collected in sturdy, labelled containers and disposed of safely at frequent intervals.

Goods receipt and storage areas

317 Storage areas **must** provide adequate space, suitable lighting, and be arranged and equipped to allow dry, clean and orderly placement of stored material under monitored temperature conditions.

318 Storage areas **must** provide for suitable and effective segregation of quarantined and released materiel. There should be clear demarcation in the storage of similar materiel.

319 There **must** be documentation to detail the receipt and storage of material and products within the premises.

Manufacturing areas

General

320 There should be easy access to areas around equipment for cleaning purposes.

321 Dedicated hand-washing facilities should be provided, and where appropriate, near working areas.

322 All persons on site should wear garments appropriate for the work carried out.

323 Eating, drinking and smoking should be prohibited in manufacturing areas.

Donor areas

324 Donor interviews **must** be conducted in a manner which ensures auditory privacy and privacy of donor information.

325 The blood collection area should be organised so as to avoid the possibility of errors in the collection and labelling of blood and samples.

326 Tissue retrieval **must** be carried out under conditions which are designed to exclude the risk of environmental contamination. When tissue is collected at a site not under the direct control of the licensed site, documented procedures should provide details of any specific requirements which will ensure that the quality of the product will not be compromised, such as condition of premises and environment.

327 Dedicated collection and retrieval areas should be designed to facilitate thorough and effective cleaning of all surfaces.

Despatch

328 If despatch areas are physically different locations from the storage areas, there **must** be provision for appropriate storage while awaiting transport.

Mobile blood collection sites

329 Premises used for mobile donor sessions **must** be at an approved location, and of sufficient size and construction to allow acceptable manufacturing practices. Each site **must** have documentation detailing the layout of the site to ensure that the site is set up according to an approved plan.

330 A mobile site should only be acceptable if the following conditions have been met:

- environmental control meets defined requirements;
- there is adequate lighting and electrical supply for equipment in use;
- the furniture and equipment is arranged for safety and logical work-flow;
- the refreshment facilities for donors and staff is separated from the manufacturing areas;
- there is an adequate donor interview area;
- product is stored according to specifications;
- there is provision for record storage, to prevent tampering or loss;
- there is availability of staff hand-washing facilities;
- there is reliable communication to the supervising site; and
- there is adequate waste containment.

Section 4

EQUIPMENT

Rationale

400 Equipment should be suitable for its intended purpose, maintained appropriately and technically applicable for use, to give assurance that product is manufactured to required specifications.

General

401 The product **must** be manufactured using equipment in good repair, within an appropriate and specified environment.

402 Equipment **must** be uniquely identifiable. This identification must be traceable to all records pertaining to the equipment.

403 To ensure adequate cleaning of equipment, equipment should be either clear of walls and floors, or movable. Documented procedures should detail cleaning requirements.

404 Where equipment is used for more than one processing batch or session, procedures **must** define the terms for re-use, including cleaning and sterilisation protocols (where applicable). Records **must** be in place to demonstrate compliance.

405 Contingency plans should be 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 equipment.

Qualification and validation

406 Equipment which is critical to the control of manufacture **must** be formally commissioned. There should be protocols which address installation (IQ), operational (OQ), and process qualification (PQ) of equipment, and IQ and OQ should include the development and implementation of procedures for operation, calibration, maintenance, and cleaning.

407 Equipment already in use, which has been moved to another location, taken out of service, modified or undergone major repairs, **must** be formally approved for re-entry into service.

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

409 Where older equipment has not previously been commissioned there **must** be evidence to demonstrate that it is acceptable for the processes for which it is used.

410 Where software has been introduced or changed on equipment, it should be validated prior to use, according to qualification protocols.

Preventative Maintenance

411 Preventative maintenance should be carried out on equipment at stated regular intervals. The checks should consist of routine in-house monitoring at short intervals, with a more formal service by the manufacturer or equivalent equipment specialist at regular longer term intervals. Maintenance may be performed by either trained personnel or external contractors.

412 Documented maintenance procedures and records should include the following:

- the name of the contractor;
- the details and frequency of preventative maintenance requirements;
- any deviation from the procedure;
- action to be taken if equipment maintenance requirements cannot be met; and
- records of preventative maintenance, including a statement or authorising signature as to the condition of the equipment following the service.

Calibration and validation

413 Each item of equipment used in manufacture, which measures or depends on a physical parameter **must** have a record indicating that it has been calibrated and/or checked according to established procedures.

414 Performance specifications for calibration purposes should be based on those provided by the manufacturer or official standards.

415 There **must** be a procedure to describe the calibration of equipment. It should include the method to be used, frequency of calibration and action to be taken when results deviate from defined acceptance limits. Parameters being tested should approximate the way the equipment is used operationally.

416 Records of any equipment calibration should indicate actual results observed and the criteria for ranges of acceptance.

417 Where practicable, each item should bear a label or tag indicating that calibration has been performed and when the next calibration is due. Evidence **must** demonstrate that the particular calibrating devices used are themselves accurate. When contractors have been utilised, the accuracy of their equipment should be guaranteed by a certification agency.

Specific equipment

Refrigeration equipment

418 Product storage facilities **must** be secured to ensure that quarantined or released product cannot be tampered with or removed by unauthorised persons. Product storage facilities should not be used for any other purpose.

419 Where controlled temperature storage is required, the environment should be controlled, monitored and recorded, as follows:

- there should be temperature recording devices, and records should be under regular stated review;
- where applicable, there should be an alarm and/or audible visual signal to indicate that a storage temperature control system has failed. The system should permit resetting only by authorised personnel, and should be checked at regular stated intervals;
- refrigerators and freezers should be defrosted regularly and cleaned; and
- in the event that a refrigerated storage facility is shut down a total clean should occur.

420 Coolants, lubricants and other chemicals such as thermal probe solutions should be evaluated and approved by a formal process.

Irradiation equipment

421 There **must** be a documented procedure to define the requirements for irradiation of a product.

Barcode equipment

422 Where barcode numbers are produced by the site, there **must** be a system to assure accuracy and reliability prior to release.

