Draft AUSTRALIAN CODE OF GOOD MANUFACTURING PRACTICE HUMAN BLOOD AND BLOOD COMPONENTS, HUMAN TISSUES AND HUMAN CELLULAR THERAPIES		
Reviewer: CTTWA - RPH-Heart Valve Bank & Cellular Therapies	Date 04/02/2010	

Clause Ref.	Page Ref.	Comment
		GENERAL COMMENTS: 1. Please delete the use of "premises" and only use the term "facilities" throughout this document. For manufacturing facilities located within Hospitals or Institutions, "premises" may include areas outside the control of the licensed facility. Eg. Section 3 – **Recommend wording:** Facilities and Equipment. 2. Please standardise the use of "Quality" vs "Quality Control". A number of terms need to be defined and their use standardised. Eg. • Material • Tissue • Product • In-process controls • Exceptional release • Sub-contractors (vs contractors)
Introduction	Page 2	Para 4: "Manufacturers will be required to develop Technical Standards Files for product groups to demonstrate Standards are met." This statement gives no indication as to whether TSF requirements will be different for the different product classes? (i.e. will the extent of requirements reflect the product risk category – Class 1, 2, 3 or 4). Product Standard templates for each class of tissues/cells are required. Demonstration of efficacy may unattainable for some products.
103	Page 5	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.

		Facility SOP define objectives and outcomes are included in product reviews. **Recommend deletion** of second sentence.
104: dot-point 1; dot point 5; dot point 8; dot point	Page 5 & 6	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 and Good Laboratory Practice; Requirements of the Code effectively cover GLP for the manufacture of human blood and blood components, human tissues and human cellular therapies. **Recommend deletion of** reference to GLP OR state the relevant section of the GLP as they apply to each product class to ensure biological therapeutic products are not required to meet medicinal standards where it may not be relevant, appropriate or possible. • all necessary controls on intermediate products, and any other in-process controls and validations are carried out; "all" and "any" are very subjective and open to broad interpretation **Recommend wording:** Risk based controls and validations on intermediate products/in-process procedures are carried out. **General Comments:** a) Unless there is a major change to the procedure or critical materials/equipment, close-out of a validation procedure by one auditor should be accepted by future auditors. b) Validation of a procedure or material by one Bank should only require verification by other Banks utilizing the same procedure/material. This would not only standardise the validation/ verification procedures conducted by the Banks thereby making it easier for the auditors to assess, but would also minimise the costs and time spent by individual Banks repeating procedural/material validations. c) Specific standards related to validation requirements should be included as references. • 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; The manufacturer can only provide storage & handling information for the distributed product. It can document responsibilities for subsequent handling procedures bya letter of agreement. The manufacturer cannot control the product once it is distributed.

		Recommend deletion: "subsequently handled". • there is a procedure for self inspection (internal audit) which regularly appraises the effectiveness and applicability of the quality system. **Recommend deletion:** – 109 covers this point.
105, 112 & 115	Pages 6 & 7	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. 112. There should be procedures for the ongoing management and review of the corrective actions to ensure timely and effective implementation. 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. Suggest combining 105, 112 & 115 as they are essentially the same points. **Recommend wording:** Documented procedures should be reviewed at appropriate and defined regular intervals, to ensure the continuing suitability, adequacy and effectiveness of the quality system. Reviews should include: • Results of self inspections; • Complaints & recalls, • Results from product reviews, • Status of preventive and corrective actions • Deviations from the quality system, test procedures & manufacturing procedures and trends • Follow-up actions from previous management reviews, • Continuous improvement requirements

		Records of these reviews should be reported to management for evaluation and assessment as to whether corrective or preventive action or any revalidations should be undertaken. Records should be maintained and follow-up actions documented.
113	Page 7	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: Regular periodic quality reviews is more appropriate than "annually" to allow reviews to be conducted based on risk rather than a timeframe. **Recommend wording** last sentence: Such reviews should take 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. **Recommend deletion** this dot point as requirements are covered in dot point 4. • 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	Page 7	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. **Recommend deletion** as these requirements are covered in 113 & 115.

