Australian Government
Department of Health
Therapeutic Goods Administration

Clinical Trials with Biologicals

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Victorian Department of Health and Human Services, Clinical Trials and Research Workshop

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TGA Health Safety Regulation

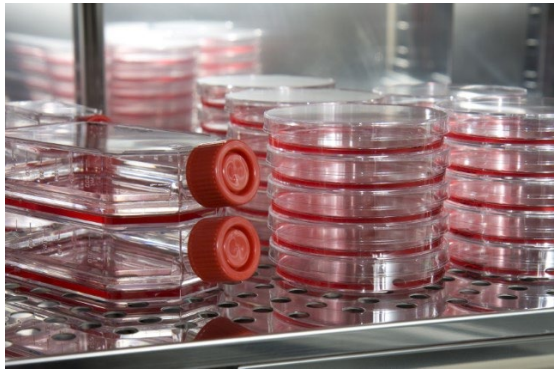
Overview

- What are biologicals
- What is the Biological Sciences Section
- Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) schemes
- What are unapproved therapeutic goods
- TGA and Stakeholder responsibilities with regard to clinical trials
- Regulatory aspects of new therapies
- Application of GMP in clinical trials involving biologicals

Biologicals

In Australia, ‘biologicals’ is the name for cell and tissue therapy products that

- Comprise, contain or are derived from **human cells or tissues**, or
- **Living animal** cells, tissues and organs, and
- Are represented in any way to be for therapeutic use



The Biologicals Framework was introduced on 31 May 2011 to provide a legislative basis for the regulation of these products

- Applies risk-based levels of regulation
- Designed to accommodate emerging technologies

- BUT, some human products are currently not regulated under the Framework (excluded goods)

Biologicals

Not regulated by TGA*

- Fresh viable organs
- Assisted reproductive technologies (in vitro fertilisation)
- Fresh haematopoietic progenitor cells (bone marrow transplants)
- Autologous cells and tissues made in a hospital by a medical practitioner for a single patient

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

Regulated, but not as biologicals^

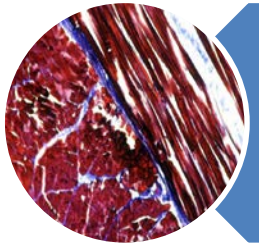
- Biological prescription medicines (vaccines, plasma derivatives)
- Labile blood and blood components
- Haematopoietic progenitor cells (non-fresh transplants)
- Non-viable animal tissue products

^These are regulated as either medicines or medical devices

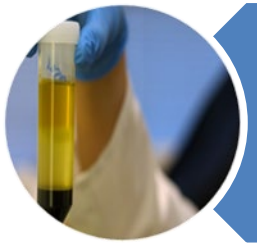
Regulated as biologicals

- 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)

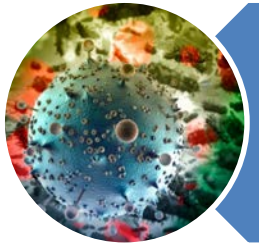
Biological Sciences Section



Cell and Tissue Therapies Unit



Biological Medicines Unit



Blood and Infectious Disease Safety Unit

- Clinical trials of biologicals
- Special Access scheme
- Evaluate quality of biologicals and biological medicines
- Evaluation of infectious disease risks of biologicals, medicines and devices
- Clinical evaluation of biologicals

Clinical Trials – CTN and CTX

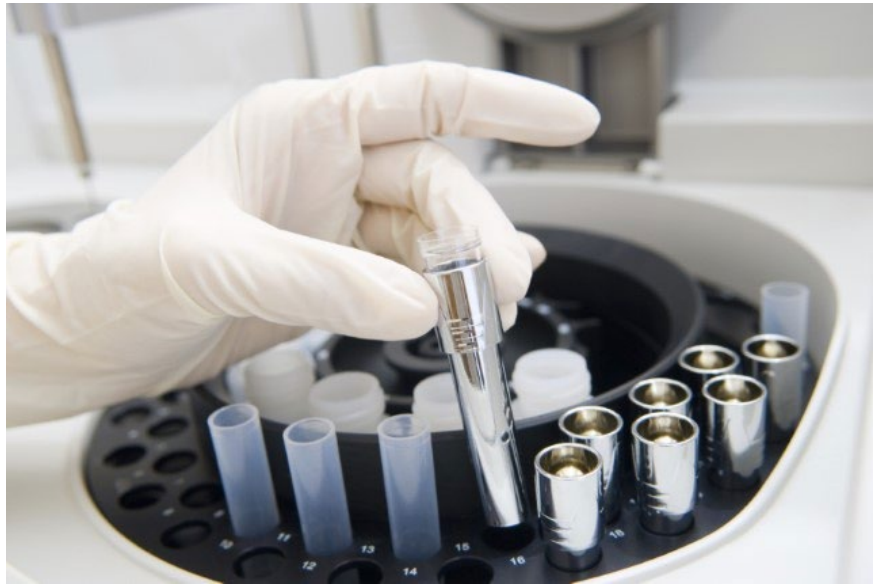
- Clinical trials conducted in Australia are subject to various regulatory controls to ensure the safety of participants.
- Clinical trials of ‘unapproved’ therapeutic goods may be subject to Clinical Trials Notification (CTN) requirements, or Clinical Trials Exemption (CTX) requirements
- Clinical trials that do not involve 'unapproved' therapeutic goods are not subject to these requirements
- The therapeutic goods legislation requires that the use of therapeutic goods in a clinical trial conducted under the CTN/CTX schemes must be in accordance with:
  - ICH Guidelines for Good Clinical Practice (GCP)
  - National Statement on Ethical Conduct in Human Research (National Statement)
  - The procedural protocol as approved by the Human Research Ethics Committee (HREC) responsible for monitoring the conduct of the trial.

