Implementing Standards Across International Borders

Australian experience in using international standards for cell therapies

June 27, 2007

Foundation for the Accreditation of Cellular Therapy

JACIE joint accreditation committee isct-ebmt

Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

- 1) How to create,
- implement and apply universal standards and 2) Experiences with
- complying with voluntary and regulatory standards in the various
- countries:

- - were the standards written to facilitate globilization
- - how was this accomplished
- - what were the challenges
- - what needs to be considered when performing assessments in a foreign
- country
- - how do you ensure consistency of inspections
- - how do your voluntary standards compare with the federal requirements
- - do both perform inspections
- - are the inspections similar or different
- - advantages to having both voluntary and federal inspections
- - can/will regulatory agencies allow resiprosity

Some definitions
Licensure

"Licensure is a process by which a government authority grants permission to an individual practitioner or health care organisation to operate or to engage in an occupation or profession. Licensure regulations are generally established to ensure that an organisation or individual meets minimum standards to protect public health and safety. Licensure to individuals is granted after some form of examination or proof of education and may be renewed periodically through payment of a fee and/or proof of continuing education or professional competence. Organisational licensure is granted following an on-site inspection to determine if minimum health and safety standards have been met. Maintenance of licensure is an ongoing requirement for the health care organisation to continue and operate and care for patients".

Rooney, AL, van Ostenberg, P.R Licensure, Accreditation, and Certification: Approaches to Health Services Quality. Quality Assurance Project, Bethesda USA 1999

Some definitions
Accreditation

"Accreditation is formal process by which a recognised body, usually a non-governmental institution, assesses and recognises that a health care organisation meets applicable pre-determined and published standards. Accreditation standards are usually regarded as optimal and achievable, and are designed to encourage continuous improvement efforts within accredited organisations. An accreditation decision about a specific health care organisation is made following a periodic on-site evaluation by a team of peer reviewers, typically conducted every two to three years. Accreditation is often a voluntary process in which organisations choose to participate, rather than one required by law and regulation".

Rooney, AL, van Ostenberg, P.R Licensure, Accreditation, and Certification: Approaches to Health Services Quality. Quality Assurance Project, Bethesda USA 1999

Cell therapy regulation in Australia Current provisions

- Cell therapies regulated as
  - Medicines
    - Eg cell based vaccines
    - Clinical trial review
    - Pre-market review
    - Manufacturing license
  - Devices
    - Eg demineralised bone
    - Therapeutic devices
  - Engineered Tissues
    - Eg ACIs
    - Manufacturing license
  - “Others”
    - Eg HPCs
    - Manufacturing license + **product standard**

The Baume Report 1991

"Australia should, whether or not it enters into further co-operative arrangements with other countries, retain its ultimate sovereign authority over the granting of marketing approvals for therapeutic substances…….

Australia should not develop its own standards for pharmaceuticals except for uniquely Australian products or in response to unique Australian conditions or in response to a demonstrated public health need……"

Case Study
Standards for haemopoeitic progenitor cells in Australia

- Prior to 2000, blood components from the Australian Red Cross were exempt from regulation in Australia
- Such exemptions did not apply to components not manufactured by the ARCBS
- Legal advice indicated that such products were captured by the TGAct
- Some provisions exempted some HPCs eg unmanipulated BM
- TGA decided to include HPCs in fresh blood framework

TGA THERAPEUTIC GOODS ADMINISTRATION

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Commonwealth Department of Health and Aged Care

COMMONWEALTH OF AUSTRALIA

Therapeutic Goods Act 1989

Therapeutic Goods Order No.66

STANDARDS FOR BLOOD COMPONENTS

I, TERRY SLATER, delegate of the Minister for Health and Aged Care for the purposes of section 10 of the *Therapeutic Goods Act 1989* and acting under that section, having consulted with the Therapeutic Goods Committee in accordance with subsection 10(4) of the said Act, DETERMINE that the matters specified in this Order constitute standards for blood and blood components.

In this order:

Definitions

“blood” means whole blood extracted from human donors;

"blood components" means therapeutic components that have been manufactured from blood (including red cells, white cells, **stem cells**, platelets and plasma), except plasma for fractionation.