423 Barcode readers, including scanners and wands, **must** be checked at regular stated intervals and the results recorded.

Section 5

DOCUMENTATION

Rationale

500 The objectives of thorough 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.

General

501 All processes and associated activities in the manufacture of product **must** be documented and the documents controlled.

502 Documents **must** be legible, readily identifiable and retrievable. They should not include superfluous data and should be written in the imperative (ie. as instructions rather than statements of what is desired or should happen). Documents should not be handwritten, and when computer-generated, should be authorised by electronic signature or by signature on a separate, but linked, document.

503 Documentation should clearly identify the way in which it is to be used, and by whom it is used. Authorisation by signature may appear on a separate but linked document. It should include, or be identifiable to, the issuing site, and should include the following information:

- the unique number identifying the document;
- the version number and date effective; and
- the page number (of the total pages of the document).

504 Documentation **must** be available to staff to cover activities at all locations, including any retrieval site(s) carrying out activities for a licensed site, or any licensed site manufacturing for a supervising licensed site.

505 Any correction to a document should permit the reading of the original information. Corrections should be handwritten clearly and legibly in permanent ink, and signed and dated by an authorised person. To permit clear interpretation of changes made to documents, they should be re-issued after a practical number of changes have been made.

506 Where appropriate, documents should be introduced after a formal commissioning and training period.

Control of documentation

507 The system for document control **must** identify the current revision status of any document and the holder of the document.

508 The system in place **must** demonstrate that all controlled documents meet the following criteria:

- they are current and authorised;
- they are reviewed at regular intervals;
- multiple copies are controlled with a distribution list; and
- obsolete documents are removed from all points of issue and use, and controlled to prevent further use.

509 Changes to documents should be acted upon promptly. They should be reviewed, dated and signed by the authorised person(s), and formally implemented. There **must** be records to show that all relevant personnel have acknowledged subsequent changes to a procedure(s).

Storage and retention

510 Documented procedures should be established and maintained for identification, collection, filing, storage, retrieval and maintenance of any working documents.

511 Master copies of obsolete documents **must** be archived in a secure and safe environment.

512 Length of time of storage of obsolete documents **must** be defined and be consistent with statutory requirements.

Section 6

RECORDS

Rationale

600 The objective of record management is to document the outcome of the processes carried out, and parameters measured, with respect to all manufacturing steps. The system should provide an unambiguous means of collating and providing confirmation of performance and traceability.

General

601 Records **must** be developed, maintained and reviewed, to demonstrate that the quality system has operated effectively and that the specified quality has been achieved.

602 The record system **must** demonstrate that there is a complete history of the donation from donor selection/registration to the release for use as final product, and should include:

- identification and traceability to all critical manufacturing steps;
- traceability to a location, including transportation between sites; and
- accountability for records which have been withdrawn and archived.

603 Records should clearly identify the way they are to be used, and should indicate, or link to, the following information :

- the name of the issuing site;
- the unique number identifying the record, including version; and
- the page numbers (of the number of total pages).

Authorisation by signature may appear on a separate but linked document.

604 There **must** be a documented system in place to enable traceability of the product to the end-user.

Donor sessions

605 At donation, any information which may affect product quality, **must** be identified on the donation record.

606 Where donors are able to sign the consent and medical information record, the donor signature **must** be witnessed and signed by an authorised interviewer.

607 Where a donor cannot sign a record of consent or medical declaration, such as for cadaveric donors, the person(s) signing on behalf of the donor **must** be authorised to do so, for both the consent and medical information. The signature, where applicable, should be witnessed by an authorised person(s). The procedure **must** be in accordance with applicable statutory requirements.

608 Any review of the medical history records of a donor **must** be carried out by an authorised and nominated person. A record **must** identify the signature of the reviewer and the date of review. The procedure **must** be in accordance with applicable statutory requirements.

609 The donation record **must** include the venue, the date, and the unique number linking the donor to the donation.

610 The record system **must** provide traceability of critical materiel used in donor retrieval or blood collection directly to the donation.

Collection/retrieval and processing records

611 There should be a documented system in place to ensure that records are regularly monitored to detect and eliminate potential problems in the steps to final product.

612 Records **must** demonstrate the following information:

- the date, and where applicable, the time of the procedure;
- the identity of the person(s) performing and authorising critical steps;
- the inspection checks and quality control tests performed; and
- the equipment used.

Final product

613 Records **must** demonstrate that all inspection checks, quality control tests, methods and equipment, results and authorising signature(s), are in place.

614 Records **must** demonstrate that products not released for issue, can be distinguished from those which conform to specification and have received their final inspection.

Storage, retention, archiving and disposal

615 Except where legislation requires longer retention periods, the complete records pertaining to each product, including critical master data such as donor assessment and processing work sheets, should be retained for a period defined by the blood or tissue bank. This period **must** be at least a minimum of twenty (20) years after the date of manufacture of the product. The requirement for disposal should be defined.

616 The record system **must** give assurance that the following conditions can be met:

- all documents are securely stored to prevent illicit copying;
- there is ready access to records during the storage period;
- distribution records are available when a rapid recall is required; and
- records kept in other than original form are readable, accessible and reproducible. Methods for verifying authenticity should be specified.

617 There **must** be a documented system which details the appropriate requirements for the method of copying and archiving documents according to the type of record system in use.

618 Pest control records **must** be available for areas where paper records are stored.

Product complaints and recall

619 Distribution records **must** be readily available, to expedite the recall of any product or materiel whenever necessary.

620 Records of product complaints **must** be held for at least twenty years, after the date of manufacture of the product or batch of materiel.

Donor deferral

621 The record system **must** demonstrate that the deferral of a donor is recorded in accordance with documented requirements and actioned, where relevant, as soon as practicable.

622 The record system **must** demonstrate that a permanently deferred donor cannot donate on another occasion, unless the donor has been appropriately re-assessed and approved again to donate, according to documented guidelines.

623 Records should detail the reasons for acceptance of a donor previously deferred.

Corrective action

624 When product quality does not meet specifications, or when deviations from procedures occur, records **must** demonstrate that effective corrective action has been taken.

