

## Status of the regulatory oversight of haematopoietic progenitor cells (HPCs)

HPCs for bone marrow transplant (BMT) are harvested in two settings:

1. As *adult* HPCs from peripheral or (rarely) marrow collections
2. As *cord blood* HPCs from placental cord blood collections

HPCs were defined as blood components in 2000. *Cord blood* is banked and used for autologous or allogeneic transplant. It has been regulated through licensure of the manufacture under the Australian Code of GMP for Human Blood and Tissues (cGMP) since 2000. It is also subject to a product Standard for quality and safety. From 2000 to 2003 this Standard was the chapter on HPCs from the *Council of Europe Guide for blood and blood components*. When this Guide excluded HPCs from its purview, the TGA removed HPCs from the definition of *fresh blood components*. Cord Blood was then brought under a new Standard, Therapeutic Goods Order 73 (<http://www.tga.gov.au/docs/pdf/tgo/tgo73.pdf>) which specifies compliance of cord blood with the international standards published by the Foundation for the Accreditation of Cellular Therapy (FACT) and NETCORD as the product Standard. Regulatory oversight via the cGMP Human blood and tissues was retained. This framework for cord blood was developed with full input by the sector and ratified by the Therapeutic Goods Committee.

The situation with *adult* HPCs is more complex. According to the **Australian bone marrow donor registry (ABMDR)**, the sector's activities in 2003 included:

- ❖ Total transplants: 1253
  - Australia 1112
  - New Zealand 141
- ❖ Autologous transplants
  - Australia 752
  - New Zealand 92
- ❖ Allogeneic related
  - Australia 210
  - New Zealand 35
- ❖ Allogeneic unrelated
  - Australia 150
  - New Zealand 14
- ❖ Institutions
  - Australia 37
  - New Zealand 6

**(AUSTRALASIAN BONE MARROW TRANSPLANT RECIPIENT REGISTRY ANNUAL DATA SUMMARY 2003)**

In all the Therapeutic Goods Orders relating to blood components, the TGA has always excluded from regulation autologous and directed components. This has been a reflection of the TGA's detachment from medical practice and was also influenced by the need to allow rapid access to emergency donor panels in the event of local and national emergencies when regulation of fresh blood was established in 2000.

As seen from the above 2001 breakdown, over 90% of adult HPC manufacture is currently exempt from the TGA's oversight if the same provisions for autologous and directed blood components apply. A number of developments have contributed to the TGA developing additional thinking on this issue:

1. Over the past three years, a number of Australian hospitals producing adult HPCs have developed GMP facilities for these cells whose operation is detached from the medical environment.
2. Two of these hospitals have sought TGA approval of their manufacture of adult HPCs as this was required by the sponsors of international clinical trials in which these hospitals were seeking inclusion.
3. While autologous/directed components constitute a minority of products in the mainstream blood sector, they represent the majority of procedures in the adult HPC sector and their exclusion from oversight is therefore incongruous. This situation is exacerbated by the inclusion of cord blood HPCs, which are used for the same indication but which are a small minority of HPC transplants, in regulation.
4. Increasingly highly manipulated HPCs are being used in innovative therapies, such as their use to repair damaged myocardium after myocardial infarction. These therapies represent a higher level of risk than mainstream transplant, but their oversight is difficult to envisage in an environment naïve to regulation.
5. Internationally and locally, HPCs are now considered to be more appropriately classified as cellular therapies rather than blood components. The TGA's development of a regulatory framework for such therapies lends itself to the inclusion of HPCs to the framework.

Therefore, in 2004 the TGA initiated a dialogue with the HPC sector with a view to extending the regulation of HPCs across the full spectrum of activity using a risk-based model. The TGA identified the Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ) and the Bone Marrow Transplants Scientists Association as the key professional stakeholders in the sector. Three meetings were held over 2004-2005 and a position was developed:

1. All HPCs would be transferred to the new cellular therapies framework.
2. The current arrangements for cord blood-derived HCPs would come into the framework as Class II therapies.
3. HCPs which were supplied by hospital units which were :
  - Not supplying HPCs which were manipulated beyond collection and storage

and

- Supplied by the transplant unit for use within that unit or by clinical units directly linked to that unit in their medical programs and infrastructure

and

- Solely supplying HPCs which were autologous and or directed

would be classified as Class I therapies.

4. These Class I facilities would be regulated through:

- The establishment of a Standard which would be recognised by the TGA through an appropriate Therapeutic Goods Order
- The identification of a competent and responsible individual who would be legally charged with demonstrating the facility's compliance with the Standard to the TGA
- The use of a Declaration of Compliance with the Standard, which would be filled and submitted to the TGA by the responsible individual on a regular and pre-established basis.

5. It was agreed that the following principles would apply:

- The responsible and competent person would be the medical director of the transplant facility or program.
- The Standard would be the FACT Standard for therapies other than cord blood.
- The structure of the Declaration to be drafted by the TGA and submitted for refinement and review by a sample of facilities, after which it would be adopted.

6. Laboratories involved in the testing of HPCs would be assessed on the basis of the types of tests. Subsequently, the TGA has initiated a dialogue with the National Association of Testing Authorities, which accredits pathology testing laboratories to a number of standards including ISO 15189. The TGA intends to mandate this standard as the Standard for testing laboratories performing testing for HPCs in Class I facilities. The TGA will require NATA accreditation as evidence of adherence to this Standard.

7. HPCs which are highly manipulated or used for non-homologous purposes, such as genetically manipulated HPCs, cord blood used for myocardial regeneration etc will be regulated as Class IV therapies requiring the highest level of pre-market review including assessment of therapeutic claims.

Currently, the TGA is continuing to work on this approach with the sector with a view to introducing this framework over 2006. The TGA will work with jurisdictions and other stakeholders to ensure a smooth transition for facilities which are currently not subject to regulation.

The TGA would welcome comments on this proposed approach to the regulation of HPCs, by contacting the Regulator Professor Albert Farrugia – [albert.farrugia@health.gov.au](mailto:albert.farrugia@health.gov.au)