Royal Brisbane and Women's Hospital
Metro North Health Service District

Queensland Government

Queensland **Health**

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Blood and Tissues Unit
Standards and Code of GMP
Office of Devices Blood and Tissues
Therapeutic Goods Administration
PO Box 100
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Dear Sir / Madam

Please find below comments in response to the consultation process for the draft Australian Code of Good Manufacturing Practice Human Blood and Blood Components, Human Tissues, and Human Cellular Therapies and the draft Therapeutic Goods Order XX:- Standards for Minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies. These comments have been submitted on behalf of the combined adult and paediatric Bone Marrow Transplant Program at the Royal Brisbane and Women's Hospital and Royal Children's Hospital.

1. The correct product names should be used for haemopoietic progenitor cells (HPC, Apheresis; HPC, Marrow and HPC, Cord Blood) as outlined by ISBT 128 labelling requirements, ICCBBA (http://iccbba.org/cellulartherapy_home.html) and the Foundation for the Accreditation of Cellular Therapy (FACT) (FACT-JACIE International Standards For Cellular Therapy Product Collection, Processing, and Administration Fourth Edition). HPC-A, HPC-M and HPC-C are not accepted abbreviations.

2. The draft code and the draft TGO do not address the collection of T cells for donor leukocyte infusion (ie. TC, apheresis and TC-T). Internationally, these products have specific infectious disease marker testing requirements. The Australian requirements should be consistent with those described by FACT.

3. Centres collecting haemopoietic progenitor cells within Australia are subject to multiple regulations and requirements. At the Royal Brisbane & Women's Hospital and Royal Children's Hospital, the clinical, collection and processing facilities of the bone marrow transplant program have been assessed by overseas inspectors and determined to be operating at a level consistent with world best practice as outlined in the FACT-JACIE

International Standards for Cellular Therapy Product Collection, Processing, and Administration Fourth Edition 2008. Accreditation by FACT / JACIE is a requirement to participate in many international clinical trials associated with bone marrow transplantation. The processing facility and apheresis units have also been inspected by NATA against the Australian National Pathology Accreditation Advisory Council (NPAAC) Requirements for Procedures Related to the Collection, Processing, Storage and Issue of Human Haemopoietic Progenitor Cells 2009 and ISO 15189. All of these standards and codes document the requirement for a robust quality system based on the principles of ISO 9001 together with requirements specific to bone marrow transplantation. Therefore inspection by the Therapeutic Goods Administration against this draft Australian Code of Good Manufacturing Practice Human Blood and Blood Components, Human Tissues, and Human Cellular Therapies burdons a hospital based clinical and laboratory transplant program with the significant additional costs associated with the application and inspection process, together with little or no anticipated benefit or change to patient outcome except an associated increase in paperwork to demonstrate compliance with another requirement. As health funding is limited these significant costs are diverted from direct patient care.

4. The draft code does not contain sufficient detail and this leaves many paragraphs open to interpretation by individual inspectors. For example, paragraph 337 of the draft code should specify to what standard balances must be calibrated ie. National Association of Testing Authorities, Australia 2009 Technical Note #13 - User Checks and Maintenance of Laboratory Balances or alternative. A further example exists in paragraph 917 that states "Where applicable, product should be appropriately labelled". This paragraph should state specifically how the product should be labelled. In addition, the labelling requirement should be consistent with the international requirements specified by FACT-JACIE.

5. Many of the quality management requirements outlined in the draft code are based on ISO 9001:2008 Quality Management Systems – Requirements and ISO 15189:2007 Medical laboratories -- Particular requirements for quality and competence. For clarity, the draft code should refer to the ISO 9001 and ISO 15189 standards for quality management issues and document specific requirements for Human Blood and Blood Components, Human Tissues and Human Cellular Therapies separately.

6. There is no clause that permits the use of directed or related donors of HPC, Apheresis; HPC, Marrow and HPC, Cord Blood for bone marrow transplantation, that have been determined as ineligible based on the results of infectious disease marker testing or donor medical history. These directed donors are permitted under international standards (FACT-JACIE) when the risk or prognosis of a recipient's underlying medical condition, usually haematological malignancy, is significantly greater than the risk of infectious disease transmission using an otherwise ineligible directed or related donor. A clause analogous to paragraph 917 of the draft code should exist that permits the use of allogeneic directed or related HPC, Apheresis; HPC, Marrow and HPC, Cord Blood for bone marrow transplantation based on "urgent medical need".

7. Similarly schedules 1, 2, 3 and 5 of the draft TGO exclude many HPC, Apheresis and HPC, Marrow donors for allogeneic bone marrow transplantation such as voluntary unrelated donors listed on the Anthony Nolan and British Bone Marrow Donor Registries (Schedule 2 (1)(i)) and donors with "ineligible medical and social" criteria. At present there appears to be no provision for "exceptional manufacture" of these HPC on the basis of urgent medical need and Schedule 2 paragraph 1 states that these HPC must not be manufactured.

8. Significant additional resources and infrastructure would be required to enable the storage of serum samples from donors of HPC for a minimum of 2 years after the expiration date of the cellular therapy product as mandated by Schedule 4 Point 10 as expiration dates of HPC stored at -196°C have yet to be determined. Current evidence indicates that HPC, apheresis and HPC, marrow may be stored for >15 years.

9. Establishment of bioburden in HPC, Apheresis, HPC, Marrow and HPC, Cord Blood would have a significant cost and resource implication on a hospital based clinical transplant program. This centre's 22 year experience with microbiological contamination of HPC has indicated that immunocompromised patients undergoing bone marrow transplantation are at far greater risk from commensal microorganisms, their disease and associated treatment than from the infusion of contaminated HPC. No adverse event has ever been observed at this centre following the infusion of contaminated HPC. Many similar reports exist in the scientific and medical literature.

Overall, the TGA should implement the already defined international FACT / JACIE standards (FACT-JACIE International Standards For Cellular Therapy Product Collection, Processing, and Administration Fourth Edition October 2008 and NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration Fourth Edition January 2010) adopted within Europe and North America for accreditation of hospital based clinical and laboratory bone marrow transplant programs. Introduction of a separate Australian code of GMP, which is in conflict with the international standards as outlined, could create significant issues concerning the access of Australian bone marrow transplant patients to international donors and international patients to Australian donors.

Yours sincerely

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