Security

625 The storage conditions of records, particularly paper and film, **must** prevent tampering, loss or degradation.

626 A system **must** be in place to ensure that records containing confidential donor and recipient information are secured from unauthorised access.

Computer records

General

627 The acquisition and subsequent modification of manufacturing systems software should follow the quality management system requirements of ISO 9001, or equivalent acceptable development methodology. Vendors should be asked to provide written assurance that software development or modification has followed a quality management system.

628 Persons responsible for the design, introduction and regular review of a computer system should have appropriate expertise.

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

630 A logic flow diagram or schematic plan for software development should be prepared to allow critical evaluation against system design criteria.

Documentation

631 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.

632 The documented procedures for the computer system should include the following information:

- the objectives of proposed computer system;
- the data and flow of data to be entered and stored;
- the information to be produced and the limits of any variables;
- the operating and test program(s);
- examples of each document produced by the program;
- instructions for testing, operating and maintaining the system; and
- the name of the person(s) responsible for computer development and operation.

633 The following documentation and records for the computer system **must** be available:

- a written protocol for the initial verification and prospective validation of the computer system;
- a general description 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.

Validation data

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

635 Any change to an existing computer system **must** be made in accordance with a documented change control procedure. Records should demonstrate that:

- each documented change includes the purpose and date of effect; and
- the changes have been checked to confirm the correct application.

Data control

636 The following procedures and controls **must** be adopted for records retained by computer storage:

- records **must** 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 **must** be checked by verification circuits/ software to confirm accuracy and reliability;
- interfaces between computers and equipment **must** be checked to ensure accuracy and reliability;
- there **must** 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 **must** be able to provide accurate printed copies of relevant data and information stored within. Printed matter produced by computer peripherals **must** be clearly legible and, in the case of printing onto forms, should be properly registered onto the forms.

637 The system in place **must** ensure that any critical data being entered into the computer manually are accurate and acceptable. Critical data, which affect the release of quarantined product, should be verified by a second verification step. The person(s) carrying out the data entry and verification should be identifiable.

638 A hierarchy of permitted access to enter, amend, read, or print out data **must** be established according to the nature of the change and the operator involved. Suitable methods of preventing unauthorised entry should be in place.

639 The computer system should create a complete time stamped record of the nature of change(s), and the operator involved, for all critical entries and amendments to the data base.

640 Critical computer-dependent systems should have alternate systems available in the event of a systems failure.

641 Unauthorised access to data identifying a person's name and/or address linked with health information about that person, that is transmitted over any public medium, or stored on the system that is externally accessible, **must** be prevented.

Section 7

CONTROL OF MATERIEL

Rationale

700 The use of dependable and verified starting materiel is a key element in ensuring that products prepared from blood and tissue are of consistent and acceptable quality.

General

701 There **must** be a documented procedure which defines the system for the assessment of critical materiel for use in the manufacture of a product.

702 There **must** be a record of the receipt of all materiel, which should include the name and type of materiel, date of receipt, quantity, name of the supplier, lot or batch number, or a unique identifying number.

703 There **must** be approved quality control specifications for any materiel which may have a direct effect on the quality of the product. Where applicable, the specifications should include the following information:

- the standard name and unique code reference used in records;
- the key physical, chemical or biological properties;
- the criteria for test and limits, physical appearance, characteristics and storage conditions;
- any sampling plans or sampling instructions and precautions; and
- a requirement that only approved critical materiel may be used.

704 Materiel requiring authorisation for use should be approved by a nominated authorised officer. The officer should maintain an inspection program and, where relevant, take samples for testing from any materiel relevant to product quality and should investigate any deviations, discrepancies or test failures.

705 The status of any materiel should be evident from the visual appearance of its status label. Materiel of uncertain status should be appropriately labelled by, eg. a "hold" or "quarantine" label.

706 Materiel **must** be stored according to the instructions of the manufacturer.

Suppliers and sub-contractors

707 There should be documentation to demonstrate that suppliers of critical materiel have been formally approved.

708 There **must** be defined specifications for critical materiel agreed between the supplier (including testing laboratories), and the site. There should be a regular stated review of the specifications to ensure that they meet the current requirements.

709 Critical materiel should not be used until it has been verified for conformity with its specification. There should be an agreement with the supplier on the limits of rejection in advance of the supply.

710 The supplier of a registered product appearing on the Australian Register of Therapeutic Goods (ARTG), should be required to provide information that it conforms to the terms of the registration.

711 Suppliers of critical materiel should be evaluated to assess their ability to supply materiel meeting requirements. This may be done by assessing supplier compliance with quality systems, direct audit or by accreditation to an appropriate quality standard.

712 Purchasing documentation should contain a clear description of materiel or services ordered.

Starting materiel

General

713 On receipt of materiel, records **must** demonstrate that checks have been performed to ensure that materiel meets agreed specifications. Where applicable, validation may be required to assess acceptability.

714 Where appropriate, expiry dates should be assigned to materiel, to indicate the maximum storage time under a given set of conditions.

Reagents

715 There **must** be documentation demonstrating that reagents conform to requirements and appropriate quality control.

716 Solutions used in ex-vivo manufacture of product should be labelled as sterile and for therapeutic use. Where solutions are not labelled accordingly, there **must** be records to demonstrate that the solution in use has been found to be sterile by a TGA-approved sterility testing laboratory.

Collection packs

717 To ensure the integrity of a sterile collection pack system, each pack should be inspected before use.

718 Where the outer packaging of collection packs has been opened and re-sealed, the instructions of the manufacturer **must** be followed. The procedure should detail measures to ensure that expired packs cannot be used.

Labels

719 The label on materiel **must** clearly identify the materiel and its status for use.

720 The design and use of finished product labels **must** comply with information in the current Therapeutic Goods Order (TGO) for labelling. Where applicable, finished product labels placed on donations **must** comply with individual State or Territory law. A file copy of all labels should be retained.

721 The adhesive used on labels should be specified, and should not have a direct effect on the product or compromise the quality of the product.

