Australian Government
Department of Health
Therapeutic Goods Administration

Biologicals framework updates

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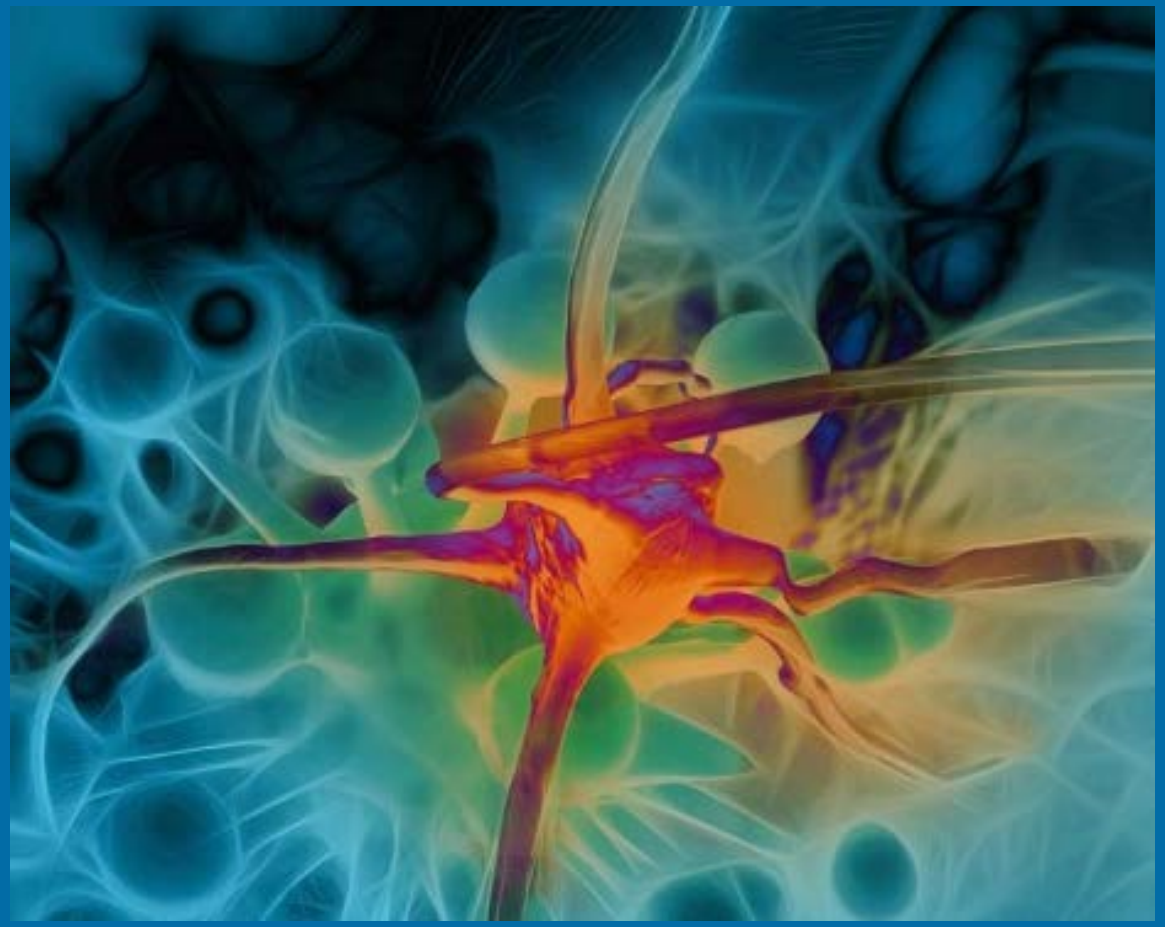
TGA Health Safety Regulation

Overview

- Biologicals framework
- Current regulatory status
- Challenges
- Changes
  - General
  - Excluded Goods Order
  - MMDR changes



Medicines and blood products

- prescription medicines
- over-the-counter medicines
- complementary medicines
- blood, blood components and plasma derivatives

Medical devices

- implants (artificial hips, breast implants)
- in-vitro diagnostics (pregnancy tests, blood glucose monitors)
- low risk medical devices (bandages, tongue depressors, condoms)

Biologicals

- human stem cells
- tissue-based products (skin and bone)
- cell-based products

What are biologicals?

In Australia, 'biologicals' is the name for cell and tissue therapy products:

- Comprises, contains or is derived from human cells or tissues
- Represented in any way to be for therapeutic use
- Live animal cells, tissues and organs

- Framework was introduced on 31 May 2011 to provide a legislative basis for the regulation of these products.
- It applies different levels of regulation to products based on the risks associated with their use, and was designed to accommodate emerging technologies.

