Regulation and Accreditation of Haemopoietic Progenitor cell transplant facilities in Australia

First American Congress for the Accreditation of Medical Laboratories, Blood Banks and Haemopoietic Progenitor cells

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What will be covered:

The Regulation of the Haemopoietic progenitor cell transplant facilities

NATA Accreditation and Standards for Haemopoietic progenitor cell transplant facilities

The Regulation of the Haemopoietic Progenitor Cell sector

The regulation of Haemopoietic progenitor cells (HPCs) transplant sector falls under the sphere of the Therapeutic Goods Administration (TGA)

The Biologicals Regulatory Framework is the term in legislation to regulate human cell and tissue-based products as a distinct group of therapeutic goods called 'biologicals

The regulatory framework for biologicals provides the legislative basis for the regulation of human tissue and cell-derived products that are supplied, in or exported from, Australia.

The biologicals legislation commenced on 31 May 2011, following a recommendation from Australian Commonwealth, State and Territory Health Ministers to improve the regulation of human tissues and cell based therapies.

The Regulation of the HPCs

The framework applies different levels of regulation to products based on the risks associated with their use

The framework has also been designed to be flexible enough to accommodate emerging technologies

All products within the scope of the framework need to comply with the requirements made under the legislation

The Legislative framework is complex !!!

The Regulation of the HPCs

The Framework is described in Australian Regulatory Guidelines for Biologicals (ARGB) Part 1 - Introduction to the Australian Regulatory Guidelines for Biologicals

The key features of the framework are:

- **The Biologicals Regulatory Framework provides a comprehensive system of assessment and controls that must be completed before products are allowed to be marketed in Australia (pre-market), and follow-up and further controls after they are marketed (post-market)**

- **Before biologicals can be legally imported, exported, manufactured or supplied in Australia, they must be:**

- **included on the Australian Register of Therapeutic Goods (ARTG) or**

- **otherwise exempted, approved or authorised.**

The Regulation of the HPCs

The Biologicals Regulatory Framework allows for four classes of biologicals based on the risk posed by the products, which are in turn related to:

- **the methods used to prepare and process the products during their manufacture**

and

- **whether their intended use is the same as their usual biological function**

The Biologicals Regulatory Framework includes provisions for biologicals to be exempt from the TGA's usual requirements for inclusion on the ARTG to allow legal supply under certain circumstances (such as for clinical trials, emergency situations or use by individual patients)

The Regulation of the HPCs

What is a Biological?

The amended Therapeutic Goods Act (TG Act) defines a biological as an item made from, or containing, human cells or human tissues, and that is used to:

- **treat or prevent disease or injury**
- **diagnose a condition of a person**
- **alter the physiological processes of a person**
- **test the susceptibility of a person to disease**
- **replace or modify a person's body part(s).**

The Regulation of the HPCs

To be included in the Biologicals Regulatory Framework, products must:

- **be a therapeutic goods (as defined in the TG Act)**
- **not be an 'excluded good'**
- **either meet the definition of a biological or are specified by legislative instrument to be a biological**
- **not be specified in the Therapeutic Goods Determination as <u>'Things that are not biologicals'.</u>**

The Regulation of the HPCs

Some biologicals that fall within the definition of a therapeutic good in terms of their use (i.e. they are used to treat, prevent or diagnose a disease or condition) have been declared not to be therapeutic goods

These excluded products include:

- **fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation (e.g. bone marrow cells and cord blood)**

The Regulation of the HPCs

Classification of Biologicals largely based on level of manipulation

Class 1 biological – low risk with high individual benefit and/or there are other appropriate means of oversight such as accreditation and/or a high level of medical oversight

Class 1 biological products are required to be manufactured in compliance with all standards applicable to that product type and manufacturers of Class 1 biologicals will not be required to hold a TGA manufacturing licence