722 Label batches should be checked for printing errors and all errors should be recorded. Duplicate number sets of barcode donation numbers **must** not be in use.

723 Where barcoded donation numbers are printed on demand, there **must** be a system, to ensure that the labels meet stated specifications.

724 Where individual sets of unique identifying numbers are used on a donation, a documented procedure **must** include the requirement to reconcile the numbered labels issued, with those remaining.

725 When not under the direct control of an authorised person, all labels for critical materiel **must** be secured in a locked storage area accessible only to authorised personnel.

726 There **must** be a system to ensure that donation numbers are repeated only within a reasonable timeframe, and/or under stated circumstances. For plasma donations to a fractionation centre, the donation numbers **must** not be repeated within a period of two years.

In-process materiel

727 There **must** be a system of quarantine for all materiel to ensure that it cannot be released for issue until approved documentation indicates that it conforms to the requirements for use.

728 Materiel not released for issue **must** be clearly distinguishable from materiel demonstrated to conform to the requirements for release.

729 The area where materiel is stored **must** ensure that there is:

- suitable and effective separation of quarantined and released materiel;
- clear demarcation of similar, but different, materiel; and
- a segregated area for rejected or returned materiel.

730 Materiel **must** be transported between sites in a manner that ensures the integrity and status of the materiel is maintained.

731 There **must** be a documented procedure to ensure control over the storage of product during its shelf life, including any transportation that may be required.

732 Storage and handling conditions **must** be monitored, and results recorded and analysed, to demonstrate the suitability of areas for their use.

Non-conforming materiel

733 Any defect or problem associated with a therapeutic good on the ARTG, or with any critical materiel used in the collection, handling, processing and testing of the manufactured product, that could harm the recipient or donor, **must** be notified as soon as practicable to the TGA and, where applicable, the relevant sponsor. Where the problem relates specifically to a medical device, a report **must** be filed with the TGA's Medical Device Incident Reporting and Investigation Scheme (IRIS).

Recall of products

734 There should, at all times, be a person, group or committee nominated to assess the need for, and where necessary, to initiate and coordinate product recalls.

735 A written procedure for product recall, based upon the Australian Uniform Recall Procedure for Therapeutic Goods and the requirements of the Trade Practices Act**, must** be developed. 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, inside or outside normal working hours and should include emergency and 'out of hours' contacts and telephone numbers.

736 The recall procedure should be shown to be practicable and operate within reasonable time. It should be revised as necessary to take account of changes in procedure or responsible person(s).

737 The recall of a product **must** be followed immediately by a thorough investigation of the reasons for the recall. The record of the recall should include all action taken on steps from initial advice to final close-out.

Section 8

DONOR SELECTION, DONATION AND TESTING

Rationale

800 Human donors provide the material from which all blood and tissue products are derived. The selection of donors and screening tests for infectious agents ensures that the risk of disease transmission is minimised and the manufactured products are suitable for their intended purpose.

General

Pre-donation

801 Documented procedures **must** define all aspects of the donor selection and collection/retrieval processes, and detail handling techniques that are in accordance with current good manufacturing practice.

802 The supervisor of a donor session **must** be an authorised person nominated by the Director, or equivalent.

803 The medical history of a donor **must** be evaluated, and the donor assessed, by a suitably qualified person trained in the use of medical assessment guidelines, and in the assessment of the information. Donor selection guidelines **must** be documented.

804 There **must** be a record of any condition affecting quality or donor safety which is declared at medical donor interview but not covered in the documented procedure. Where deemed appropriate, it should be further discussed with an authorised person or medical officer.

Donation

805 There **must** be a system for collection and retrieval, defined in documented procedures, to ensure that quality of the donation is not compromised.

806 Donation numbers should be handled so as to avoid crossover or duplication of the numbers. The donation numbers **must** be handled as follows:

- there **must** be a record to link the donor name to the unique donation number which should be issued pre-donation;
- in the rare circumstance when it is necessary to issue a second donation number to the same donor at the same session, the first number issued **must** be destroyed and records updated. A second donation number **must** never be issued after blood flow has commenced; and
- at each critical stage of the collection or retrieval procedure the donor name and numbers **must** be checked to ensure that they correspond on all donor records and collection or retrieval packs.

807 The collection or retrieval area should be organised to avoid any potential errors with donor records or labels. Each donor collection or retrieval area should have individual handling facilities for donation, samples, recording and labelling.

808 There **must** be documented procedures for the taking of laboratory samples from donors. These should include the following requirements in each donor collection or retrieval area:

- blood samples for laboratory testing of blood donors should be taken at the time of the donation;

- for tissue donors where this is not practicable, an acceptable stated timeframe should be in place for samples taken either before or after donation; and
- sample tubes with anticoagulant should be mixed as soon as possible.

Post donation

809 The donation number, or a unique identifier to the donor, **must** be on all containers and packs that will contain product, sample tubes and donor records. This should be checked and recorded at the completion of the donation, before any items or records are removed from the donor area.

810 All donation numbers allocated **must** be used or destroyed before removal from the donor area, and a reconciliation recorded for the numbers used and destroyed. Where numbers continue to be used at various steps of the manufacture, there **must** be a system in place which requires this reconciliation step at each critical step of the manufacture.

811 There should be documented procedures for the safe disposal of single-use materiel.

Whole blood donors

Pre-donation

812 Medical assessment of the donor, **must** be evaluated on the day of donation. During private interview, the donor **must** sign a declaration form of the assessment information discussed, which is witnessed and signed by the interviewer.

813 The current Council of Europe guidelines for the selection of donors are the minimum acceptable requirements, together with any additional legislation requirement of the State or Territory in which the donation is taking place**.**

Donation

814 Where localised anaesthetic is used, the following precautions **must** be taken:
- single-dose vials **must** be used;
- the donors given anaesthetic **must** be recorded;
- the anaesthetic batch numbers **must** be recorded.

815 The venepuncture **must** be done using an aseptic technique, and the procedure used should ensure that the quality of the product will not be compromised.

816 Documented procedures **must** detail labelling requirements. After the commencement, but before completion of the donation process, the donation number should be placed on sample tubes, and all packs that will contain product.