The Australian biologicals framework

Not regulated by TGA*

- Fresh viable organs
- Assisted reproductive technologies (in vitro fertilisation)
- Fresh haematopoietic progenitor cells (bone marrow transplants)
- Cells and tissues made by a medical practitioner for a single patient under the care of that medical practitioner

*It is not practical to regulate these products. There are appropriate checks in place because of professional practice.

Regulated, but not as biologicals^

- Biological prescription medicines (vaccines, plasma derivatives)
- Labile blood and blood components
- Haematopoietic progenitor cells (non-fresh transplants)
- Non-viable animal tissue products

^These are regulated as either medicines or medical devices

Regulated as biologicals

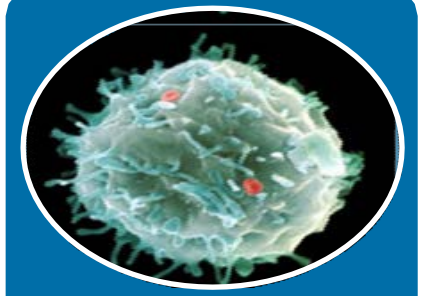
- Tissue-based products (skin, bone, ocular, cardiovascular)
- Cell-based products (T cell therapies, human stem cells)
- Combined cell and tissue products (collagen matrices for localised cell delivery)
- Viable animal tissue products (xenotransplantation)

Biologicals are grouped into classes

Examples:

Acellular skin for wound covering

Class 2



Mesenchymal stem cell for treatment of graft-versus-host disease

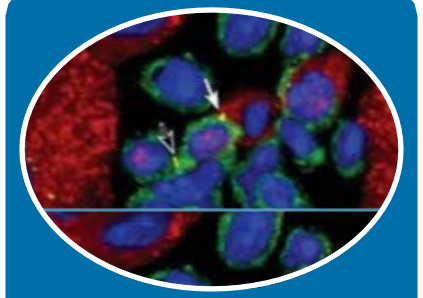
Class 3

Demineralised bone mixed with carrier

Class 3

Dermal fibroblasts transformed for skeletal muscle repair in primary myopathy

Class 4

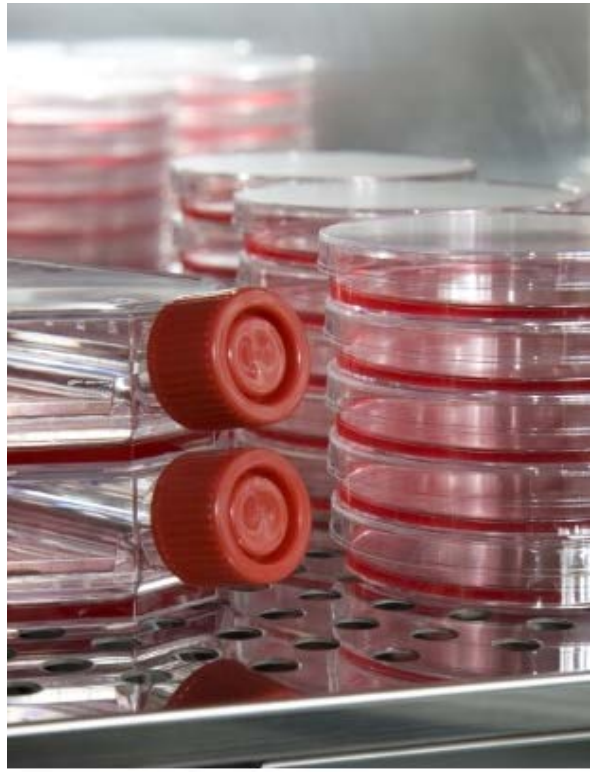


Genetically-modified T cells used to treat specific virus infections

Class 4

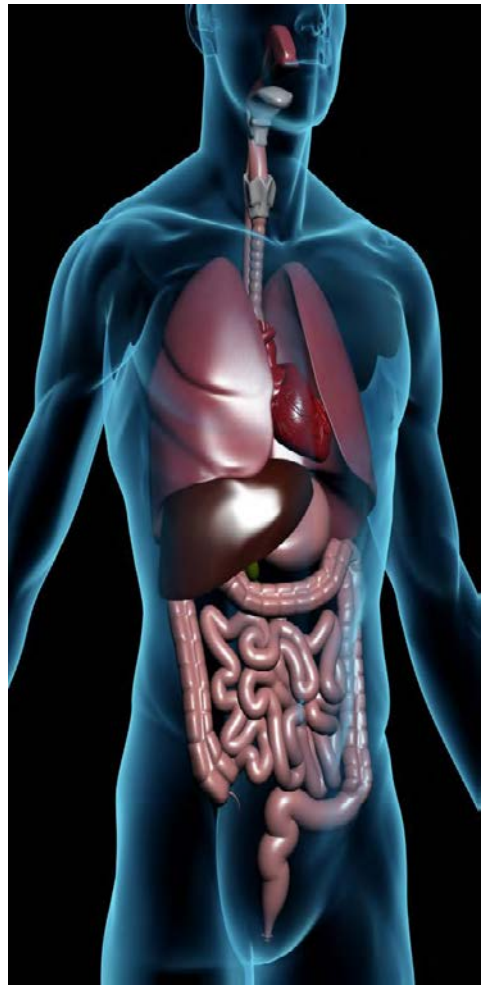
Current approvals

- Class 2
  - All domestic tissue banks (eye, skin, musculoskeletal, cardiovascular)
  - Some overseas tissue e.g. acellular skin
- Class 3
  - Ortho-ACI
  - Demineralised bone matrix - mixed with carrier (overseas)
- Class 4
  - Approved 4 CTX applications for CAR T cells and parthenogenically-derived stem cells



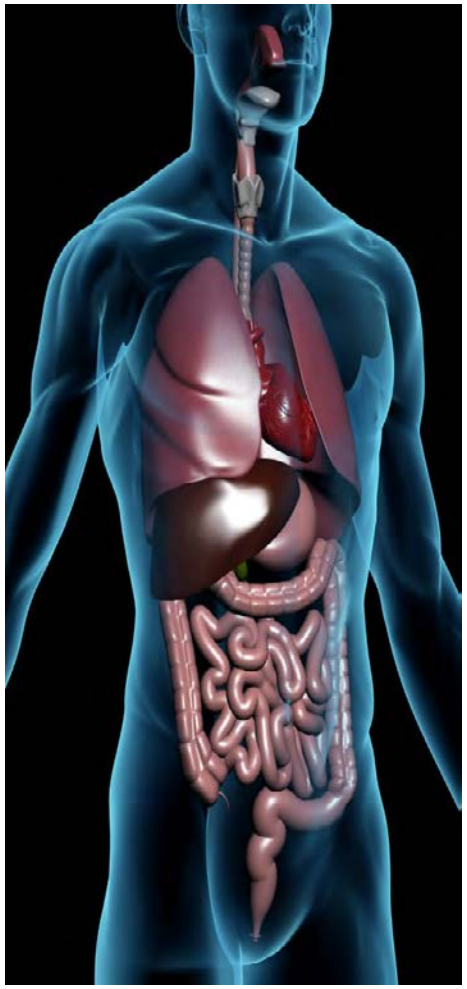
Challenges

- Clinical trials
  - Focus on quality aspects that relate to safety e.g. donor selection and testing, control over manufacturing, control of vector, insertional mutagenesis
  - No review of potency
  - Control and quality of critical materials
- Product registration
  - Poor product characterisation – defines the design of the manufacturing process
  - Development of surrogate potency assays
  - Scale-up, changes to the manufacturing process (comparability)



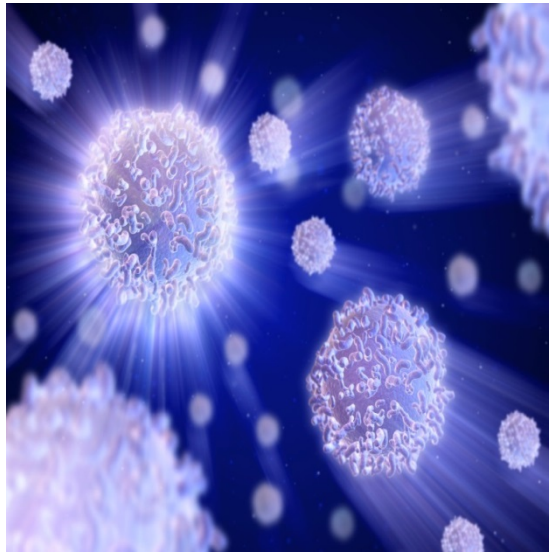
Recent and proposed changes

- Live animal cell & tissue therapies now under the biologicals framework
  - Number in clinical trial development e.g. encapsulated porcine islets
  - Non-living animal tissue still to be regulated as Medical Devices
- Update to TGO 75 – Standards for cord blood-derived HPC
- Update to TGO 81 – Standards for blood & blood components (2018)
- Update to the Australian Regulatory Guidelines for Biologicals
  - Major structural update to guidance
  - Revision of content and expansion
  - Change to dossier structure – CTD
- Biovigilance and RMP guidance