205	Page 9	205. The quality and production nominees should have a relevant tertiary level qualification, (eg. in medicine, science, medical laboratory science, nursing), and have had practical experience, at management level, in the manufacture of therapeutic products. There would only be a limited number of people who would fulfil all aspects of this clause. **Recommend wording**: …and have had practical experience, at management level, in the manufacture of therapeutic products and/or quality or laboratory management.
206 & 207	Page 10	206 The Production nominee generally has the following responsibilities: 207. The Quality nominee generally has the following responsibilities: **Recommend inclusion** for both 206 & 207: The Production/Quality nominee or delegate has the following responsibilities. 207. The Quality nominee generally has the following responsibilities: • to approve or reject, as appropriate, materials and therapeutic products; IF "approve or reject, as appropriate, materials and therapeutic products" relates to release of product, then both the Quality nominee and the Production nominee should share responsibility for this activity. This statement needs to be clarified to minimise the risk of misinterpretation. **Recommend inclusion** as a dot point under 206: 206 The Production nominee generally has the following responsibilities: to approve or reject, as appropriate, materials and therapeutic products prior to review by the Quality nominee or delegate;
209	Page 10	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. The need for continuing training is stated in 200 and does not need to be restated here. In addition, "its practical effectiveness" is open to interpretation. **Recommend deletion of** sentence. Please standardise the use of "Quality" vs "Quality Control".
211	Page 11	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.

		Recommend wording: "Visitors or untrained personnel should be discouraged from entering manufacturing and quality areas and, if unavoidable, must be closely supervised"
300	Page 12	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. a) "Premises" is a broad term and should be removed from use in the entire document. b) Recommend the first sentence be simplified to minimise the risk of interpretation differences. In addition, meeting requirements may not be possible, especially for collection sites. **Recommend wording:** "Facilities and equipment should be suitable for the manufacturer's intended purpose and maintained to ensure product requirements are met. In order to minimise the risk of microbiological, particulate or pyrogenic 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. a), The relevant Standard or BP pertaining to special environmental control measures for minimising the risk of pyrogenic contamination should be provided as a reference. b) The applicable code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products need to be identified/documented so that "where required" is clear. **Recommend wording:** Where required, the following code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products should apply. And then list the clauses as dot points.
301	Page 12	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. The design of mobile sites and other collection sites is beyond the control/scope of the manufacturer. **Recommend wording:** The manufacture of products should be carried out under appropriate and specified conditions, and each area, including mobile sites, should be suitable for its intended purpose and maintained to ensure product requirements are met.
302	Page 12	302. Premises should be designed and equipped so as to afford maximum protection against

		the entry of insects or other animals. Please replace “premises” with “facilities”. The term “maximum” is open to interpretation. **Recommend wording:** “…as to afford protection against the entry of insects or other animals”.
305	Page 13	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. These parameters are too prescriptive for product storage areas/equipment or the correct functioning of equipment. **Recommend wording**: Lighting, temperature, humidity, air quality and ventilation should be appropriate and such that they do not adversely affect the products during their manufacture. Records should demonstrate that manufacturer stipulated storage conditions and equipment function are being met.’ (e.g. temperature, light, humidity).
306	Page 13	306. Premises for the manufacture of products should be specifically designed and used so as to avoid mix-ups or contamination. Premises is an inappropriate term and should not be used in this Code – Facility (ies) should be used throughout. Old facilities were not specifically designed for the manufacture of products and this should not be a requirement if the facility is able to meet GMP requirements. In addition, “premises” may refer to the entire building of which the Facility is a part and definitely wouldn’t have been “specifically designed” for product manufacture. The requirement to avoid “mix-ups or contamination” is covered in 300. **Recommend wording:** Facilities should be appropriate for the products manufactured and be used so as to avoid errors or contamination.
310	Page 13	310. For products requiring control of microbiological bioburden, the manufacturer should establish and document the environmental requirements to which product is exposed during processing. Specific product Standards dictate the environmental requirements for processing of products (eg. Grade B with a Grade C bg – 8c; page 7). Also, by definition Bioburden is not the appropriate term **Recommend deletion** this statement.
314	Page 14	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 (eg temperature, light, humidity)