Class 2 biological – low risk

- **Processed by minimal manipulation (refrigeration, freezing, trimming, flushing, washing) and for homologous use (same function in recipient as donor)**

  e.g. milled bone for allografts, heart valves and corneas

The Regulation of the HPCs

Class 3 biological – medium risk

- **Processed by more than minimal manipulation (e.g. enzymatic) and in a way that does not change inherent biochemical, physiological or immunological properties**
- **Either for homologous use or functions other than their original, natural function**

e.g. cultured fibroblasts for skin repair, chondrocytes for cartilage repair

e.g. mesenchymal stem cells for repair of myocardial ischemia

Class 4 biologicals – high risk

- **Processed in a way that changes an inherent property**

e.g. genetically modified fibroblasts for repair in Duchenne muscular dystrophy

Regulated as biologicals	Excluded from regulation as therapeutic goods	Regulated as therapeutic goods but not as biologicals
Human cellular therapy products, such as: • stem cells and progenitor cells; e.g. –haematopoietic progenitor cells for uses other than haematopoietic reconstitution –other stem cells (e.g. neural, epithelial) –other progenitor cells (e.g. nasal cells)	Fresh viable haematopoietic progenitor cells (e.g. bone marrow, cord blood) used for blood regeneration	Haematopoietic progenitor cells used for haematopoietic reconstitution

The Accreditation of the HPCs

NATA has offered accreditation to the HPC sector since 1998 when 1st Ed of the National Pathology Accreditation Advisory Council (NPAAC) requirements for Haemopoietic Progenitor Cells was published

Until recently accreditation covered Laboratory activities only

Now accredits against ISO 15189 and the National Pathology Accreditation Advisory Council (NPAAC) requirements

- **Requirements for procedures related to the collection, processing, storage and issue of Human Haemopoietic Progenitor Cells (2015)**

NATA Medical Testing now accredits:

- **Human Progenitor cell collection units**
- **Progenitor cell transplantation procedures**
- **Haematological and other Pathology testing if performed in HPC laboratory (otherwise covered in the "Pathology lab"**
  - **Flow cytometry etc**

The Accreditation of the HPCs

- Who are NPAAC?
- A section within the Commonwealth Department of Health
- is comprised of representatives from all states and territories, nominees from peak professional bodies and the Department of Health.
- NPAAC advises the Commonwealth, state and territory health ministers on matters relating to the accreditation of pathology laboratories
- plays a key role in ensuring the quality of Australian pathology services
- is responsible for the development and maintenance of standards and guidelines for pathology practices in the Australian context

The Accreditation of the HPCs

- NPAAC Requirements state that a processing facility must only accept product from a NATA/RCPA accredited or TGA Licensed collection site
- Also that a Collection site can only send product to a NATA/RCPA accredited or TGA Licensed processing unit
- NATA/RCPA accreditation does NOT include stem cell bio-banks for research purposes or higher risk “Biological Classes”
- NATA R&D Accreditation can include Bio-banks

The Accreditation of the HPCs

- **NATA/RCPA scope of Accreditation falls under Haematology:**

- ***Human progenitor cell collection***
  - **Product sent to Accreditation number AN 1234**

- ***Progenitor cell transplantation procedures***
  - **Product received from AN 2345**

- **35 Progenitor cell Collection units linked to**
- **28 Progenitor cell transplantation procedure laboratories**

The Accreditation of the HPCs

Assessments are performed so as to acknowledge the relationship between collection and processing

- **usually on consecutive days if logistics allow**

Any issues identified at the Collection unit can be followed up at the processing unit

Assessments include :

- **Nursing staff involved in collection activities (new area of technical assessors)**
- **Directors of Oncology services responsible for service provision in Oncology clinics**
- **Haematologists and Clinical Scientist specialists in HPC procedures**

The NPAAC Standards for HPC assessments

The Standards apply to Laboratories and other facilities involved in donor selection, collection, processing, storage and issue or disposal of directed minimally manipulated:

- **haemopoietic progenitor cells (HPC)**
- **cord blood; and**
- **donor lymphocytes which are used for haemopoietic reconstitution**

Activities related to other cellular therapies, including, but not limited to, HPC sourced from autologous or unrelated cord blood, are outside of the Scope of these Requirements

Collection of HPC sourced from, or on behalf of, overseas international Donor Registries are not captured by these Requirements