Review of the Therapeutic Goods (Excluded Goods) Order No.1 of 2011

- **Autologous cells and tissues (Medical practice)**
  - 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
- Under review due to concerns raised by stakeholders
- Two rounds of public consultation (2015 & 2016)
- Recommendations shortly to be provided to the Minister
- Guidance is being prepared
- Communication plan



Medicines and Medical Devices review (MMDR)

- Biologicals were not within the scope of the review
- Where possible the legislative changes and new pathways will also be rolled out for biologicals
- MMDR updates:
  - Changes to advertising powers and enhanced post-market monitoring capability
  - Orphan drug program – not for biologicals
  - Expedited pathways - comparable overseas reports, priority review, provisional approval
  - Self-assessable notifications, electronic forms for variations
  - Support and advice for SME's
  - SAS C process

MMDR expedited pathways

- To facilitate earlier access to medicines that address unmet clinical needs for Australians, without compromising standards for safety, efficacy and quality.
- Two new 'expedited' pathways for prescription medicines based on the government response to the recommendations of the MMDR review:
  - **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances

    Implemented 1 July 2017
  - **Provisional Approval** on the basis of early data on safety and efficacy, where the immediate availability of the medicine outweighs the risk that more data is required

    Under development, planned for first quarter of 2018

Expedited pathways: Eligibility criteria

- New prescription medicine or new indication
- High level eligibility criteria for Priority Review and Provisional Approval
  - ✓ Serious condition; and
  - ✓ Major therapeutic advance; and
  - ✓ Positive comparison against existing therapeutic goods

  Priority Review based on '*substantial evidence*'

  Provisional Approval based on '*promising evidence from early clinical data*'

- Sponsors may apply for the Orphan designation prior to or simultaneously with a Priority Review or Provisional Approval designation application

Comparable overseas regulator

- Expedited review process where a report from a Comparable Overseas Regulator (COR) is available
- To replace the current Category 2 process
- Consulted on the COR criteria and TGA considerations
- The report would be submitted along with a complete dossier, some Australian-specific information and additional evidence, as required.
- Further targeted consultation on conditions and proposed pathways to be consulted with industry

Provisional approval

Provisional Approval implementation scheduled for first quarter of 2018 (subject to legislative amendments)

- Provisional registration of goods in the initial absence of full clinical data on safety and efficacy
- Granted for specified time periods (2 years + up to 2 extensions of 1-2 years each)
- Sponsors required to collect and submit further clinical data to demonstrate efficacy and safety for full registration
- Enhanced post-market monitoring and surveillance
- Subject to the provision of clear advice to consumers and healthcare professionals and any other conditions imposed by the TGA

Risk-based approach to minor variations - notifications

All registered medicines:

- OTC
- Registered complementary medicines
- Prescription (chemical and biological medicines)
- Biologicals (human cells and tissues)

Staged implementation

New electronic form for prescription medicines minor variations

One-stop shop

- Consolidating six PDF forms into one electronic form
- Reduced time and effort in making applications
- Allows a real-time view of ARTG entries
- More efficient processing of requests

Launch

- 18 sponsors were involved in testing
- Progressive soft launch during July
- Full launch 25 July 2017
- Paper forms will be turned off as an option by legal instrument in the near future.

Notifications for biologicals

Change	Conditions
Infectious disease test kit change	a. No decrease in specificity, sensitivity, limit of detection and accuracy b. Performed as per kit instructions, including the intended use c. Same level of regulatory approval of the kit d. TGA GMP certification of the testing facility
Reduction in shelf-life of product or shipping timeframes	a. Revised specifications are still within the scope of the TGA approved validation studies b. No quality or safety concerns triggered the change
New manufacturing site	a. No changes to the approved manufacturing processes b. TGA GMP certification of the manufacturing site for that step c. No need to perform validation of the manufacturing process at the site d. The new manufacturing site is not responsible for donor screening and testing

