

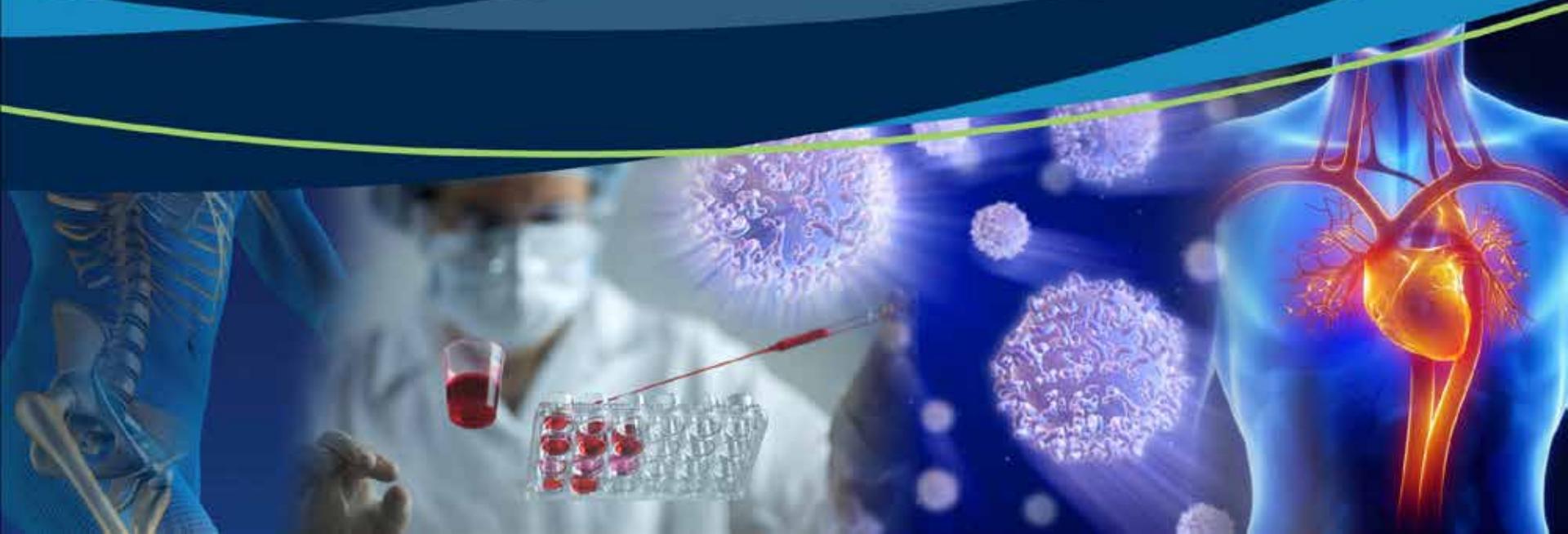


Australian Government

Department of Health

Therapeutic Goods Administration

# The regulation of biologicals in Australia



# Overview

- What are biologicals?
- The Australian biologicals framework
- Products regulated as medicines
- New and experimental products
- Clinical trials
- Risk management
- Classes of biologicals
- Current uses of biologicals
- The registration process
- Exceptional release provisions
- Postmarket monitoring
- Other education modules

# What are biologicals?

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

- products in tissue banks
- stem cell therapy products
- excludes in vitro fertilisation products
- excludes blood.

Other countries use different names for these products.

On 31 May 2011 a new regulatory framework was introduced 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 the TGA\*

Fresh viable organs

Assisted reproductive technologies  
(in vitro fertilisation)

Fresh hematopoietic 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^

Animal tissue products  
(xenotransplantation)

Biological prescription medicines (vaccines, plasma derivatives)

Labile blood and blood components

Haematopoietic progenitor cells (non-fresh transplants)

^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)