817 When collecting blood into collection packs the following points should be addressed:
- the pack containing anticoagulant should be mixed gently during blood collection either by a mechanical device or by manual inversion;
- the volume of blood collected should be controlled by a method other than visual estimation;
- where appropriate, at the end of donation the blood in the collection tubing should be "stripped" back into the packs, and the cut end permanently sealed as soon as possible; and
- the volume should be within specified limits.

Apheresis donors

Donation

818 The minimum acceptance criteria for apheresis donors requires that they **must** meet at least the requirements for whole blood donors, unless otherwise specified in a documented procedure.

819 Additional acceptance criteria, donor session specifications, frequency of donation, volume collected, and specifications for automated machines, **must** meet at least the requirements for apheresis set down in the current Council of Europe guidelines for selection of donors.

820 The frequency and requirements for review and reassessment of donors **must** be documented. It should include the requirements for full blood count, albumin, immunoglobulins, and total protein levels, and results should be reviewed by a medical officer.

Tissue donors

Pre-donation

821 Medical assessment of the donor **must** be evaluated and recorded. There **must** be a documented procedure for defining the medical assessment requirements for live and cadaveric donors, including the acceptable timeframe for assessment, if not able to be done on the day of donation.

822 The medical assessment of a live donor should be made on the day of donation. Where this cannot be met, it should be made as near to donation as possible. Donor medical assessment information obtained at interview **must** be signed by the donor, and witnessed and signed by the interviewer.

823 In the case of cadaver donation, the medical assessment records examined **must** be individually recorded and there must be a statement of acceptability of the donor signed by a nominated authorised officer. The medical assessment should be made as close as possible to retrieval. The autopsy report should be part of the assessment.

824 Where State or Territory law, local regulations or ethics committees require consent for the retrieval of tissue, the consent **must** be obtained. In exceptional circumstances where consent cannot be obtained at retrieval, the consent **must** be obtained before the tissue can be released for supply.

Donation

825 There **must** be documented procedures which detail all requirements for retrieval.

826 Where applicable, the documented procedures **must** include the following information:

- the person(s) authorised to assess medical and autopsy information on the donor;
- the medical assessment criteria for acceptability of a donor, including any legislation requirement of the State or Territory in which the donation is taking place;
- the medical conditions contraindicating the use of a tissue for transplant;
- requirements for medical assessment of live donors;
- requirements for medical assessment of autopsy donors; and
- requirements for consent of donors.

Post donation

827 The documented procedure **must** include the requirement that when a tissue from a living donor is able to be stored for 180 days without impairing its fitness for use, the donor should be re-tested for HIV, HBV and HCV. Where this is a requirement, and one or all of these tests are confirmed as positive, the tissue **must** be discarded.

Testing of donor samples

General

828 Mandatory screening tests for donor suitability **must** be carried out at a TGA licensed laboratory. Mandatory tests are those which are the minimum requirement for release for supply of a product, and are determined by the TGA, in communication with industry. Mandatory tests may be changed or extended as required. Blood and tissue products **must** test negative to the following tests using the most current screening test procedures:

- HIV-1/-2;
- HCV;
- HBV;
- HTLV-1 (eye tissue and plasma are exempt);
- syphilis (eye tissue and plasma are exempt); and
- microbiological contamination testing (tissue, other than eye tissue, only).

In cases where product is manufactured from donors with repeatedly reactive mandatory screening tests, with the intended purpose of reintroduction into that donor, records **must** be available to demonstrate the rationale for this use. Authority for the release of this product **must** also be documented.

829 Documented procedures **must** detail the laboratory screening tests required to be in place, and the rationale for inclusion, before a product can be released for supply. Documentation should include the acceptance and rejection criteria for individual screening tests.

830 Any changes to test methodology **must** be formally documented.

831 Where screening protocols change during the life of a product in storage, where possible and practicable the donor should be re-tested with the new screening test protocol.

832 Where the individual product specification(s) requires that additional mandatory tests (to those noted above) **must** be found acceptable before product can be released for supply, records **must** demonstrate that the product has met the requirements for those additional mandatory tests.

833 The testing of plasma or serum samples **must** take into account any factors which may cause dilution sufficient to alter test results. In particular, recognition should be given to the transfusion of blood or other fluids within 48 hours of the sample being taken.

834 The test methodology and equipment **must** be validated. If testing of donors is to be undertaken concurrently with other samples then the methodology **must** be shown to be equally suitable for possible haemo-diluted samples.

835 Donor samples tested with kits registered on the ARTG, **must** be performed in accordance with the instructions of the manufacturer. Where the kit instructions offer options such as a choice of incubation times, procedures **must** detail the option(s) chosen.

836 Where a kit is not registered on the ARTG, has been modified for use, or there is an “in-house” protocol used, there **must** be validation data to verify acceptability of the test system. Any

reagents which have been introduced additional to the kit reagents, **must** have validation data to verify suitability of the reagent.

837 The ongoing quality of test kit performances should be monitored. Quality assurance measures should be taken to demonstrate the acceptable performance of the test methods. No series of tests, (tests set up at the same time and under the same conditions), should be considered acceptable unless the controls of the test kit manufacturer (the controls supplied with the test kit) and external quality controls have satisfied stated acceptance criteria. Periodic quality assessment should be undertaken for comparison of performance.

838 There **must** be a record which identifies the test system, and should include any calculations or manipulation of data required to reach a conclusion on the test result. Results not satisfying specified acceptance criteria **must** be clearly identified to ensure that the blood product and samples are held for further testing.

839 A documented procedure **must** define the retention time for the donor sample, which **must** be stored for a period of at least 15 months at a temperature at or below -15ºC, except where a manufacturer's recommendations, or validated data, identifies a different storage requirement.

Contracted laboratories

840 Any laboratories doing mandatory donor screening tests for blood and tissue banks **must** be licensed for those tests by the TGA, as this is a step in the manufacture of a product.

841 There should be a contract/agreement between the bank and the laboratory conducting the mandatory tests. The contracted laboratory **must** not sub-contract all or any part of the contract to a third party without the consent of the bank to which it is contracted. The sub-contracted laboratory **must** have a TGA licence for the tests involved.