		The terms “adequate” and “suitable” are open to interpretation and many materials do not identify environmental condition requirements. **Recommend wording**: Storage areas should be arranged to allow dry, clean and orderly placement of stored material under monitored environmental conditions which meet material requirements (eg temperature).
317	Page 14	317 Storage facilities should 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.* Provided the storage facility is properly controlled and segregated, there is no reason why it can’t be used for other purposes eg. storage of materials and quarantined/in-process product in a secure, alarmed refrigerator. **Recommend deletion of** second sentence.
318	Page 14	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. Equipment design is beyond the control/scope of the manufacturer. **Recommend wording** (~to current Code): “Manufacturing equipment should be suitable for the manufacturer’s intended purpose”.
319	Page 14	319. There should be protocols which address installation (IQ) and operational (OQ) qualification of equipment. 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. This statement should apply only to equipment which is critical to the control of manufacture. **Recommend clarification**: There should be protocols which address installation (IQ) and operational (OQ) qualification of equipment which is critical to the control of manufacture.
325	Page 15	325. Defective equipment should, if possible, be removed from production and quality control areas, or at least be labelled as defective. Defective equipment should be labelled as defective whether it can be removed from the area or not. **Recommend wording:** Defective equipment should be labelled as defective and, if possible, removed from the processing area..
327	Page 15	327. Fixed pipe-work for gases and liquids should be labelled to indicate the contents and the

		direction of flow. **Recommend deletion:**: This is Part of an Australian Std and does not need to be in Code.
328	Page 15	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; Dot point 2 is not appropriate during transport and needs to be clarified. **Recommend wording:** • "for fixed site equipment (eg. fridges; freezers) 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	Page 15	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. Water systems are maintained and monitored by the supplier in accordance with the systems manufacturer's instruction. These responsibilities should be included in the letter of agreement, not in product manufacturer's written procedures. **Recommend wording:** Documentation should be in place which identifies responsibilities and procedures for sanitising and monitoring water systems used in manufacturing to ensure that it meets specification for its intended purpose.
330	Page 15	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

		Recommend reword of "premises" with "facilities". Final dot point needs to be clarified – does this apply to all cleaning agents (where the date of expiry will vary with each batch) or just cleaning agents diluted for use by the manufacturer. **Recommend wording:** the dilution and duration of use of cleaning agents prepared by the manufacturer.
333	Page 16	333. Where the removal of traces of material or product is important to minimise risk, cleaning methods should be validated. 822 makes it a requirement that "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"….. without any reference to "risk", which suggests that validation is required for cleaning methods for these areas/equipment **Recommend combination of** these two points and clarifying that this applies to areas/equipment that come into contact with the product: "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. Cleaning methods for critical work areas and equipment should be validated and records should be maintained". Relevant standards and/or BP should be specified and included in references.
336	Page 16	336. Preventive maintenance should be carried out on *premises,* facilities and equipment at defined regular intervals. **Recommend Deletion** "premises".
403	Page 17	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). Instructions may be too prescriptive for some procedures. **Recommend wording:** (i.e. as instructions or guidelines rather than statements of what is desired or should happen).
411, 412, 413	Page 18	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. **Recommend Inclusion** in Section 10 – Computers
503, 504, 510	Page 19, 20	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. **Recommend wording** second dot point: "instructions for sampling and testing or reference to procedures, if relevant:; 504. Incoming materials should be quarantined and *assessed* to ensure that they meet approved specifications, before being released for use. 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. **Clarification/definition** "assessed". Provided the material is supplied by "suppliers that have been evaluated and approved" and who have conducted, documented and provided results of QC and screening tests as per specifications and/or regulatory requirements, and the material is quarantined and inspected in accordance with documented receipt procedures prior to acceptance by the manufacturer, physical re-assessment of "qualitative & quantitative" requirements by the manufacturer should not be required, unless relevant to the intended use (eg. support of cell growth). The potential risk of the material adversely affecting the quality of the product if it is not physically re-assessed by the manufacturer is an acceptable risk.
511	Page 20	511. Reagents should be of appropriate quality *and suitable for intended use*. "Intended use" needs to be defined – i.e. the manufacturer's intended use or the suppliers. Some materials/reagents are used for processing steps which are not the supplier's intended use of the material/reagent. **Recommend wording:** Reagents should be of appropriate quality and suitable for the manufacturer's intended use.
512	Page 20	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 Control Department 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. . **Recommend inclusion** in Section 9, under Product Release rather than in the Control of Material Section, between 917 & 918. **Recommend wording**: "critically assessed by Quality Management" as not all manufacturers have a Quality Department.
601	Page 21	601. The subcontractor (eg 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. **Definition Required** "Subcontractor" vs "Contractor".
Section 7	Page 22	**Section 7** **COMPLAINTS AND RECALLS** For tissue allografts and cellular autografts, hazard alerts are far more likely to be required than recalls. **Recommend Inclusion:** Hazard Alerts needs to be covered in this section.
702	Page 22	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. "All reasonable contingencies that may be anticipated" is open to broad interpretation. **Recommend wording:** The procedure should specify contingency actions to be taken.
801	Page 23	801. Collection and processing should be performed and supervised by competent people. This statement is in Section 2 (Personnel & Training; 210 & 212). **Recommend deletion**
802	Page 23	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. This statement is covered in Section 4 (Documentation; 401). **Recommend deletion**

