Regulation of autologous cell and tissue therapies in Australia

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Regulation of Therapeutic Goods

Product

Therapeutic Good
- Medical Device
- Medicine
- Other
- Biological
  - Not Included
  - Included
    - Therapeutic Goods (Things that are not Biologicals) Determination

Excluded Good
- Therapeutic Goods (Excluded Goods) Order
Australian biologicals regulatory scheme
‘The Biologicals Framework’

• Introduced May 2011 (fully in place by 2014)
• Set standards relating to manufacturing processes and standards for individual products
• Minimise risk of infectious disease transmission (TGO 88)
• Match level of regulation to the level of risk/ manipulation of products
• Provide ability to respond to changes in technology
• Support greater international harmonisation
• Develop appropriate GMP - recognising lack of control over starting materials and that many cells and tissues are not batch produced
What is a biological?

Comprises, contains or is derived from human cells or human tissues, (OR is specified by the Secretary to be a biological), AND is used to
- treat or prevent disease, ailment, defect or injury; or
- diagnose the condition of a person; or
- influence, inhibit or modify a physiological process in persons; or
- test the susceptibility of persons to a disease or ailment;
- replace or modify parts of the anatomy in persons.

UNLESS it is determined to be a ‘thing that is not a biological’
Classification of biologicals

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

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. demineralised bone matrix for repair, reconstruction of bone defects
  - 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
Current Class 2 biologicals

Human tissues currently in Australian tissue banks

- Ocular tissue
- Skin
- Cardio-vascular tissue
- Bone and tendons
The **Therapeutic Goods (Excluded Goods) Order No.1 of 2011**

- Non-viable **tissues of animal origin** e.g. porcine heart valves
- **Fresh viable human organs** for direct donor-to-host transplantation
- Fresh viable human **haematopoietic progenitor cells** (e.g. bone marrow cells, cord blood) for direct donor-to-host transplantation
- **Reproductive tissue** that have not been processed apart from freezing
- **Autologous tissue and cells (including stem cells)**  
  - collected **under the care of a medical practitioner, and**  
  - manufactured for treatment of a **single indication, and**  
  - in a **single course of treatment** of that patient **by the same medical practitioner**, or by a person under their supervision

*Other autologous uses* are not exempt in Australia
Public consultation on regulation of autologous stem cell therapies

Concerns from industry
• Increasing number of companies and medical clinics offering ‘autologous stem cells’ that are not regulated under the Act
• Business models designed to limit regulatory oversight
• AHPRA and medical boards insufficient powers to investigate
• Patients not concerned

The boundary between human cell and tissue products derived and used as part of medical practice and those supplied as products manufactured for therapeutic use is not always clear

Medical practice is regulated by the Australian Health Practitioner Regulation Agency and state and federal Medical Boards

Therapeutic goods are regulated by TGA
Is current Australian regulation of autologous stem cells appropriate?

- **USFDA** takes a narrow view of 'minimal manipulation' and 'homologous use' for adipose-derived stem cells in Dec 2014 draft industry guidance documents.
- Interpretation of 'minimally manipulated' and 'homologous use' is relevant.
- **80 submissions received** – from businesses, industry groups, hospitals, professional bodies, individual patients.
Autologous procedures/products specifically excluded from the consultation

- Skin grafts, including keratinocyte sprays
- Skull flaps
- Vascular conduits
- Pancreatic islet cells
- Bone grafts
- HPCs for reconstitution of blood after treatment of cancer
- Blood to seal cerebrospinal fluid leaks
- Blood components
- Cosmetic/reconstructive procedures (skin, bone, fat transfers)
Regulatory options

Five options that variously address one or more of

- Concerns about public **advertising**, by restricting advertising of stem cells to healthcare professionals only
- Application of **standards** under the Act to the production of stem cells (infectious disease, product specific, pharmacopeial)
- Requiring the reporting of **adverse events**
- Evaluation of stem cell products for **safety and/or efficacy**
- Application of **manufacturing quality standards** to stem cell products
Consultation views

• **Submissions posted** at www.tga.gov.au/submissions-received-regulation-autologous-stem-cell-therapies

• **Wide range of views** – from maintaining *status quo* to regulation of autologous stem cell products as class 2-4 biologicals

• Many current private clinics argued for the *status quo*, with concerns re costs of regulation and constraints on business

• However, several private clinics
  – acknowledged that autologous stem cells are **therapeutic goods**
  – supported **mandatory adverse event reporting**
  – and some supported **some controls over advertising**

• Some called for an **industry code of conduct** instead
Consultation views – medical professional bodies, research groups, consumer groups

- **Limited evidence for adverse events** but
  - but some harm from 'radical' procedures
  - not known since there is no requirement to report adverse events

- **Need to clarify definitions of** 'homologous use' and 'minimal manipulation'

- **'Single course of treatment'** more liberal than in some other OECD countries

- Issue of **practitioner expertise** in the procedures offered

- Important for **clinical trials to generate efficacy data**
  - but there is currently limited incentive to conduct proper trials
  - Regulation as class 2-4 biological would mandate efficacy data
Overarching considerations

- The **case for regulation** needs to identify actual risk (or harm) and to consider costs of regulation.
- Government requires regulation to be considered as an option only **after other approaches have been shown not to work**.
- Practice and product regulation intersect.
- Changes in regulation are likely to affect other autologous cell and tissue therapies.
- Concerns may also arise under the **Australian Consumer Law** where consumers are misled or deceived into believing that certain treatments are safe or effective when that is not the case.
Next steps

- **Response to the consultation** will help inform what, if any, change is required to therapeutic goods regulation.
- **Policy discussion** with Minister on options.
- Determination of the **legal nature** of any change.
- If any regulatory change is proposed, a **Regulation Impact Statement (RIS)** is required along with **further consultation**, including on costs and benefits to affected parties.
Regulatory status of allogeneic skin and keratinocytes

- Regulated under the Biologicals Framework as Class 2 Biologicals, if
  - Processed by minimal manipulation (refrigeration, freezing, trimming, flushing, washing) and for homologous use (same function in recipient as donor)
- Regulated under the Biologicals Framework as Class 3 Biologicals, if
  - Processed by more than minimal manipulation (e.g. enzymatic dissociation, culture) 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
Regulatory status of autologous skin and keratinocytes

- Currently excluded from regulation by the TGA by the Excluded Goods Order, if
  - Collected under the care of a single medical practitioner, and
  - Manufactured for treatment of a single indication, and
  - Used in a single course of treatment of that patient by the same medical practitioner, or by a person under their supervision

- Not included in the consultation on regulation of autologous stem cell therapies
  - Application of any potential regulatory changes to autologous skin and keratinocytes would require further consultation
Minimal manipulation

• A process involving any of the following actions:
  – centrifugation;
  – trimming, cutting or milling;
  – flushing or washing;
  – refrigeration;
  – freezing;
  – freeze drying (of structural tissues only);
  – the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents;
  – irradiation for the purpose of bioburden reduction;
  – any other action that is similar to an action mentioned in paragraph (a), (b), (c), (d), (e), (f), (g) or (h).
Things that are not biologicals

- Haematopoietic progenitor cells (used for haematopoietic reconstitution), other than those which are excluded from regulation
- Samples of human cells or tissues that are solely for diagnostic purposes in the same individual
- Blood, blood components
- In-vitro diagnostic devices
- Biological medicines including
  - Vaccines (that do not contain viable human cells)
  - Recombinant products
  - Plasma-derived products (or that contain plasma-derived products)