Stem cells now and in the future: regulation in Australia

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ARCS Scientific Congress 2015

5 May 2015
Australian biologicals regulatory scheme introduced May 2011 (fully in place by 2014) to:

- Sets 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 specific biologicals
- 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
Classification largely based on level of manipulation

**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

**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
Standards

• **Product-specific standards** specify the minimum technical requirements for safety and quality
  – TGO 84 (Standards for human cardiovascular tissue)
  – TGO 83 (Standards for human musculoskeletal tissue)
  – TGO 85 (Standards for human ocular tissue)
  – TGO 86 (Standards for human skin)

• **Infectious disease transmission minimisation** (TGO 88)

• **Default standards** in the latest editions of the British, European or the US Pharmacopeias

• **Therapeutic Goods (Manufacturing Principles) Determination**
  – sets out the manufacturing and quality system requirements by referencing the code of GMP for blood and blood components, human tissues and human cellular therapy products
Examples of regulated biologicals

Tissues
- skin replacement after severe burns
- heart valves
- bone, tendons and ligaments to repair injuries
- corneas to restore eyesight

Cells
- chondrocytes for cartilage regeneration
- pancreatic islet cells for treatment of diabetes
- fibroblasts, epithelial cells, chondrocytes
- immunotherapy products, such as cell-based tumour vaccines
Stem cells refresher

- **Hematopoietic stem cells**: precursors of mature blood cells
- **Embryonic stem cells**: replicate, pluripotent (form all other cell types)
- **Mesenchymal stem cells**: Bone marrow stromal cells that can give rise to a number of tissue types such as bone, cartilage, fat and connective tissue
- Cell, tissue or organ transplant from one person to a different person is **allogenic** transplantation, back to the same individual is **autologous** transplantation
Exemptions under the Biologicals framework

- 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 for direct donor-to-host transplantation** (e.g. bone marrow cells, cord blood)
- **Reproductive tissue** (e.g. sperm, eggs, embryos) that have not been processed in any way apart from freezing

- **Autologous tissue and cells**
  - collected from a patient **under the care of a medical practitioner, and**
  - manufactured for therapeutic 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
Understanding of risks of cell therapies is limited

• Can risk of infectious disease transmission ever be eliminated?
  – Cells and tissues often cannot be sterilised fully
  – Donor screening – difficult to obtain complete history for deceased donors
  – Subjective nature of exclusion decisions
  – Evolving knowledge e.g. prions and degenerative neurological diseases

• Many biologicals cannot be stopped once in a recipient’s body

• Limited adverse event reporting because only some stem cell therapies are in formal clinical trials and adverse events can also be masked by poor progress of critically ill patients

• Unforseen reactions have been reported
  – e.g. heart attack, severe thrombosis, encephalomyelitis, bone tissue
Practice and product regulation intersect

- Different regulatory frameworks oversee medical practice (Medical Board of Australia/ AHPRA) and therapeutic products (TGA), but the boundaries can overlap.

- 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.

- As mentioned earlier - some autologous stem cell products are excluded from TGA regulation under the Therapeutic Goods (Excluded Goods) Order 1 of 2011 under certain conditions.
What are some other regulators doing?

FDA
- New guidances are more prescriptive about what defines ‘homologous use’ and ‘minimal manipulation’
- ‘Right to try’ movements also have momentum

Europe
- Only about five ‘advanced therapy medicinal products’ have been approved by EMA
- ‘Hospital exemption system’ for some cell and tissue products rather than private clinics performing treatments

Japan
- ‘Provisional licensing’ system for cell therapies (SAKIGAKE initiative)
- Where initial safety and manufacturing results positive; limited term commercial licensing to establish product efficacy and confirm safety
Concerns with the current regulatory model

- Lack of evidence to support the efficacy of autologous stem cells
- Large sums of money being charged for unproven treatments
- Safety of some stem cell products – either direct safety impacts or safety issues incidental to the therapy
- Lack of mechanisms for reporting of adverse effects of the products
- Inappropriate advertising of the products
Is current Australian regulation of autologous stem cell appropriate?

- Interpretation of ‘minimally manipulated’ and ‘homologous use’ is relevant

- **USFDA takes a narrow view** of ‘minimally manipulation’ and ‘homologous use’ for fat stem cells in Dec 2014 draft industry guidance documents

- In Australia, a **public consultation** (Jan-Mar 2015) held to seek input on **five potential options for regulation** of these cells as therapeutic goods

- 80 submissions received
In the discussion paper a range of options are proposed for comment

*These 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
- 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
<table>
<thead>
<tr>
<th>Option 1: Continue to exclude autologous cells from regulation under the Act#</th>
<th>Option 2: Exclude autologous stem cells from regulation under the Act in defined circumstances</th>
<th>Option 3: Regulate autologous stem cells under Act, but exempt from registration and manufacturing requirements</th>
<th>Option 4: Regulate under the Act as Class 1 biologicals</th>
<th>Option 5: Regulate under the Act as Class 2, 3 or 4 biologicals</th>
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</thead>
<tbody>
<tr>
<td>Advertising to health practitioners only</td>
<td>No (still subject to ACCC and AHPRA)</td>
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<td>TG Act standards</td>
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<td>Adverse effect reporting</td>
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<td>Safety requirements</td>
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<td>Efficacy requirements</td>
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Next steps

- Cell and tissue regulation is a **new and evolving area** internationally
- **Response to the autologous stem cell 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) would be required and undergo **further consultation**, including on costs and benefits to affected parties