842 A laboratory conducting confirmatory testing on a donor with a reactive screening test is not required to have a TGA licence if product is discarded on a positive screening test result. However, if the release for supply of the product is dependent on a confirmatory test or on supplemental testing results, then the laboratory doing the test **must** have a TGA licence.

Section 9

PROCESS CONTROL

Rationale

900 The quality assurance in the manufacture of products is maintained by ensuring that all manufacturing processes meet specified requirements.

General

901 There **must** be documentation which defines the materiel, procedures and controls used in the manufacture of product.

902 Suitable materiel **must** be provided for all steps of manufacture to ensure quality of the product is maintained.

903 The procedures and conditions for the manufacture of the product **must** ensure that the quality of the product is maintained throughout manufacture.

904 The product **must** be placed on a clean surface through all steps of manufacture.

905 Products should be periodically sampled or subject to microbial contamination testing to ensure both the reliability of the manufacturing process and the quality of the final product. Where contamination is demonstrated, records **must** show the corrective action taken.

Validation

General

906 There should be data validating each critical process in the manufacture of product, and where applicable, quality control data to demonstrate that the process is under adequate control.

907 Any quality control tests performed on product **must** be in accordance with validated methods detailed in, or referenced to, documented specifications.

908 There **must** be a re-validation performed whenever there is a significant change in any of the critical processes of manufacture of the product. The data should identify the change which should be documented, reviewed and approved by the quality assurance manager, or nominee, before implementation.

Quality Control

909 Where applicable, there **must** be a documented procedure for quality control, including the use of a sampling plan, to ensure that the critical manufacturing steps from collection to final product meet defined criteria of acceptance. The following points should be taken into account:

- the number of samples required should be assessed according to pre-determined documented criteria;
- the samples should cover all sites, and should be relevant to the step(s) in manufacture carried out at a site;
- where pooling of samples occurs, the procedure and records should define when pooling occurred before the testing, and should be supported by validation data verifying that the pooling procedure is acceptable; and
- the record should clearly identify the donation numbers of the samples selected.

Monitoring

910 There **must** be a record of any deviation from the defined procedure, and any action taken should be authorised by a nominated authorised officer. The quality assurance manager should review critical deviations from procedures.

911 There **must** be stated regular reviews of process records. The frequency of review may depend on the incidence of non-conformances discovered at internal audit and/or the frequency of product out of specification.

Product release

912 There **must** be a system of quarantine for all products to ensure that they cannot be released for supply until they have met the defined mandatory acceptance criteria for release. There **must** be a documented procedure which defines the requirements for release of product for supply.

913 Acceptance criteria for release of product **must** be defined for each individual product, and **must** include as a minimum requirement, but is not restricted to

- the medical assessment;
- mandatory screening tests for infectious disease on the donor; and
- regulatory and licence requirements.

Section 10

STORAGE, PACKAGING AND TRANSPORT

Rationale

1000 Quality assurance in the manufacture of products is maintained by controls to ensure that storage, packaging, labelling and transport meet specified requirements, before the release for supply of the product.

Storage

General

1001 There **must** be a documented system established and maintained to control the storage of products before release for supply, including any storage under transportation.

Labelling

1002 The system **must** ensure that the status of any product is identifiable to the particular step in its manufacture. If a product has uncertain status, it **must** be securely segregated or status-labelled, and the reason for the uncertain status investigated. There **must** be a record which details the reason for segregation, and any further investigative action taken.

1003 The label on a product which has been released for supply **must** include the following information:

- the donation identification number;
- the name of the product and, where applicable, the product code;
- where applicable, the date of expiry, the date of manufacture; and
- a warning label that it could transmit infectious agents (except for plasma for further fractionation). Where the product is accompanied by a product information leaflet, this warning can be included in the product information.

1004 All product labels **must** be secured in a locked storage area accessible only to authorised personnel.

Quarantine

1005 There **must** be a documented procedure which defines the system in place which gives assurance that products which are still under quarantine, can be distinguished from those which conform to specification and are released for supply. The following points **must** be considered:

- there **must** be a record of the product donation number and the reason for its quarantined status;
- the product **must** be individually labelled to identify quarantine status. (It may be acceptable to label the storage area only, depending on the level of security of the facility);
- the storage area **must** be labelled to identify storage of quarantined product; and
- quarantined product **must** be secured for access by only nominated authorised personnel.

Discard

1006 There **must** be a documented procedure which defines the disposal requirements for product not suitable for use. Product which is to be discarded **must** be labelled to reflect its status, stored in an allocated and secure area, and disposed of appropriately within a stated time-frame. There **must** be a record of discarded product, including the reason for discard.

Packaging

General

1007 There **must** be a documented procedure which details the packaging and container requirements, including environmental control, for transport of product.

1008 The transport container **must** protect the integrity of the product.

Labelling

1009 The transport container **must** be labelled with the following information:

- the address and contact name for the site of origin of the product and its destination;
- the contents of the container; and
- for products under quarantine, a "quarantine" label, or equivalent.

Records

1010 The container with product **must** be accompanied by a record, (consignment note), which is packaged so as to prevent damage to the record. The record should include the following information:

- the name of the site despatching the product;
- the name of the site to receive the product;
- a unique identifier to link the individual consignment to the container;
- the product type, including the status of each product;
- the unique identifying donation numbers on the product(s) in the consignment;
- the total number of products in the consignment;
- the date and time of despatch; and
- the signature(s) of the authorised nominee responsible for the despatch.

Transport

1011 There **must** be a documented procedure which defines the system of transport to ensure that product remains within specifications at all times, prior to the release of product for use. The procedure should define specific transport requirements for individual sites and, where applicable, should define the specific requirements of a licensed site for product transported from an external source site.

1012 There **must** be validation data to support the transport systems in place. It is the responsibility of the licensed site to ensure that the transport system(s) in use do not compromise the quality of the product, prior to the release of product for use.