805	Page 23	805. A procedure should be established implemented and maintained for obtaining medical and other required statutory information prior to donation. There may be instances where completion of information is obtained after donation. **Recommend wording**: A procedure should be established, implemented and maintained for obtaining medical and other required statutory information prior to, or soon after donation.
806	Page 23	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. First sentence – need to specify allogeneic". **Recommend wording:** "documented procedure that defines the medical assessment requirements for allogenic donors, live and deceased, including….. Second sentence needs to be reworded as some of the information in the donor selection records are not obtained until after donation (eg screening test results). In addition, the donor does not sign the doctor's medical history records. **Recommend wording:** For a live donor, the donor consent and medical and social history documentation that has been collected from the donor, should be signed by the donor and witnessed and signed by an authorised person **Clarification/ definition:** "authorised person".
807	Page 24	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. **Recommend wording:** 'For a deceased tissue donor, there should be a statement signifying that medical records have been assessed and the donor has been found acceptable, by a nominated authorised person.'
814 & 816	Page 24	814. The donor identification and any critical materials used should be traceable to the donation and associated records. Donation numbers should not be repeated, unless after a reasonable timeframe. 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. Sentence number two of clause 814 should be moved to clause 816.

		Recommend wording: 814. The donor identification and any critical materials used should be traceable to the donation and associated records. 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.
818	Page 25	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 therapies should be packaged using sterile containers and in a manner which will minimise contamination. **Clarification/ definition** "controlled conditions". Eg. Non clean room, clean, secure Can a Mortuary be considered as "under controlled conditions".
819	Page 25	819. Collection documentation records should include: The Term "documentation" is not necessary. **Recommend wording:** Collection records should include: • The donor identity • The date, time and place of the procedure • The identity of the person(s) performing the procurement • For Cellular Therapies; the Cells retrieved, Donor and cell selection information • For Tissues; The tissue(s) retrieved, Donor and Tissue selection information, Details of the physical examination of the donor prior to collection Last dot point – Requirement for physical examination as defined in the Infectious Diseases Standard is not workable for live donors. In addition, "tissue selection information" is not relevant. **Recommend wording:** For Tissues; The tissue(s) retrieved and Donor selection information. For deceased donors, details of the physical examination of the donor prior to collection should also be recorded.
821	Page 25	821. Tissue and cellular therapies should be processed in an environment and manner which will prevent contact or cross contamination with tissues or cellular therapies from other donors. This statement is not compatible with some current therapies (eg. milled bone; cultured skin grown on a feeder layer from another donor/source) as well as a number of potential, future biotherapies (e.g stem cells grown on a feeder layer, or any cells grown on a tissue or scaffold provided by another donor or source).