Standards and requirements:

1. Blood and blood components must meet the requirements of the Council of Europe document titled "Guide to the preparation, use and quality assurance of blood components" 6th Edition, dated January 2000, Council of Europe Publishing. This guideline represents the minimum standard that must be met by blood and blood components.
2. Blood and blood components must only be manufactured from blood that tests negative for HIV-1 and HCV using Nucleic Acid Amplification Technology.

This Order shall commence to operate on the date it is gazetted.

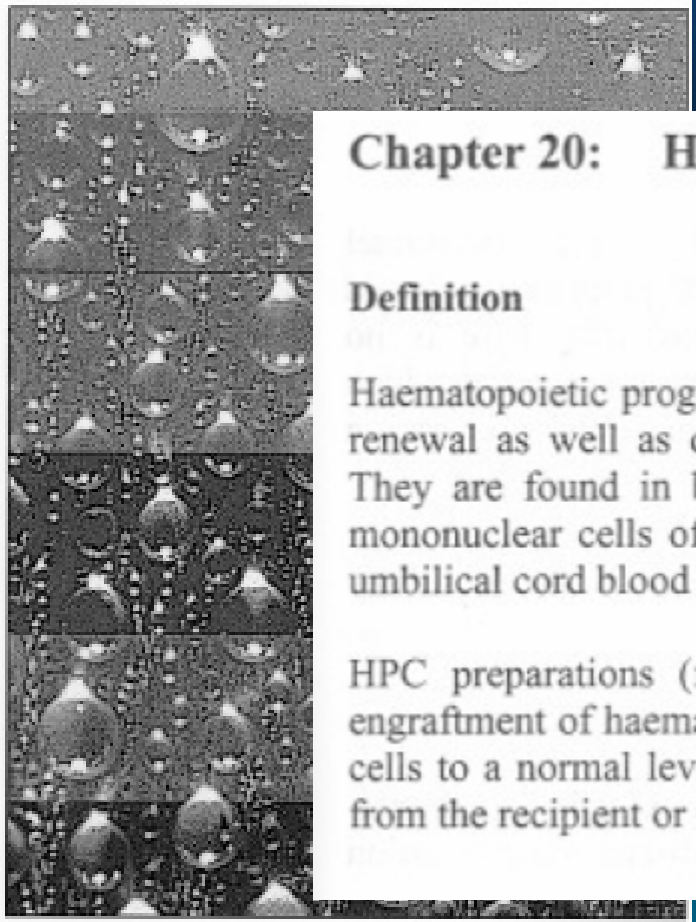
Dated this 23rd day of August 2000

Exemptions

HPCs which are

- collected by a medical practitioner in the course of medical treatment and for the purposes of diagnosis of testing for, a medical condition
- manufactured by a medical practitioner for therapeutic application to a particular patient under the practitioner's care
- manufactured by a blood collection centre for a medical practitioner for therapeutic application to a particular patient under the practitioner's care

These exemptions are generally considered to cover **autologus and directed donations under the supervision of a medical practitioner** where the blood or blood components are immediately supplied for a named patient on a pre-determined basis. Where storage occurs and supervision of that storage by the same medical practitioner can not be guaranteed, the blood or blood components may not be exempt.



Guide to the preparation, use and quality assurance of blood components

6th edition

Council of Europe Publishing
Editions du Conseil de l'Europe

Chapter 20: Haematopoietic progenitor cells

Definition

Haematopoietic progenitor cells (HPC) are primitive pluripotent cells capable of self renewal as well as differentiation and maturation into all haematopoietic lineages. They are found in bone marrow [bone marrow cells (BMC)], fetus liver, in the mononuclear cells of circulating blood [peripheral blood stem cells (PBSC)] and in umbilical cord blood [umbilical stem cells (USC)].

HPC preparations (from all four sources) are intended to provide a successful engraftment of haematopoietic stem cells leading to a restoration of all types of blood cells to a normal level and function in the recipient. The infused HPC can originate from the recipient or from another individual.

Introduction of new standards – 2003 -

- CoE dropped Ch 20 in 2002
- HPC sector considered CoE not suited to their program
- TGA consulted with sector on best Standard
- CB stakeholders agree on Netcord
- Other stakeholders - FACT best option but some provisions unsuited to Australia:
  - Medical accreditation
  - Laboratory organisational structure
  - Research/ethical/GMP issues
- Propose adopting FACT with necessary excisions

TGA Proposed Order 2003

- The Second Edition of the *Standards for Hematopoietic Progenitor Cell Collection, Processing & Transplantation* of the Foundation for the Accreditation of Cellular Therapy is the Australian Standard for haemopoietic Stem Cells harvested from sources other than placental cord blood.