What is an unapproved therapeutic good?

- Any medicine not entered in the ARTG
- Any medical device not entered in the ARTG
- Any biological not entered in the ARTG
- A therapeutic good already in the ARTG that is being used beyond the conditions of its marketing approval, including labelling
- Does not apply to any good that has been excluded from regulation by the TGA

The CTN scheme

- Notification process
- TGA does not review/evaluate any data relating to clinical trials at the time of submission
- All material relating to the proposed trial, including the trial protocol is submitted directly to the HREC for review and approval
- Supply of goods cannot commence without valid notification and payment of fee
- Each additional trial site needs to be notified to the TGA before commencing the trial at that site



The CTX scheme

- Designed for complex therapies – REQUIRED for certain Class 4 biologicals
- TGA evaluates the proposed Usage Guidelines
- Supply of goods cannot commence without HREC and TGA approval
  - Primary responsibility of TGA is to review the safety of the product
  - HREC responsible for considering the scientific and ethical issues of the proposed trial protocol
- May conduct any number of clinical trials provided the use of the product falls within the approved usage guidelines
- Each trial must be notified to TGA

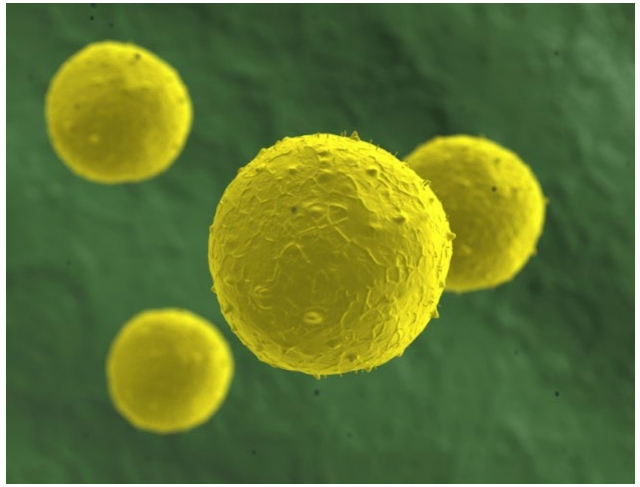
Responsibilities

Sponsor • Overall responsibility for trials • Submit CTN/CTX forms • Ensure trial is in accordance with Good Clinical Practice, the National Statement and the protocol • Safety reporting	HREC • Assess the scientific validity of the trial design, the safety and efficacy of the product, the ethical acceptability of the trial process • Monitor the conduct of the trial • Approve the trial protocol
Approving Authority • The institution or organisation at which the trial will be conducted (trial sites) • Gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC	Principal Investigator • Personally supervises the trial at that site • Conduct the clinical trial in accordance with the protocol • Monitor safety • Comply with record management and reporting requirements for adverse events

Role of TGA

- Request certain information about therapeutic goods exempt under the CTN/CTX scheme
- CTX scheme: inspect clinical trial sites
- If the conditions of exemptions are not complied with:
  - Automatically cease the CTN exemption
  - Revoke a CTX approval
- Release information if required to the Commonwealth, a state or a territory, as well as medical boards

New therapies and not so new therapies



Autologous cells and tissues: excluded from regulation by the TGA under certain conditions

