ATBF Comment to

Draft Australian Code of Good Manufacturing Practice
Human Blood and Blood Components,
Human Tissues and Human Cellular Therapies

February 2010

This response only includes those items wherein the ATBF wishes to submit comments at this time.

Section 1

QUALITY MANAGEMENT

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.

ATBF seeks clarification and definition of "efficacy" and the information that TGA would consider to be sufficient to establish "efficacy" as it pertains to the Human Tissue Sector.

We note that the term does appear in numerous locations in the document and this comment would apply to all instances wherein the term is used.

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;*
- *production and control operations are clearly specified and Good Manufacturing Practice adopted;*
- *managerial responsibilities are clearly specified;*
- *arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;*
- *all necessary controls on intermediate products, and any other in-process controls and validations are carried out;*
- *the finished product is correctly processed and checked, according to the defined procedures;*
- *therapeutic products are not supplied before an authorised person has verified that they have been produced and controlled in accordance with the requirements and any other regulations relevant to the production, control and release of therapeutic products;*
- *satisfactory arrangements exist to ensure, as far as possible, that the therapeutic products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;*
- *there is a procedure for self inspection (internal audit) which regularly appraises the effectiveness and applicability of the quality system.*

ATBF queries the apparent inclusion of an entire Code of GLP by reference. Would TGA expect a Tissue Bank to demonstrate compliance to the Code of GLP in addition to this Code?

In reference to Dot point 8, the ATBF is concerned that this would imply an obligation on the manufacturer to ensure that the storage and handling of product even when no longer in the manufacturer's control (e.g.. when at a Hospital

Measurement and monitoring

109 A program for self inspection should be established, documented and implemented to periodically assess the effectiveness of the quality system.

We note that this clause essentially duplicates the last Dot Point under Clause 104. We suggest a deletion of either entry to avoid such duplication.

Section 2

PERSONNEL AND TRAINING

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.

We would suggest the addition of "quality" to the list of examples of relevant tertiary education

206. The Production nominee generally has the following responsibilities:

- *to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;*
- *to approve the procedures relating to production operations and to ensure their strict implementation;*
- *to ensure that facilities and equipment are maintained;*
- *to ensure that the appropriate validations are done;*
- *to ensure that the required initial and continuing training of production personnel is carried out*.

We seek confirmation that these responsibilities can be delegated when required.

207. The Quality nominee generally has the following responsibilities:

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

We seek confirmation that these responsibilities can be delegated when required.

Training

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.

We suggest the use of the term Production Nominee and Quality Nominee in lieu of "head of Production" and head of "Quality" for consistency with Clauses 206 & 207

Section 3

PREMISES AND EQUIPMENT

Principle

300. Premises, facilities and equipment should be located, designed, constructed, adapted, maintained, and suitable for its intended purpose. Their layout and design should aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, build up of dirt and, in general, any adverse effect on the quality of products.

In order to minimise the risk of microbiological, 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.

Premises, facilities and equipment which is critical to the control of processing should be formally qualified.

ATBF seeks a definition of “premises’ and “facilities” as these appear from this clause to be considered as different.

There are queries regarding the use of the term ”designed” as it implies that the facility would need to have been “designed” ad initio for Tissue banking activities. Many facilities have been converted from other prior uses. Clarification on the intent of this term is sought.

ATBF would also request the inclusion of a definition of “pyrogenic”

ATBF requests clarification of the intent of “where required” in Para 2. We are querying who would determine that this is applicable? In the same light we would inquire as to which clauses of the Annex are contemplated as being applicable

PREMISES

General

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

We request definition of “premises” as noted in comment to 300

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.

We seek clarification of what is included under the term “product” in this clause.

306 Premises for the manufacture of products should be specifically designed and used so as to avoid mix-ups or contamination.

We request definition of “premises” as noted in comment to 301.

We suggest the replacement of the word ”mix-ups” with “errors” in this clause and wherever else the term “mix-ups” occurs.

Storage areas

314 Storage areas should provide adequate space, suitable lighting, and be arranged and equipped to allow dry, clean and orderly placement of stored material under monitored environmental conditions (eg temperature, light, humidity)

ATBF would seek a definition of the term “dry” as unless specified it may be a relative term.

ATBF requests the deletion of all words after “material”.

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.

ATBF seeks clarification of the term “Storage Facilities” in this context. Does this clause refer to the storage vessel (such as an ultra low freezer) or does it refer to the room wherein the storage vessel is located?

EQUIPMENT

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

The use of the term “designed” in this clause is concerning as Tissue Banks often of necessity utilise items which were “designed” for other purposes. We recommend the use to the term “suitable for its intended purpose” as in the current Code.

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;*

ATBF seeks clarification of the term "where appropriate" in this clause. We are concerned that this level of monitoring which may well be appropriate for a storage freezer at a "fixed site" would be inappropriately applied to the transport of an individual allograft in an esky under previously validated conditions.

We suggest a distinct clause which would refer to the expectations during the transport of allograft.

Section 4

DOCUMENTATION

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

ATBF would request a definition of "permanent ink".

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.