The NPAAC Standards for HPC assessments

For the purposes of the Requirements, '<u>product</u>' is defined as one of:

- **Haemopoietic progenitor cells, apheresis (HPC(A)) —**
  - **HPCs collected from the peripheral blood of a donor using an apheresis technique, usually after administration of recombinant haemopoietic growth factor and/or chemotherapy.**
- **Haemopoietic progenitor cells, marrow (HPC(M)) —**
  - **HPCs aspirated from the iliac crests, sternum or other bones of a donor.**
- **Haemopoietic progenitor cells, cord blood (HPC(CB)) –**
  - **whole blood, including HPC, collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.**
- **T cells, apheresis — donor lymphocyte products collected by apheresis.**
- **T cells, whole blood — donor lymphocyte products collected as whole blood.**
- **T cells, marrow – donor lymphocyte products collected by bone marrow aspiration.**

The NPAAC Standards for HPC assessments

Overview of contents:

- **Quality management**
- **Donor evaluation and selection**
- **Product collection**
- **Product processing**
- **Product testing**
- **Labelling**
- **Product storage**
- **Cellular product issue and distribution**
- **Transport and disposal**
- **Adverse events**
- **Health and safety**

The NPAAC Standards for HPC assessments

Donor selection

- **Donor evaluation procedures must be in place and the results of the evaluation and selection recorded**
- **All donors must be tested for evidence of clinically relevant infection by any of the following communicable disease agents within 30 days before collection:**
- **(a) human immunodeficiency virus, type 1**
- **(b) human immunodeficiency virus, type 2**
- **(c) hepatitis B virus**
- **(d) hepatitis C virus**
- **(e) human T lymphotropic virus I/II**
- **(f) Treponema pallidum (syphilis)**
- **(g) cytomegalovirus (CMV) antibodies (allogeneic only)**

The NPAAC Standards for HPC assessments

Donor testing

- **Donors must be tested for ABO group and Rh (D) type at least seven days before the first collection.**

- **Laboratory testing of all donors must be performed by a NATA/RCPA-accredited or Therapeutic Goods Administration (TGA)-licensed or equivalent accredited Laboratory.**

Additional requirements for allogeneic donors

- **Allogeneic donors must be tested for human leukocyte antigen (HLA)-A, -B and -DR type by a laboratory that is accredited or licensed to perform such testing**

- **Allogeneic donors must be assessed for infectious disease risk using a current blood donation statement**

The NPAAC Standards for HPC assessments

Donor consent

- **Informed consent from the donor must be obtained and recorded by the transplant medical practitioner or other health care provider familiar with the collection procedure.**

- **Allogeneic donors must give written informed consent and authorisation to permit release of their health information to the transplant physician and recipient as appropriate.**

- **This consent must be viewed by the collection facility staff before the collection procedure.**

The NPAAC Standards for HPC assessments

Product collection

- **The collection facility staff must perform product collections for at least one year before being eligible for accreditation**
- **A satisfactory NATA/RCPA Advisory Visit must be undertaken prior to procedures commencing in any new collection facility**
- **A minimum of 10 HPC-A procedures must be performed by the new collection facility prior to a NATA/RCPA accreditation assessment**
- **New collection facilities must achieve NATA/RCPA accreditation within 18 months of the Advisory Visit.**

The NPAAC Standards for HPC assessments

Collection facility

- **Product collection and storage must occur in separate areas.**
- **Collection equipment must not be used for non-patient related work.**
- **There must be designated, physically separate areas for the storage of products during quarantine.**

Personnel

- **There must be a Collection Facility Medical Director.**
- **All staff performing collection procedures on paediatric patients must have specific training and experience for patients of this age.**

The NPAAC Standards for HPC assessments

Procedures

- **For every collection, the recipient's transplant medical practitioner must submit to the collection facility a written and signed request that includes approved identifiers for the recipient and donor, details of the procedure, target cell number and the expected date and time of the collection**
- **A duplicate of this request must be forwarded to the processing facility.**
- **A donor blood test to determine HPC numbers must be performed during the**

  24 hours before HPC collection by apheresis
- **Collection procedures must be validated to ensure acceptable cell recovery and viability**