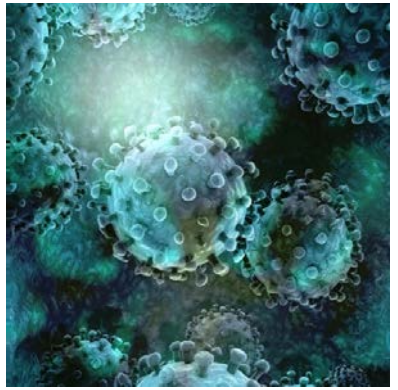
Genetically modified cell therapies - CAR T-cells: biologicals

Adipose-derived mesenchymal cells

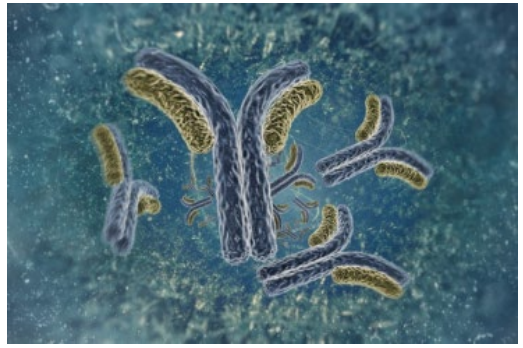
Placental derived mesenchymal cells

“In vivo” gene therapies: medicines

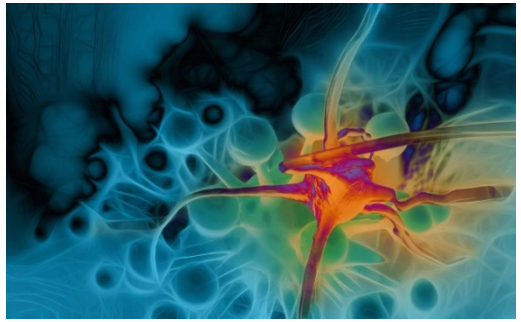
Faecal microbiota transplantation: biologicals

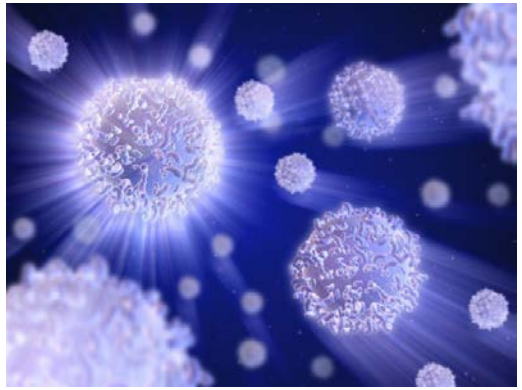


CTX for biologicals



- The CTX scheme is applied to Class 4 biologicals (significantly manipulated products eg gene-modified), unless:
  - a trial with the same product for the same indication has been approved in a comparable jurisdiction
- Four clinical trials and three variations to clinical trials of Class 4 biologicals have been reviewed in the last five years





Safety reporting to TGA

What should be reported?

- Suspected unexpected serious adverse reactions (SUSARs) arising in Australian trial sites
- Unanticipated serious adverse device effects (USADEs) arising in Australian trial sites
- Significant safety issues requiring urgent safety measures
- Action with respect to safety that has been taken by a regulatory agency in another country

Refer to NHMRC Guidance: Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods

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Clinical Trials with Biologicals

Manufacturing investigational products

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Victorian Department of Health and Human Services, Clinical Trials and Research Workshop

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TGA Health Safety Regulation

Manufacturing investigational products

Australian facilities manufacturing investigational medicines and biologicals must be licensed by the TGA unless exempt:

- Prepared for initial experimental studies in humans
- Manufactured by a pharmacist at premises that are open to the public and supplied to individual patients and the goods are not biologicals
- Manufactured by a pharmacist at a public hospital for supply to patients in hospitals in the same State and the goods are not biologicals
- A person applying supplementary labels, where the label only contains a name and address or registration number

Manufacturing licences

To obtain a manufacturing licence a sponsor must apply to the TGA

- Manufacturers need to comply with:
  - the manufacturing principles specified in Australian legislation
  - relevant Therapeutic Goods Orders
  - relevant default standards
- The manufacturing principles define different codes of GMP for:
  - medicines and biologicals that comprise or contain live animal cells, tissues or organs
  - human blood, blood components, haematopoietic progenitor cells (HPCs) and biologicals that comprise, contain or are derived from human cells and tissues, or are specified as a biological by the Secretary
- An Australian manufacturing site would need a GMP inspection before a licence is granted