		Recommend wording: Tissue and cellular therapies should be processed in an environment and manner which will prevent unintended contact or cross contamination with tissues or cellular therapies from other donors.
822	Page 25	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. As per 333 above. **Recommend combination** of these two points and clarifying that this applies to areas/equipment that come into contact with the product: "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. Cleaning methods for critical work areas and equipment should be validated and records should be maintained".
827	Page 26	827. There should be a system in place to maintain and control work-in-process Tissue or Cellular Therapies, including any transportation required. **Clarification/ definition:** "work in process"
830	Page 26	830. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. **Recommend wording:** "Material handling procedures should avoid errors occurring between irradiated and non-irradiated materials.
836	Page 27	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. **Clarification:** Is it intended that the risk assessment approach requirement will be applied retrospectively to validations that have already been established for existing equipment/processes?
900	Page 28	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. **Clarification/ definition:** A definition and requirements for exceptional release need to be included in

		this Section.
903	Page 28	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. **Clarification**: Is it the intent for supplied solutions, in direct contact with the product, to be listed or registered on the ARTG.
905-910	Page 29	These comments relate to 905-910 The majority of licensed product manufacturers are not licensed to conduct testing procedures (eg. screening tests, microbial contamination tests; sterility tests etc..). Instead, product manufacturers contract TGA licensed testing laboratories to conduct the required test in accordance with clause 905. Product manufacturers that contract testing to a TGA-licensed testing laboratory should not be held responsible for ensuring that the contracted testing laboratory meets their TGA-license requirements as indicated in clauses 906-910; that is the responsibility of the TGA. Product manufacturers should only be responsible for ensuring that the contracted laboratory is licensed by the regulatory authority for the required tests (905), an agreement is in place which states the responsibilities of both parties (601), and for auditing the testing laboratory to ensure is compliant with the quality system (601). For this reason, the requirements of clauses 906-910 should only apply to manufacturers who are also licensed to conduct testing procedures. **Recommend inclusion** of the following statement after clause 905: Clauses 906-910 apply only to product manufacturers licensed to conduct testing procedures. 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. "Appropriately validated" is open to interpretation. **Recommend wording:** Tests should be performed using qualified equipment and validated methodology.

		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: a. reference to the donation; b. details of equipment and materials used; c. references to the relevant specifications and testing procedures; d. test results, including observations and calculations, e. date(s) of testing; f. identification of the person(s) who performed the testing; g. identification of the person(s) who reviewed the results, including a check of calculations, where applicable
912	Page 29	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. Schedule 4; (9 & 10) of the Infectious Disease Transmission Standard specify serum archiving requirements. As this Standard applies to all blood, tissue and cellular therapies banks, it does not need to be repeated in the Code. **Recommend deletion**
913	Page 29	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. This requirement is covered in both the Infectious Disease Transmission Standard and the Tissue Specific Standards; it does not need to be repeated in the Code. **Recommend deletion**
915	Page 30	915. The manufacturer should ensure that where Tissue and Cellular Therapies does 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 are 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. **Clarification/definition:** Under what circumstances does “exceptional release” apply?.
916 & 918	Page 30	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 and products prepared from previous donations (where applicable) given by such donors have been identified. There should be an immediate update of the donor record to ensure that the donor cannot make a further donation, if appropriate. 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. These points are listed under the sub-section entitled Product Release. Given they cover requirements for products not suitable for release and/or disposal requirements, a separate sub-section (eg. Failed Product) would be more appropriate. **Recommend inclusion:** additional sub-section: Failed Product.
917	Page 30	917. Where applicable, autologous Blood or Blood Components and Cellular Therapies from donors with repeatedly reactive mandatory screening tests, intended to be reintroduced 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. Tissue Therapies need to be included **Recommend inclusion:** autologous Blood or Blood Components, Tissue and Cellular Therapies from donors with….
1000	Page 31	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. The specific purpose or function of the implemented computerised system needs to be defined to ensure this statement applies only to systems involved with product quality and safety or data security and integrity? (as per Clause 1001). **Recommend wording:** Where a computerised system is implemented in connection with a step in the manufacture of the product; there should be no adverse affect on product quality and safety, or security and integrity of data **Recommend inclusion:** Clauses 411, 412, 413 in this Section
Glossary	Page 34	Several definitions need to be added to the Glossary some of which are indicated above in General Comments.