# These products are regulated as medicines

Antibiotics

Heparin

Antivenoms

Immunoglobulins

Monoclonal  
antibodies

Hormones such as  
insulin and growth  
hormone

Blood products  
and clotting  
factors

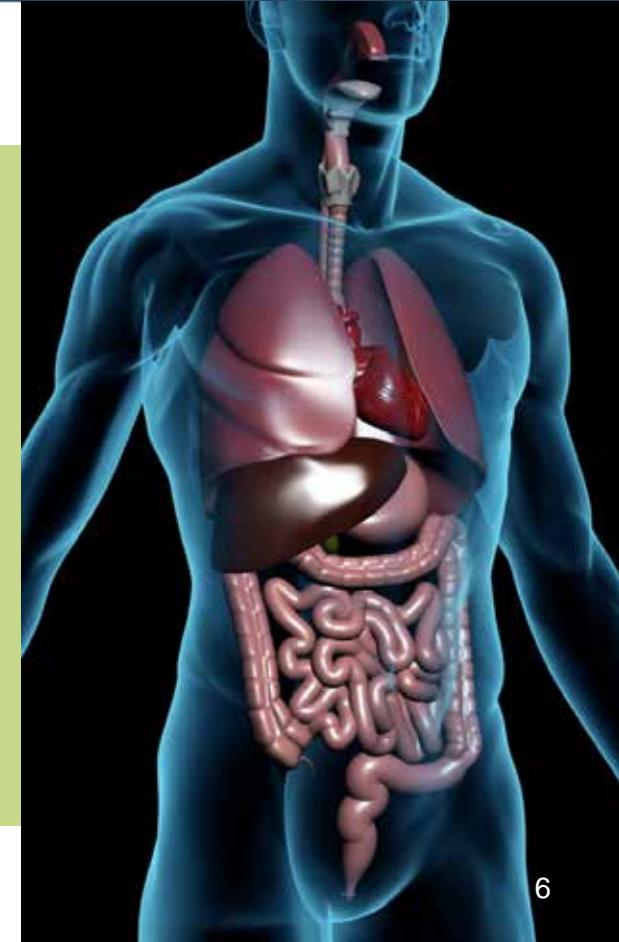
Vaccines

Enzymes such  
as pancreatin



# New and experimental products

- Stem cell therapies are largely new and experimental
- These offer great hope to people with serious incurable diseases:
  - Parkinson's disease and other neurodegenerative diseases
  - spinal cord injury
  - heart disease, stroke and arthritis
- Patients are sometimes desperate for these therapies to become a reality, however there are risks involved; the therapy is generally delivered via surgery, and the patients may require immunosuppressants for the rest of their life
- But a lot of work is still needed to turn the research into safe and effective treatments



# Clinical trials

- One or more ethics committee approves every Australian clinical trial
- The TGA is **notified** of all clinical trials (the Clinical Trials Notification scheme – CTN)
- Some clinical trials are in the Clinical Trials eXemption scheme (CTX)
  - the details of these trials are examined, and commented on, by TGA staff
  - the ethics committee may then give approval to proceed

Clinical trials with biologicals in Australia offer access to new (but unproven) therapies.

Each trial has a research purpose, and patients need to provide informed consent

It is expected that most clinical trials for higher risk biologicals will take quite a few years

# Higher and possibly unknown risks

- Global clinical and regulatory experience with biologicals is more limited than with medicines
- There is an increased risk of infectious disease transmission. It is difficult to obtain complete history for deceased donors
- Because of limited clinical experience with biologicals unforeseen side effects are more common

Biologicals usually cannot be removed once they're in the recipient's body, but there is new work where researchers are introducing 'suicide genes' which can be turned on if something goes wrong and these genes kill the introduced cells

# Transplanted cells became bone

## In the Flesh: The Embedded Dangers of Untested Stem Cell Cosmetics

- A report in the December 2012 edition of Scientific American gave details of a patient having a facelift that used her own adult stem cells.
- During the procedure, the cosmetic surgeons combined mesenchymal stem cells with a dermal filler containing calcium hydroxylapatite, a mineral with which can encourage mesenchymal stem cells to turn into bone—a fact that escaped the patient's clinicians.
- The transplanted cells turned into bone in the tissue surrounding the eye.
- The patient experienced pain and loss of mobility, and had to undergo surgery to remove the bone fragments.