GMP Inspections

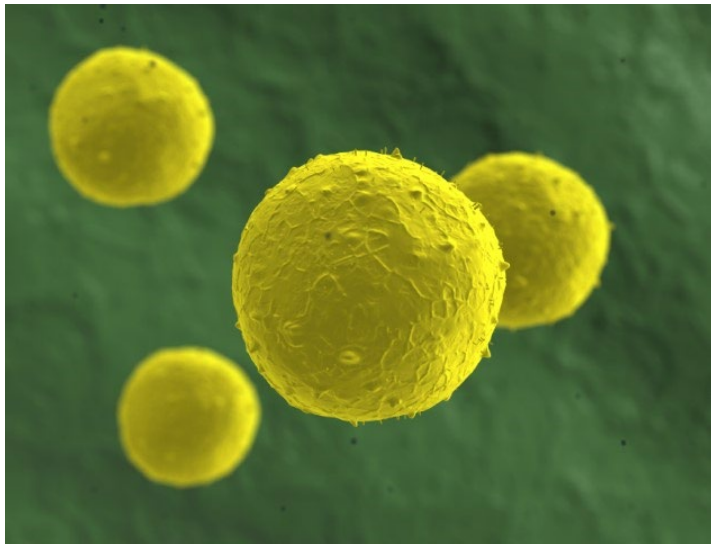
The TGA website has information on GMP inspection including a step by step guide from application to invoicing.
Typical inspection information is also available

- https://www.tga.gov.au/publication/australian-manufacturing-licences-and-overseas-gmp-certification
- https://www.tga.gov.au/manufacturer-inspections-overview
- https://www.tga.gov.au/manufacturer-inspection-typical-example

GMP for biologicals

- The Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (2013) is specified in the legislated manufacturing principles for:
  - biologicals that comprise, contain or are derived from human cells and tissues, or are specified as a biological by the Secretary,
  - human blood, human blood components and HPCs

- GMP is a set of principles that helps ensure the manufacture of medicines and biologicals is consistent and of high quality.
- All sponsors of medicines and biologicals need to provide evidence that the manufacture of their product complies with GMP.



GMP for biologicals

- GMP covers:
  - how products are manufactured, packaged, labelled and stored
  - how therapeutic goods are tested to ensure that products are of a suitable quality
  - e.g.
    - safe and non-contaminated manufacturing environment
    - adequately trained personnel
    - properly documented procedures
    - appropriate packaging methods

GMP for biologicals

- The Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products (2013)
  - Quality management
  - Personnel and training
  - Premises and equipment
  - Documentation
  - Control of material
  - Subcontracting
  - Complaints and recalls
  - Collection and processing
  - Quality control
  - Computer

GMP Inspections

Pre-inspection

- Notification, planning and preparation
- Agenda, logistics and initial document requests

Inspection

- Opening meeting
- Interview sessions and document reviews
- Review of facility and equipment
- Closing meeting

Post-inspection

- Issuance of Post inspection letter
- CAPA response
- Close-out and issuance of the inspection report

Inspection of biologicals

Class 2 biological – Minimal manipulation for homologous use

- Donor related assessment
  - Medical assessment ensures donor meets requirements of TGO 88
  - Deferrals applied correctly
  - Labelling and traceability of donations
  - Aseptic collection technique
- Product related processes
  - Traceability of donation to product
  - Outsourced testing
  - Closed system – collected in an operating suite or processed in a biological safety cabinet
  - Terminal sterilisation ISO 11137-2:2012

Inspection of biologicals

Class 3 biological – Minimal or more than minimal manipulation for non-homologous use

- Donor related assessment
  - Medical assessment ensures donor meets requirements of TGO 88
  - Deferrals applied correctly
  - Labelling and traceability of donations
  - Aseptic collection technique
- Product related processes
  - Traceability of donation to product
  - Outsourced testing / in house testing, osteoinduction testing
  - Open systems – manufactured in a clean room or processed in a biological safety cabinet
  - Terminal sterilisation ISO 11137-2:2012
  - Annex 1 applies if labelled as sterile

Inspection of biologicals

Class 4 biological – where the intrinsic function of the biological has changed eg CAR-T cells

- Donor related assessment
  - Medical assessment ensures donor meets requirements of TGO 88
  - Deferrals applied correctly
  - Labelling and traceability of donations
  - Aseptic collection technique
- Product related processes
  - Traceability of donation to product
  - Oversight of collection and administration at remote sites
  - Product specific In house testing – eg quantitiative PCR testing of cell markers
  - Open systems – manufactured in a clean room
  - Additional manufacturing controls apply if labelled as sterile

GMP licences

- There are ongoing responsibilities for licensed manufacturers:
- During manufacture;
  - Comply with standards and conditions
  - Keep records
  - Label batches
- Informing the TGA
  - Information relating to quality safety or efficacy
  - Exceptional release of a biological
- Notifying changes to the manufacturer
- GMP inspections
- Routine re-inspections

Questions

Australian Government

Department of Health

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