SME Assist

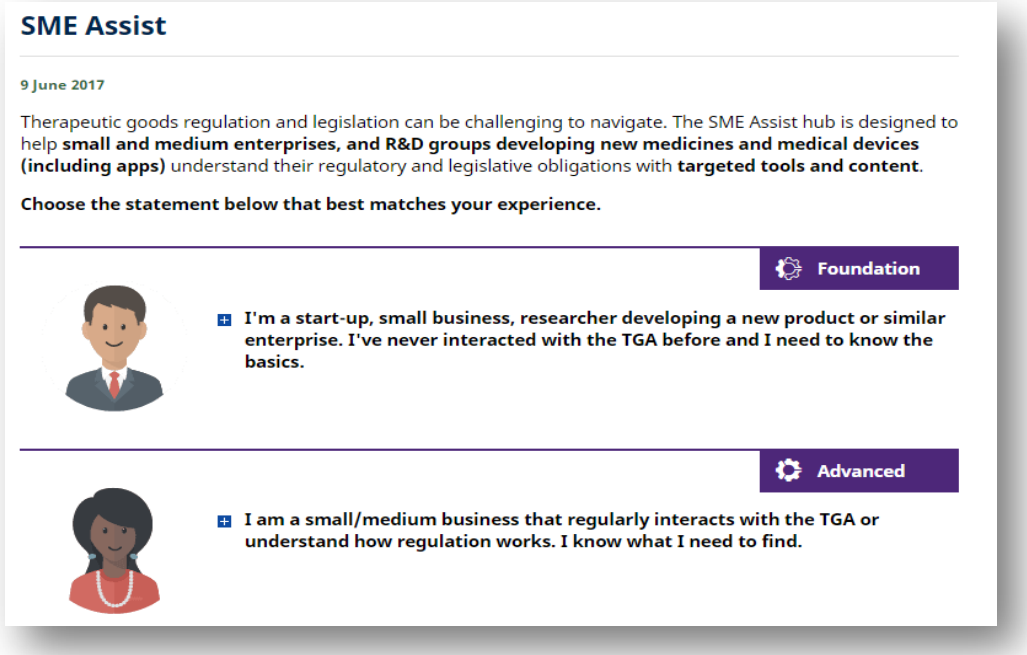
Guidance materials should be easily accessed and understood by a range of audiences, including small and medium enterprises (SMEs)

- Launched **Friday, 9 June 2017** at the Translational Research Institute, Brisbane by the Hon Greg Hunt, Minister for Health and Sport.
  - → Targets the needs of SMEs and R&D groups
  - → Assists them to meet requirements for local and international markets
  - → Provides Australian consumers with earlier access to innovative therapeutic goods

SME Assist – 5 key components

1) SME Assist web page

- Articles covering basics, market authorisation, when to engage with the TGA
- Targeted at SMEs and organisations that have not previously interacted with TGA



2) Education and training

- Activities and programs (face-to-face workshops, webinars)
- Videos and presentations

SME Assist – 5 key components

3) **Interactive tools**
   - Decision trees to better understand therapeutic goods regulation relevant to their product
     - *Is my product a therapeutic good?*
     - *What classification is my biological?*

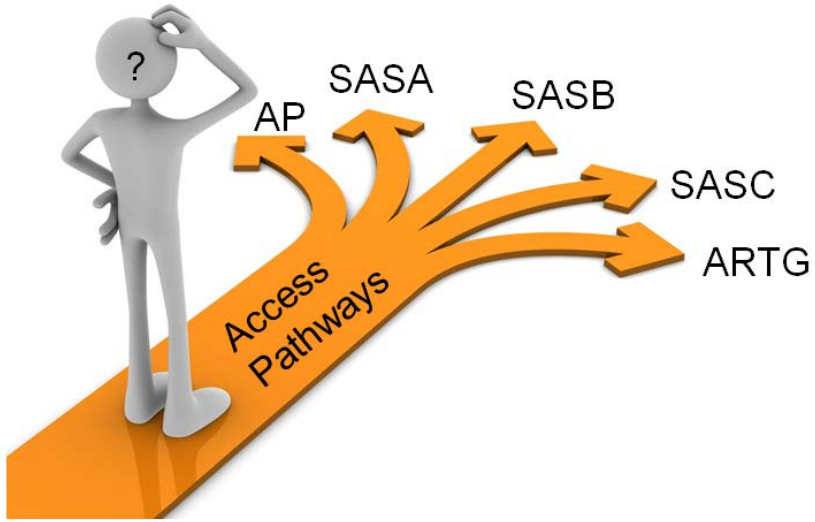
4) **Triage and improved phone/email support**
   - To provide more tailored and efficient assistance to SMEs

5) **Improved data capture**
   - To better identify SMEs and sponsors and direct their queries
   - Subscription list

Access to unapproved biologicals

Special Access Scheme (SAS) Category C

- Certain unapproved therapeutic goods with an established history of use to be supplied
- Goods which can be notified under Category C are listed in legislative instruments which specify:
  - the specific therapeutic good
  - the approved indication(s) for use and
  - the health practitioner authorised to supply
- Prior approval is not required from
- Copy of the completed Category C form must be sent to TGA within 28 days of the therapeutic goods being supplied



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