# Regulation takes into account risk

- A risk classification system is used for biologicals to be included on the Australian Register of Therapeutic Goods (ARTG)
- The risk class depends on:
  - how far removed they are from their naturally occurring state (how much they have been manipulated during the extraction and production process)
  - how closely the intended use matches the natural biological function



Centrifugation is an example of minimal manipulation of a biological. Genetic modification is an example of high manipulation

# Biologicals are grouped into classes

## Examples:



Acellular skin  
for wound  
covering



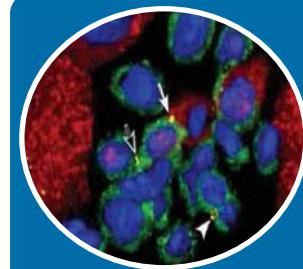
Mesenchymal  
stem cell for  
treatment of  
graft-versus-  
host disease



Demineralised  
bone mixed  
with carrier



Dermal  
fibroblasts  
transformed for  
skeletal muscle  
repair in primary  
myopathy



Genetically-  
modified T cells  
used to treat  
specific virus  
infections

Class 2

Class 3

Class 3

Class 4

Class 4

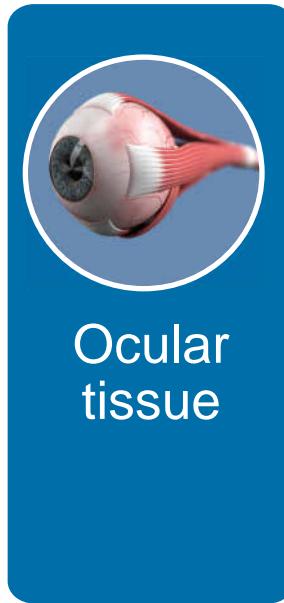
# Current uses of biologicals

- Corneal transplants can restore sight in patients whose eyes have been affected by disease, injury or infection
- Skin grafts are used for patients with burns
- Biological heart valves
- Bone transplants are often donated by hip replacement patients
- Tendon transplants are used to help restore mobility to arms, elbows, hands etc
- Turning human stem cells into heart cells, pancreatic beta cells, intestinal cells, liver cells, and nerve cells



# Current biologicals

## Human tissues currently in Australian tissue banks:



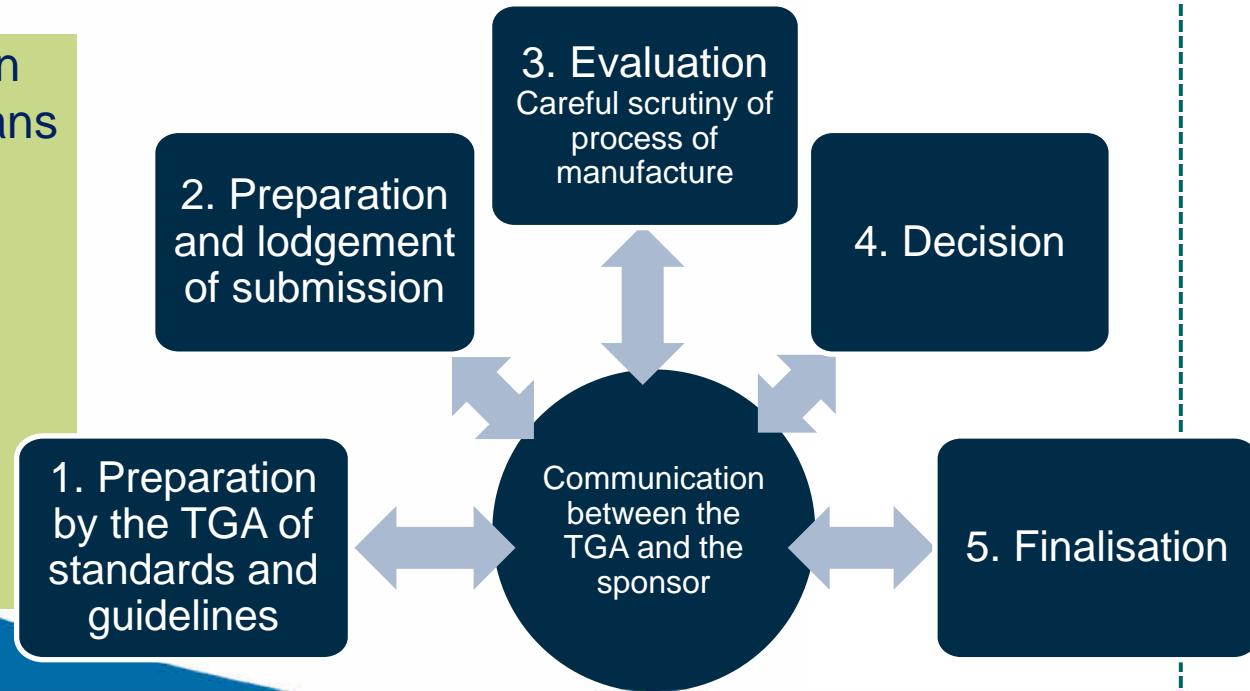
Australian tissue banks are principally owned and operated on a not-for-profit basis by charitable organisations or state governments