ATBF seeks clarification as to whether these three clauses (411, 412, 413) should not appear under Section 10

Section 5

CONTROL OF MATERIAL

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*.

ATBF seeks confirmation that a Certificate of Analysis from an appropriate approved supplier for such a material would satisfy Dot Point 3 of this clause.

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

ATBF seeks clarification of the term "assessed" and its implications. As an example, would a material which his ARTG listed be considered as assessed.

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.

ATBF seeks clarification of the term "assessed" and its implications. As an example, would a material which his ARTG listed be considered as assessed?

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.

ATBF recognises and endorses the intent of this clause but would suggest a review for consistency with This Section of the code deals with "material" and this is the only cluse relative to a "product" other clauses. There is reference to a "Quality Control Department" and thus by extension implies the existence e of such a unit, whereas this is not a reality inmost tissue banks.

Section 6

SUBCONTRACTING

The ATBF suggest a definition of subcontractor versus contractor as these terms appear to be used interchangeably.

Section 7

COMPLAINTS AND RECALLS

Principle

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

ATBF wishes to comment that there interpretation of "all reasonable contingencies that may be anticipated" may be quite subjective.

Section 8

COLLECTION AND PROCESSING

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

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

ATBF suggest deletion of 801 & 802 as these statements are unnecessary as they are covered in Section 2 (Personnel & Training; 210 & 212), Section 4 (Documentation; 401) and Tissue Specific Standards.

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

ATBF suggest removal of :medical" form this clause as thus is addressed in Clause 806. It should also be noted that medical information can come to light at any time during and after donation process

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.

ATBF seeks clarification of the term ”authorised person” in this clause. .

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

ATBF seeks clarification of the term ”authorised person” in this clause

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.

ATBF seeks clarification of “controlled conditions” in this clause

818. Collection documentation 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*

Confidentiality of the donor should be maintained.

ATBF suggests the insertion of “deceased” between “the” and “donor” in the last dot point

PROCESSING

910 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.

ATBF suggests the insertion of “unintended” between “prevent” and “contact”.

TREATMENT BY RADIATION

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

ATBF suggest the review and reword of tis clause with the input of a radiation specialist.

Section 9

QUALITY CONTROL

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

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

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

910 Test records should include at least the following data:

- *reference to the donation;*
- *details of equipment and materials used;*
- *references to the relevant specifications and testing procedures;*
- *test results, including observations and calculations,*
- *date(s) of testing;*
- *identification of the person(s) who performed the testing;*
- *identification of the person(s) who reviewed the results, including a check of calculations, where applicable*

ATBF seeks clarification whether these clause (906. 907, 909 & 910) refer to the performance by the testing labs or by the tissue bank? Since testing is require to be carried out by a TGA licensed laboratory wherever possible, would not the intent of this clause be met by TGA licensure of the laboratory?

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.

The Infectious Disease Transmission Standard clause 10 specifies serum archiving requirements. We seek clarification as to what is intended here as “test samples”.

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.

There may be contamination inherent in the nature of collecting tissues (e.g. an expected contamination rate), hence corrective action of all contamination is not appropriate. ATBF recommends the removal of “corrective” from the last sentence.

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.

ATBF seeks clarification whether this clause is specific to blood donors only.

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.

ATBF suggests the inclusion of "Autologous Tissue" in this clause.

SECTION 10 COMPUTERS

PRINCIPLE

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

ATBF seek clarification the scope of this entire section. There is concern that expectations for a computer which controls automated processes will be applied to systems which are used for data handling.

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

ATBF suggest deletion of this clause as this is superfluous due to 1006 which lists the expected documentation required to support a computer system.

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 does not include terms such as ‘Blood’ or ‘Blood Component’,

‘Tissue’ or ‘Cellular Therapies’ which have interpretations in the legislation under which the Code applies and must be taken to have these interpretations for the purposes of the Therapeutic Goods (Manufacturing Principle –Human Blood and Blood Components, Human Tissues and Human Cellular Therapies) Determination No 1 of xxx.

AUTOLOGOUS A collection from an individual with the intention of subsequent transfusion or transplantation back to the same individual.

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

Installation Qualification (IQ): The documented verification that the equipment, as installed or modified, complies with the approved design and the manufacturer’s recommendations.

Operational qualification (OQ): The documented verification that the equipment, as installed or modified, performs as intended throughout the anticipated operating ranges.

Performance qualification (PQ): The documented verification that the equipment and systems can perform effectively and be replicated based on the approved process method and product specification.

There are many additional definitions which should be included.

References

1. Australian Code of Good Manufacturing Practice – Human Blood and Tissues. 2000. TGA.

2. Australian Code of good Manufacturing Practice for Medicinal Products, 2002
3. Guide to the preparation, use and quality assurance of blood components. 14th ed, 2008. Council of Europe

4. Recommendations on Validation Master Plan, Installation and Operation Qualification, Non-Sterile Process Validation, Cleaning Validation. PI 006-2, 1 July 2004. PIC/S.
5. Guide to Good Manufacturing Practice for Medicinal Products. PE 009-5, 1 August 2006. PIC/S.