Qualifier to proposed Order 2003

- ***The provisions of this document shall apply to those areas of haemopoietic stem cells related to product quality and quality system management****. Areas in the document related to medical practice, organisational structure, personnel qualification and others not directly related to product quality and quality system management are not mandatory. Areas in the document reflecting areas of good manufacturing practice specified in the Australian Code for Good Manufacturing Practice for Human Blood and Tissues shall be subservient to that Code. Areas in the document reflecting the practice of clinical research as specified by the National Health and Medical Research Council shall be subservient to the relevant guidelines of that organisation. Areas in the document relating to the disposal of haemopoietic stems cells addressed by provisions in the relevant legislation of the individual states and territories shall be subservient to those provisions.*
- *The TGA will negotiate with individual agencies when areas of possible contention arise.*

FACT Acceptance
18 July 2003

On behalf of FACT and the Board of Directors, we endorse your public adoption of the FACT Standards as the official Australian Standard for the Quality of Hematopoietic Progenitor Cells. The language that you have provided in your letter is very good, and is acceptable to us.

Phyllis I. Warkentin, MD

Chair, Inspection and Accreditation

Foundation for the Accreditation of Cellular Therapy

Problem

- Proposed qualifier considered too general by legal unit
- Requested specific excisions from the FACT document for exemptions
- Excisions would have altered FACT document substantially
- FACT (UNDERSTANDABLY) hesitant about authorising excisions

Fact Standards for Hematopoietic Progenitor Cell Collection, Processing &Transplantation

✓ keep

X remove

PART B: CLINICAL PROGRAM STANDARDS	
B1.000	**Clinical Transplantation Program**
B1.100 ✓	The Clinical Transplantation Program consists of an integrated medical team housed in geographically contiguous or proximate space with a single Program Director and common staff training programs, protocols and quality management systems. The Program shall use haematopoietic cell collection and processing facilities that meet FACT Standards with respect to their interactions with that clinical program. Programs that include non-contiguous institutions in the same metropolitan area shall demonstrate common protocols, staff training procedures, quality management systems, and review of clinical results and evidence of regular interaction. Several clinical sites, particularly with different Directors, or outside a single metropolitan area, joining together for the purpose of meeting criteria to qualify as a program do not fulfil the intent of these Standards.
B1.200 ✓	The Clinical Program shall abide by all applicable governmental laws and regulations.
B1.300 X	**Program Size**
B1.310 X	A minimum of 10 new patients shall have been transplanted during the twelve-month period immediately preceding the application for program accreditation and annually thereafter.
B1.320 X	If the Program requests accreditation for both allogeneic and autologous transplantation, a minimum of 20 new patients, including at least 10 new allogenic patients and at least 5 new autologous patients shall have been transplanted during the twelve-month period immediately preceding the application for program accreditation and annually thereafter.
B1.330 X	If accreditation for only one type of transplant (allogeneic or autologous) is being requested, 10 new recipients of transplants of that type shall have been treated during the twelve-month period immediately preceding the application for program accreditation and annually thereafter.

B2.130 X	Provisions for prompt evaluation and treatment by a transplant attending physician available on a 24 hour basis
B2.140 X	Nurse experienced in the care transplant patients
B2.150 X	A nurse/patient ratio satisfactory to cover the severity of the patients' clinical status
B2.160 X	A Collection Facility and a Haematopoietic Progenitor Cell Processing Facility that meet these Standards with respect to their interaction with that Clinical Program.
B2.170 X	A transfusion service providing 24-hour availability of CMV appropriate and irradiated blood products needed for the care of transplant patients.
B2.180 X	A pharmacy providing 24-hour availability of medications needed for the care of transplant patients.
B2.181 X	If clinical research is performed, the pharmacy shall have a mechanism for tracking, inventory and secured storage of investigational drugs.
B2.190 J LTo be adapted for Australian setting	Programs performing allergenic haematopoietic cell transplants shall also use HLA testing laboratories, licensed by the TGA, with the capability of carrying-o deoxyribonucleic acid (DNA)-based HLA-typing.
B2.200	**Safety Requirements**
B2.210 J	The Program shall be operated in a manner to minimize risks to the health and safety of employees, donors, volunteers and patients. Suitable quarters, environment and equipment shall be available to maintain safe operations.
B2.220 J	There shall be procedures for biological, chemical and radiation safety, as appropriate and a system for monitoring training and compliance.
B2.230 J	Haematopoietic progenitor cells shall be handled and discarded with precauti that recognise the potential for exposure to infectious agents.

