Regulation of cell and tissue therapies and clinical research in Australia

Scientific Evaluation Branch

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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.
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 (homologous use)

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

The main risk with using biologicals is the spread of infection
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
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**

<table>
<thead>
<tr>
<th>Evaluated by biologists, virologists and others working for the TGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Donor selection and testing</td>
</tr>
<tr>
<td>• Control of manufacturing and transport</td>
</tr>
<tr>
<td>• Microbial control</td>
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<tr>
<td>• Stability</td>
</tr>
<tr>
<td>• ‘Critical materials’: quality of materials that come into contact with the product</td>
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<tr>
<td>• Labelling to allow donor traceability</td>
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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.

Donor traceability is an important consideration when evaluating quality data.
Decisions are based on evidence

**Safety and efficacy data** is supplied by the applicant

<table>
<thead>
<tr>
<th>Nonclinical data</th>
<th>Clinical data</th>
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<tbody>
<tr>
<td>Evaluated by toxicologists</td>
<td>Usually evaluated by a medical doctor</td>
</tr>
<tr>
<td>• Biological dynamics and kinetics – laboratory data regarding efficacy</td>
<td>• Mostly results of clinical trials conducted by pharmaceutical companies or research organisations, using patients who have volunteered to participate</td>
</tr>
<tr>
<td>• Toxicology data – laboratory data regarding safety</td>
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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.
Regulation of Clinical Trials in Australia

Background

• TGA’s role differs from other regulators:
  – TGA does not evaluate or approve clinical trial protocols or provide advice on clinical trial design
    ▪ Exemption provided for unapproved therapeutic goods rather than end-to-end regulation of trials
    ▪ TGA has two schemes for clinical trial regulation
      • CTN – notification only with no trial evaluation by TGA
      • CTX – evaluated by TGA for safety considerations prior to trial being allowed to proceed
  – **Either CTN or CTX is required** for supply of any unapproved good in a clinical trial
    ▪ Fees: CTN $345, CTX $25,200

Regulation of cell and tissue therapies and clinical research in Australia
Clinical trials

• The vast majority of trials proceed via the Clinical Trials Notification scheme – CTN
  – later stage clinical trials
  – where the product has been previously used in human trials
  – use of an approved product for an unapproved indication
  – if there is a history of use in trials approved in a comparable regulatory jurisdiction

• Determination if a CTN is required is the responsibility of the Sponsor and/or HREC

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
Clinical Trials

- Clinical trials for higher risk products may be required to proceed via the Clinical Trials eXemption scheme (CTX)
  - Sponsor or HREC decide on need for CTX submission
  - Trials are evaluated by TGA primarily for safety considerations
    - Advice is provided to the HREC by TGA
    - Trial may not proceed until any objections by TGA have been addressed
      - The HREC may then give approval to proceed
- The CTX Scheme is mandatory for a trial of any Class 4 biological unless:
  - Use of the biological is supported by evidence from previous clinical use; or
  - Has received clinical trial approval for an equivalent indication from a national regulatory body with comparable regulatory requirements.

It is expected that most clinical trials for higher risk biologicals will take some years
Determining regulatory efficacy

- Regulatory efficacy:
  - Established by clinical trials against a suitable comparator:
    - placebo if no effective treatment available, or
    - ‘current standard of care’
    - Takes into account the clinical need and favourable risk/benefit analysis
    - May require more than one study to demonstrate consistent effect
  - Superiority trials are preferred, but many commercial regulatory applications are powered only for equivalence:
    - shorter and less expensive process for sponsor
    - may be scientifically unreliable
Quantifying therapeutic effect:

• Surrogate markers/endpoints
  – may help in understanding mechanisms
  – establish proof of concept in early stage trials

• Demonstration of clinical efficacy requires validated endpoints that ensure a minimum clinically significant difference is established
  – should be appropriate to treatment aim
  – reflect benefit to the patient
    ▪ eg OS, QOL, symptom control
Limitations of licensing studies

- Clinical trial design e.g. comparator intervention different from current standard treatment
- Overly strict inclusion criteria not representative of ‘real-world’ patient need
- Endpoints that are not patient-relevant
- Short trial durations (weeks to months) with no or insufficient follow-up data
- Study populations too small to identify rare adverse events
Efficacy vs effectiveness

Demonstration of clinical efficacy for regulatory purposes is often not the same as establishing comparative clinical effectiveness vs other interventions.

- Often requires post-marketing studies and surveillance to:
  - Verify initial studies
  - Refine safety profile
  - Inform resource allocation
  - Establish patient groups most likely to benefit

- May in some circumstances be mandated by the regulator as a condition of approval/registration.
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.
Thank you for your attention

• Questions during the panel discussion at the end of the session