# The process for inclusion of biologicals in the ARTG

Evaluation is undertaken by scientists and clinicians who look at data on:

- quality
- safety
- efficacy

More information about what this means is provided later in the presentation



The Advisory Committee on Biologicals provides independent expert advice to the TGA about issues related to biologicals

# Decisions are based on evidence

## Quality data is supplied by applicant

Evaluated by biologists, virologists and others working for the TGA

<ul style="list-style-type: none"><li>• Donor selection and testing</li><li>• Control of manufacturing and transport</li><li>• Microbial control</li></ul>	<ul style="list-style-type: none"><li>• Stability</li><li>• ‘Critical materials’: quality of materials that come into contact with the product</li><li>• Labelling to allow donor traceability</li></ul>
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For example, when using banked ocular tissue from deceased donors, tests for viruses (such as HIV, HCV) must be validated through testing of the blood of the deceased donor.

# Decisions are based on evidence

## Safety and efficacy data is supplied by the applicant

### Nonclinical data

Evaluated by toxicologists

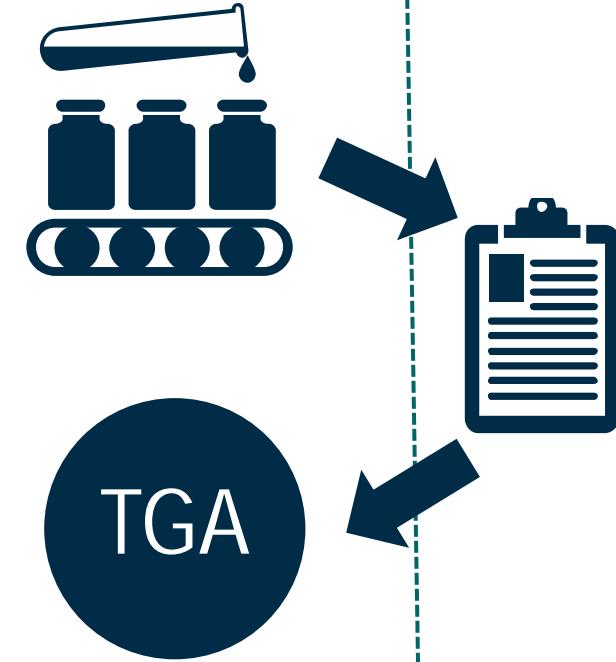
- Biological dynamics and kinetics – laboratory data regarding efficacy
- Toxicology data – laboratory data regarding safety

### Clinical data

Usually evaluated by a medical doctor

- Mostly results of clinical trials conducted by pharmaceutical companies or research organisations, using patients who have volunteered to participate

TGA



Tumorigenicity is an important consideration when evaluating safety data

# Other requirements

Therapeutic Goods Orders are legally binding instruments that:

- specify donor selection, to minimise the chance of infectious disease transmission
- require traceability of each product to the donor
- require bioburden (microbial growth) testing
- describe acceptable storage and transport conditions



Like medicines, biologicals are required to be manufactured according to Good Manufacturing Practice (GMP). All manufacturers are inspected to ensure GMP-compliance.

# Exceptional release provisions

- The TGA can apply exceptional release provisions to treat life-threatening conditions
- For example, a paediatric heart valve becomes available at a valve bank for a critically ill baby but it is not possible to wait 10 days for tissue microbial testing results
- This paediatric heart valve does not meet the required safety standards or current manufacturing standards but the TGA releases the product due to the exceptional circumstances



# Postmarket monitoring

## Reporting adverse events

- Adverse event reporting relates to unintended harmful effects or new information that contradicts existing knowledge about the quality, safety or efficacy of a biological
- For biologicals, the reporting process is based on existing processes established within the TGA
  - Sponsors are required to monitor, record and report all adverse events to the TGA
  - Medical practitioners, patients, and others are also encouraged to report
- The TGA will investigate and respond to adverse events as appropriate
- In addition to the mandatory reporting requirements there is also a voluntary incident reporting scheme where any incidents involving a biological can be reported.



There are also five other modules in this suite of educational material, including one specific to postmarket monitoring. These can be accessed by the links on the next slide.

# Other education modules include:

Introduction to the TGA

Medicines

Medical devices

Postmarket monitoring

Good Manufacturing Practice