Deleted: accredited by the American Society of Histocompatibility and Immunogenetics (ASHI)

Deleted: X

B3.220 X	The Program Director shall have at least one year of specific clinical training in haematopoietic progenitor cell transplantation as defined in B3.400, or two years experience as an attending physician responsible for the clinical management of haematopoietic progenitor cell transplant patients in the inpatient and outpatient settings. The Program Director shall have written confirmation of his/her training or experience comm the Director of the program, department, or institution in which that training or experience was obtained. The Program Director should participate regularly in educational activities related to the field of haematopoietic stem cell transplantation.
B3.230 J	The Program Director is responsible for the administrative and clinical operations including compliance with these Standards. The Program Director shall have oversight of all elements of the program including the selection of patients and donors, collection of cells, and processing of cells whether internal or contracted services.
B3.231 J	The Program Director shall be responsible for the quality management of the entire program.
B3.232 J	The Program Director shall be responsible for the policies and procedures for donor evaluation, selection and pre and post donation care and compliance with these Standards as listed in Section B6.000.
B3.240 J	The Program Director shall have oversight of the medical care provided by the Program including medical care provided by the physicians on the transplant team. The Program Director is responsible to verify the knowledge and skills of the physicians of the transplant team. Management of the Clinical Unit may be delegated to a Medical Director who fulfils the requirements in B3.300.
B3.300 X	**Other Attending Physicians**
B3.310 X	Transplant Program attending physicians shall be appropriately licensed to practice medicine in the United States or Canada (or appropriate governmental agency), and should be board certified or eligible in one of the specialities listed in B3.210.
B3.320 X	Transplant Program attending physicians should have specific clinical training in haematopoietic progenitor cell transplant medicine as defined in B3.400, and should participate regularly in educational activities related to the field of haematopoietic stem cell transplantation.

Progression with stakeholders

- Consultation with the Bone Marrow Transplant Society of Australia and New Zealand and the Bone Marrow Transplant Scientists Association of Australia
- Agreed that Standard would be developed based on FACT principles but with “Australian” flavour
- Agreed to progress Standard development through National Pathology Accreditation Advisory Council (NPAAC)

Role of NPACC

- NPAAC established under the *Health Insurance Act 1973*
- Primary role is to advise Australian governments on standards development and policy for accreditation of pathology laboratories.
- Sets standards and guidelines for safe and quality laboratory practice that pathology
- laboratories must meet in order to be accredited.
- NPACC uses international standards and Australian standards to set standards for pathology laboratories in Australia

Requirements for Procedures Related to the Collection, Processing, Storage and Issue of Haemopoietic Progenitor Cells

National Pathology Accreditation Advisory Council

First Edition 2006 Draft 2

Bibliography

These Requirements have been developed with reference to current Australian and other international requirements, including:

ABMDR (Australian Bone Marrow Donor Registry) (2005) -NO- Guidelines-001-05.

FACT (Foundation for the Accreditation of Cellular Therapy) and JACIE (Joint Accreditation Committee – ISCT and EBMT) (2005). International Standards for Cellular Therapy Product Collection, Processing and Administration, 3rd edition (draft). http://www.jacie.org/portal/jacie/standards (Accessed 3 Aug 2006).

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NHMRC (National Health and Medical Research Council) (1999). National Statement on Ethical Conduct in Research Involving Humans. NHMRC: Canberra.

TGA (Therapeutic Goods Administration) (2000). *Australian* Code of Good Manufacturing Practice – Human Blood and Tissues. http://www.tga.gov.au/docs/html/gmpbltic.htm (Accessed 3 Aug 2006).

Lessons and conclusions

- Introduction of international standards desirable but not always possible
- Equivocality not possible in regulatory measures
- Accreditation bodies can contribute to good regulation