The NPAAC Standards for HPC assessments

Product processing

Processing facility

- **Processing facilities must only accept products from:**
  - **(a) NATA/RCPA accredited collection centres; or**
  - **(b) TGA licensed apheresis units; or**
  - **(c) new collection facilities that have undergone a satisfactory NATA/RCPA Advisory Visit**

- **Processing facilities may only accept product from a new collection facility for a period of 18 months from the date of the NATA/RCPA Advisory Visit unless the new collection facility gains NATA/RCPA accreditation.**

The NPAAC Standards for HPC assessments

Procedures

- **Cryopreservation procedures must be described in the processing facility's standard operating procedures manual and must include the following information:**
- **(a) proper name of the product**
- **(b) cryoprotectant solution and its final concentration**
- **(c) maximum cell concentration that can be frozen**
- **(d) cooling rate(s)**
- **(e) endpoint temperature of cooling**
- **(f) storage temperature**
- **(g) Alternative validated procedure in case of equipment failure during the freezing process.**

The NPAAC Standards for HPC assessments

Procedures

- Processing procedures must be validated in the processing facility to indicate acceptable target cell viability and recovery.
- Critical control points must be identified and associated assays performed on each product
- Procedures for processing must use aseptic techniques and must be performed in a manner that minimises the risk of cross-contamination
- The objectives and acceptable endpoints for each procedure must be specified in the standard operating procedure manuals.

The NPAAC Standards for HPC assessments

Product testing

Routine processing

- **A nucleated cell count must be performed on each product after collection and after all subsequent processing**
- **A CD34+ cell count and/or clonal progenitor cell assay must be performed on the final product**
- **A target CD34+ or nucleated cell count must be monitored against transplant outcomes for each product**
- **For products undergoing cryopreservation, at least two test samples of the product (cryopreserved and stored under conditions that ensure a valid representation of the clinical product) must be available for testing, as and when required**
- **Before the issue of a cryopreserved product, the viability and enumeration of a relevant target cell population must be evaluated from a cryopreserved sample of the product using a relevant and validated test**

The NPAAC Standards for HPC assessments

Product testing

Routine processing

- **The Laboratory must validate a time interval of storage after which testing must be repeated before issue**
- **Immediately prior to cryopreservation, a sample of the product must be tested for microbial growth**
- **Tests not performed by the cell collection or processing facility must be performed in a NATA/RCPA-accredited or TGA-licensed or equivalent accredited Laboratory**

The NPAAC Standards for HPC assessments

Labelling

- **Extensively refers to the International Society of Blood Transfusion (ISBT) 128 Standard for the identification, labelling, and information transfer of human blood, cell, tissue, and organ products across international borders**

Collection label

- **On completion of the collection procedure, the primary container or associated documentation must be labelled before being disconnected from the donor, with the following information:**

(a) proper name of product or accepted abbreviations, as defined in the ISBT 128 Standard2

The NPAAC Standards for HPC assessments

Adverse events

- **These Requirements apply to any incidents, adverse event or reaction that occurs during the collection, processing, storage, issue or transport or any other related activity associated with performing these procedures.**

- **Adverse events include, but are not limited to, suspected disease transmission, significant accidental loss of cells, equipment failure that may affect the final cellular product integrity or any other unintended event associated with infusion of the HPC product.**

The Accreditation new facilities without “history”

- No previous records
- Cannot use “real” patients to set up processes
- All critical equipment should have completed an Installation Qualification (IQ) and Operational Qualification (OQ) prior to seeking accreditation
- Many critical aspects can be verified by using saline or plasma as a substitute for HPC
- Mock runs using sterile HPC substitute can be performed prior to assessment and can be used to provide an evidence base for aseptic techniques
- Protocols and practices for minimising risk of cross-contamination can be described in SOP's prior to assessment
- The apheresis equipment and collection method will be fully validated once collections begin. The validation is reviewed at assessment

Resources

NATA – www.nata.com.au

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NPAAC - www.health.gov.au/npaac

TGA - www.tga.gov.au

Thank you for your attention

Any questions?