1013 Where transport time is critical to the final product quality, the time despatched and received should be recorded.

REFERENCED AND RECOMMENDED STANDARDS

AND PUBLICATIONS

These documents are intended to supplement and give guidance to requirements of the Code.

AS/NZS ISO 10013:1996	Guidelines for developing quality manuals.
AS/NZS ISO 9000:1994	Quality system guide to selection and use.
AS/NZS ISO 9001:1994	Quality systems – Model for quality assurance in design, development, production, installation and servicing.
AS 1057-1985	Quality assurance and quality control – glossary of terms.
AS 1386-1989	Cleanrooms and clean workstations
AS3864-1997	Medical refrigeration equipment – For the storage of blood and blood products
ISO 14644-1:1999	Cleanrooms and associated controlled environments.
EN46001:1996	Quality systems - Medical devices – Particular requirements for the application of EN ISO9001
EU:	Guide to GMP for medicinal products. Annex 1- Manufacture of sterile medicinal products.
TGA:	Guidelines for sterility testing of Therapeutic Goods. October 1998.
COUNCIL OF EUROPE PUBLISHING:	Guide to the Preparation, use and quality assurance of blood components, 6th Edition (January 2000)
IATA:	Dangerous Goods Regulations, International Air Transport Association.

GLOSSARY

The following explanations of terms used in the code are given to assist the reader and as source material for GMP training programs. They are not intended to be "definitions" in the scientific sense or "interpretations" in the legal sense, and are not meant to be read in any context other than the Code.

The Glossary also includes some terms not used in the Code but commonly used in its application. It does not include terms such as "therapeutic good" or "manufacture" which have interpretations in the legislation under which the Code applies and must be taken to have these interpretations for the purposes of the Act. Some of these terms are given in a separate list.

ACCURACY: The closeness of the result obtained, during measurement or analysis, to the true value. Bias is a systematic deviation from the true value.

APPROVED SUPPLIER: A supplier of starting materiel of known origin who is recognised as reliable, based on a history of deliveries which meet specifications and were well packaged and intact on receipt and, where possible, based also on a vendor audit (see also Certified Supplier).

APHERESIS: The process which separates whole blood into its components and returns remaining components to the donor.

ARTG: Australian Register of Therapeutic Goods.

ASEPTIC TECHNIQUE: The measures used to prevent contamination of the product by micro-organisms.

BATCH: A defined quantity of materiel processed in one process or series of processes so that it may be expected to be uniform with respect to composition and probability of chemical and/or microbiological contamination. However, 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.

BATCH NUMBER: A number or combination of numerals, symbols and letters which uniquely distinguishes a batch of product from all other batches of that product, or other products, at all stages of manufacture and permits a correspondence to be established between the batch and all tests carried out on it in the course of processing and quality control.

A number of sub-batches may be combined by mixing to form a single batch. However, where the bulk batch is divided into lots for different processes such lots must be distinguished from one another by suitable means by labelling. It is permissible to use one unique series of numbers (processing numbers) on product up to the point of packaging and another for the packed product, with or without an affix as described above, provided that they are unambiguously correlated in batch records.

It is also permissible to combine a series of batches of bulk product into a continuous series of packaging operations (not significantly separated in time, place or equipment) and apply a single batch number to the packaged batch, bearing in mind that if a fault occurs or reconciliation fails, the whole series may have to be rejected or recalled.

Incoming materiel will usually carry the batch, lot or equivalent number of their manufacturer, but will be allocated instead a Unique Identifying Number by which they are identified within the premises of the user. This avoids the use of the term "batch number" with two different meanings.

BLOOD MOBILE SITE: Designated premises licensed to operate off-site from a licensed fixed site. The blood products collected from a mobile site are directed to the fixed site. (See also “Fixed Site”).

CALIBRATION: The operations carried out to determine the accuracy of measuring instruments, of "materiel measures" such as masses or gauges and of measurement standards. Properly it does not include adjustment, but in this Code it is assumed that adjustment follows the detection of unacceptable error.

CERTIFIED SUPPLIER: An Approved Supplier who has been formally audited by the purchaser and who meets ISO requirements and is certified by Standards Australia or equivalent (See also approved Supplier).

CHANGE CONTROL: a) Ensures the disciplined adaptation of changes and additions to the original processes. b) The term given to the cyclic processes of software and data system maintenance.

CLEAN AREA: A room(s) with defined environmental control of particulate and microbial contamination, used in such a way as to minimise the introduction, generation and retention of contaminants within it.

CLEAN SURFACE: Any dedicated surface which is required to be cleaned regularly, and is used for product during its manufacture.

CLEAN ROOM: A room(s) in which the concentration of airborne particulate matter is strictly controlled as specified and where other factors may be controlled to within limits necessary to cater for particular needs.

CLOSED SYSTEM: A system (such as a multiple pack system) where the registered assembly is manufactured under clean conditions, sealed to the external environment and sterilised by an approved method. Apart from collection/retrieval requirements, such as venepuncture for blood, the integrity of the assembly must not be breached.

When components of a system are connected (such as for apheresis), these connections can be regarded as 'closed system" provided it can be shown that the process of joining and sealing two packs does not lead to the possible microbial contamination of the products in either pack. (See also "Open System").

CODE: The Code of Good Manufacturing Practice (cGMP). In this document applies to the Code for Human Blood and Tissues.

COMPUTER SYSTEM: The combination of hardware, software and operating procedures that determine computer functions.

CONFIRMATORY TESTING: Additional testing, using an alternative method or marker, undertaken on a sample repeatably reactive on a primary screening assay, to confirm or exclude the presence of a specific viral marker.

CONTRACT LABORATORY: Work associated with the manufacturing process performed by another organisation.

CONTROLLED ENVIRONMENT: An environment which is controlled with respect to particulate contamination, both viable and non viable particles are controlled. May also include temperature and humidity controls. (See also Clean Room)

CRITICAL LABELS: A label which identifies a product or status, including critical materiel, used in manufacture. It includes any label which indicates and controls release of product.

CRITICAL MATERIEL: All components, materials or supplies which could have a direct negative impact on the quality of the end product.

