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

To:

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On behalf of the Centre for Blood Cell Therapies at the Peter MacCallum Cancer Centre we thank you for the opportunity to review this much improved version of the cGMP.

We are very pleased with its structure and general content but have the following comments to make.

Clause	Page	Clause and Comment
104	5	• *therapeutic products are designed and developed in a way that takes account of the requirements of this Code and **Good Laboratory Practice**;* What is meant by the term 'Good Laboratory Practice'? Does it, for example, refer to the OECD Principles of GLP?
113	7	*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.* What is relationship between this annual review and the annual updates of a TMF?
Section 2		The role of the Director – as specified in section 1 of the current code –no longer exists. The new code should specify the position that the Production and Quality nominees report to, and which has the authority to arbitrate in matters relating to areas such as staffing.
Section 2		There is no requirement for the people provided the training to be appropriately qualified.
209	10	*Training programmes should be available, approved by either the **head of Production or the head of Quality Control**, as appropriate.* i) This clause should state 'Production nominee' and 'Quality nominee'. ii) Does 'head of Quality Control' refer to the Quality nominee, or is a separate 'Quality Control Department' envisaged? Our preference is that departmental structures are a matter for the manufacturer.
211	11	*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.* This clause is overly strict. Would it, for example, preclude auditors from entering these areas? We suggest the following rewording: *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.* (The reference to visitors in clause 303 uses more appropriate terminology.)
300	12	*Where required, applicable code clauses in Annex 1 of the mandated Code of GMP for Medicinal Products should apply.* It would be helpful to state that the applicable clauses of Annex 1 apply when a label claim is made that a product is sterile.

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304	12	***Where appropriate,*** *contingency plans for breakdowns in critical services or equipment should be developed and regularly reviewed. For example, in the event of power failure, where necessary there should be access to a power source to allow the maintenance of critical services and equipment* ***to permit the safe conclusion of activities in progress****.* i) What does 'where appropriate' mean? Does this decision rest with the manufacturer? ii) The option of discarding material should be clearly stated. iii) What are the expectations regarding manufacturers that chose to allow 'safe conclusion' of all activities or discard product as necessary because there could be substantial capital expenditure involved if all services must be 100% available?
317	14	*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.*** The phrase "where this poses a risk to the product" should be added to the final sentence otherwise quarantined product stores will not be able to store other relevant material such as in process or retention samples (ie -140 °C storage).
321	14	*Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned and sterilised if applicable, according to detailed and written procedures and stored only in a clean and* ***dry*** *condition.* This clause is overly specific. A steam steriliser, for example, may need to be left wet.
327	15	*Fixed pipe-work for gases and liquids should be labelled to indicate the contents and the direction of flow.* This seems a rather specific requirement for cells and tissues- should the outlets not be labelled? Labels on long piping runs may be remote from user.
328	15	*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;* i) Replace 'recording' with 'monitoring'. This permits use of devices that do not store data, otherwise this becomes a burdensome requirement with limited benefit. ii) Does this requirement extend to internal transfer? For example, between processing areas within the same building, or to/from on-site storage?
334	16	*Equipment already in use, which has been* ***moved to another location****, taken out of service, modified or undergone major repairs, should be re-qualified before re-entry into service.* This clause needs to allow for the use of mobile equipment.
408	18	*The manufacturer should establish, implement and maintain a procedure for controlling documents.* There should be a requirement for the version of a document to be uniquely identified. This is a separate task from that of controlling multiple copies.
503	19	*There should be approved quality control specifications for any material which may have a direct effect on the quality of the product.* i) Is the use of 'quality control' rather than 'materiel' meant to imply testing? Is it implying pharmacopeial quality testing? ii) Will this require QC testing of all material – for example, storage bags? Is ARTG listing not sufficient?

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508	19	*Material which does not conform to specifications should be prevented from unintended use and its **disposition** recorded.* Whilst the use of 'disposition' is correct, this meaning of the word is not in common usage.
510	20	*Materials should only be obtained from suppliers that have been evaluated and approved to ensure their ability to supply material meeting requirements..* i) This broad requirement would preclude the use of hospital purchasing systems. This puts in it conflict with Victorian State Law with respect to Hospital Purchasing Victoria. ii) It should be limited to material that has a direct impact on product quality or safety. iii) Do manufacturers (as opposed to suppliers) also need to be assessed?
512	20	*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. 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.* This clause implies the existence of a Quality Control Department that is not defined within the code. It should be made clear that this assessment is the responsibility of the Quality Nominee.
804	23	*Donors should be **chosen** according to documented procedures defining the selection criteria, infectious disease screening tests and any other relevant tests.* Replacing 'chosen' with 'evaluated' would make it more appropriate to the clinical setting, and for autologous use.
805	23	*A procedure should be established implemented and maintained for obtaining medical and other required statutory information **prior** to donation.* Specifying 'prior' is overly strict. Some information could be obtained 'at' donation, and other information may only be available after the collection has been completed.
819	25	*Collection documentation records should include:* • *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.* i) The physical examination could be done 'at time of' collection. ii) Why is a physical examination required for tissues, but not for cellular therapies? iii) Why do the <u>details</u> of the physical examination need to be documented on the collection record? For example, it may raise issues of patient (donor) confidentiality when collection records are sent to the manufacturing facility.
900	28	*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.* This clause implies the existence of a Quality Control Department that is not defined within the code.

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910	29	*Test records should include at least the following data:* • *reference to the donation;* • *details of equipment and materials used;* The clause should specify that it is the responsibility of the testing agency to maintain the information for all the bullet points listed in this clause, ie would a end-user subcontracting a test service require to have the machine model used for testing appear on the report? This is more than is generally required for test reports and exceeds NATA's requirements. A test method might be a more reasonable request.
913	29	*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 clause should contain a qualifier that for fresh product, this information may not be available at time of release.
916	30	*Products not released should be **identifiable** from those which conform to specification and have received their final inspection.* Does 'identifiable' mean by a label, or is physical separation sufficient? Note: Additional labelling may not be possible for frozen product. The common practice is for frozen products to be quarantined until release from frozen storage at which point such labelling might be possible.