DEDICATED FACILITY: A room(s) with attendant equipment and services, including air handling, used only for the manufacture of one product or a closely related group of products. Equipment may be similarly "dedicated".

EQUIPMENT QUALIFICATION:
Installation Qualification (IQ): Provides documented verification that all key aspects of the installation of equipment adhere to the approved design intentions, and are in accordance with the advice of the manufacturer.

Operational qualification (OQ): Provides documented verification that the system and sub-systems perform as intended throughout all anticipated operating ranges.
Process qualification (PQ): Provides documented verification that the process does what it purports to do.

FIXED SITE: Licensed premises, with a designated street address, undertaking a step(s) in the manufacture of product. (See also "Blood Mobile Site").

FRACTIONATION FACILITY: The facility to which plasma designated for further fractionation is transported.

GOOD MANUFACTURING PRACTICE (GMP): All the elements in established practice that will collectively lead to final products or services that consistently meet expected specifications.

INSTALLATION QUALIFICATION (IQ): (See "Equipment Qualification")

IRRADIATION: (1) A process intended to produce sterile goods (2) Reduction of the probability of the presence of viable micro-organisms to an acceptable level (3) used to prevent GVH disease by decreasing the number of viable T lymphocytes. Sterilisation is effected by noise or dry heat, treatment with a gaseous sterilant such as ethylene oxide, irradiation with ionising radiation or to solutions by filtration method. (See also "Sterilisation").

LEARNING AND DEVELOPMENT: The acquisition of skills, knowledge and attributes through formal and informal processes. Assessment of these skills, to determining competency, is required.

LINEARITY: (of analytical method): The ability of the method to produce results (within a defined range) that are directly or indirectly proportional to the concentration of the analyte in the sample.

MASTER DOCUMENT: A document from which copies are made for use in any step in the manufacturing process, including testing of donor samples. The master is checked, authorised and filed until required for copying. It is convenient to distinguish the master copy, which can be done by the use of coloured paper, coloured logo or the use of red ink signatures, ensuring that the copies will be distinguished by their lack of colour.

MATERIEL: All components, materials or supplies which are to be incorporated or to be used in the manufacture (including testing) of a therapeutic good.

OPEN SYSTEM: A system which has been breached but where every effort is made to maintain sterility by the use of sterile materiel and aseptic handling techniques in a clean environment (See also "Closed System").

OPERATIONAL QUALIFICATION (OQ): (See "Equipment Qualification").

PROCESS CONTROL: That part of quality control and quality assurance concerned with minimising variations in the characteristics which occur during the manufacturing process.

PROCESS QUALIFICATION (PQ): (See "Equipment Qualification").

PRODUCT RELEASE: The process which enables a product to be released from a quarantine status by the use of systems and procedures to ensure that the finished product meets its release specifications. (See also "Release for supply").

QUALITY ASSURANCE: The function which has responsibility for creating quality systems and procedures, and ensuring their effectiveness. Quality assurance is concerned with preventative as well as corrective action.

QUALITY CONTROL: The function responsible for the actual sampling and testing of materiel, including products, to verify that specifications are met.

QUARANTINE: The status of materiel, including products, whether physically or by a system, whilst awaiting a decision on their suitability for further processing.

RECONCILIATION: Comparison and assessment of any discrepancy between the amount of materiel entering and leaving a given operation or series of operations.

REGISTERED GOODS: A therapeutic good registered (in some cases only listing is required) on the Australian Register of Therapeutic Goods (ARTG).

RELEASE FOR SUPPLY: The process which enables a product to be released from a quarantine status by the use of systems and procedures to ensure that the finished product meets its release specifications. (See also "Product Release").

SENSITIVITY : A term defining the limit of detectable specific reactions using reagents or test systems. The document specifies levels of sensitivity which must be achieved.

SESSION RECORD: Record(s) which link relevant details of the collection or retrieval session directly to the donation number, and contains information linking critical materiel used to the donor.

SPECIFICATION: A document(s) giving a description of starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and (possibly) biological properties together with methods of testing. A specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances.

SPECIFICITY (of analytical method): The ability of the method to measure the analyte in a manner that is free from interference from other components that may normally be expected to be present, such as ingredients, impurities and degradation products. Specificity is a term defining the ability of a reagent or test system to react selectively. In practical terms, it represents the absence of false positive reactions.

STANDARD NAME: A name assigned to starting materiel that uniquely identifies it within the manufacturing establishment. It is used to cite the material in specifications, on identity status tags, in analytical reports, in stores records and in product documents. It is chosen to avoid the possibility of confusion between similar-looking or similar-sounding names.

STARTING MATERIEL: Any materiel employed in manufacture which may contact or be included in the finished product, including packaging materiel. The term does not include ancillary chemicals such as cleaning agents or adhesives, though these are not to be overlooked for their possible hazards or effects on the product.

STATUS: The classification of any materiel or product in relation to their acceptance (or otherwise) for use, further processing or distribution. Terms used could include "Quarantine", "Released", "Hold", or "Rejected".

STERILE: Free from viable micro-organisms.

STERILISATION: (See "Irradiation").

STERILITY: The concept of the complete absence of living micro-organisms.

SUPPLEMENTAL TESTING: Additional testing undertaken to clarify the serological status of a sample repeatably reactive on a primary [or frontline] screening assay.

UNIQUE IDENTIFYING NUMBER: See "Batch Number".

VALIDATION: The action of proving that any materiel, process, procedure, activity, system or equipment used in manufacture or control can and will reliably achieve the desired and intended results.

VALIDATION (PROSPECTIVE): The validation taken before manufacture begins. It is an orderly approach to development of procedures.

VALIDATION (RETROSPECTIVE): The conduct of validation studies performed after manufacture has begun and designed to show that the processes and procedures are effective and robust, within the likely ranges of variables affecting them. (A collection of data demonstrating that product always meet specifications is not, in itself, validation.

WORKING STANDARD: A preparation prepared nationally or locally containing a known or agreed concentration of the activity being measured. It should be assayed with each group of tests to establish the sensitivity or calibration of the unknown tests in the group.

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