Pathways for supply of biological CGT products



Dennis Dowhan, PhD
Blood, Biological and Infectious Disease Unit
Biological Science Section, TGA

Overview

- The TGA
- Regulation and classification of cell and gene therapies in Australia
- Application pathways for inclusion or registration
- Manufacturing Quality of the cell therapy
- Post-market monitoring and RMPs
- Useful resources



Therapeutic Goods Administration (TGA)

- The TGA was established in 1990 to "**safeguard** and **enhance** the health of the Australian community through **effective** and **timely regulation** of therapeutic goods"
- It provides a national system of controls relating to the **quality, safety, efficacy** and timely availability of therapeutic goods used in, or exported from, Australia
- All decisions the TGA makes are based on the *Therapeutic Goods Act 1989*
- The TGA regulates therapeutic goods (the product) not medical practice



Types of therapeutic goods



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

- **Comprise, contain or are derived from human cells or human tissues**
- **Comprise or contain live animal cells, tissues or organs**
- **Includes Faecal Microbiota Transplant (FMT), Cell therapies and CAR-T cells**

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Regulation of cell therapies in Australia

- We don’t have a dedicated advanced therapies framework in Australia
- We regulate cell and gene therapies under our biologicals or prescription medicines frameworks

Advanced Therapies

Biologicals

Involve ex-vivo manipulation of human cells
e.g. CAR-T cells

Regulated under the biologicals framework

Gene therapies

Involve in-vivo manipulation of human cells

Regulated under the prescription medicines framework

- Different options for submission pathways
- Different GMP requirements
- Different fee requirements/options

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Application pathways for inclusion or registration

Provisional Pathway - Medicines

- 255 working days
- Treatment serious and life-threatening conditions
  - new and promising or existing but with promising new indications.
- provisionally register them based on preliminary clinical data
  - whether the potential benefit outweighs the risk
  - clinical study plan to collect additional clinical data to support transition to full registration.

Priority Pathway – Medicines and Biologicals

- Requires product has received a priority determination
- Determination applies to one product for one therapeutic indication or intended use
- 150 working days
- TGA Website: Priority review pathway for biologicals

Orphan drug designation Pathway - Medicines

- New prescription medicines for medical conditions that affect fewer than 5 in 10,000 people or it is not likely to be financially viable for the sponsor to market the medicine
- One indication & Treatment serious condition
- Apply for a prescription medicine via orphan drug designation | Therapeutic Goods Administration (TGA)

Comparable overseas regulators (CORs) – Medicines

(EU / HC / Japan / HSA / SwissMedic / MHRA / FDA)

COR-A - critical review of the COR assessment reports and an evaluation of the Australian label, Product Information (PI) and where required, the Risk Management Plan (RMP)

- 120 working days / reduced fee

COR-B - decision will still be **mostly based** on a critical review of the COR assessment reports + PI / RMP etc.

- 175 working days / reduced fee

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Application pathways for inclusion or registration

Application Pathways	Medicine (Gene Therapy)	Biological (Cell Therapy)
Orphan	Y	N
Provisional	Y	N
Priority	Y	Y
Orphan & Provisional	Y	N
Orphan & Priority	Y	N
Orphan & Provisional & Priority	N	N
Provisional & Priority	N	N
COR-A and COR-B	Y	N
Clinical trial approval (CTA) for first in human trials by TGA	N	Y
Export only	Y	Y

Standard Pathway - Biologicals

- 255 working days
- Consolidated Round 1 questions at 100 WD
- https://www.tga.gov.au/resources/resource/guidance/biologicals-application-form-step-step-guide

Priority Pathway - Biologicals

- Requires product has received a priority determination
- Determination applies to one product for one therapeutic indication or intended use
- 150 working days
- Rolling questions
  - Questions will be sent out as identified or reports are completed
- TGA Website: Priority review pathway for biologicals

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Collaborative/Reliance Frameworks and Initiatives

New Entities (Cat1/2)

ACCESS work-sharing initiatives

- TGA, Swissmedic, HSA, MHRA and Health Canada collaboration

Project Orbis

- FDA initiative for concurrent review of oncology products

COR pathway(s)

- Reliance pathway leveraging comparable overseas regulator decisions

EMA OPEN initiative

- Information-sharing and collaboration initiative
- No formal TGA arrangement currently in place

Post-approval Changes

EMA–WHO/EMA-MHRA Reliance Pilot

- Reliance model for post-approval changes - one regulator performs the primary assessment, and other regulators rely on that assessment to support their own decision-making

International Coalition of Medicines Regulatory Authorities (ICMRA) Collaborative Assessment Pilot

- Collaborative assessment approach for post-approval changes - everyone reviews together

ACCESS work-sharing

- Collaborative work-sharing pathway for post-approval changes - the assessment work is shared across agencies

Quality and Manufacturing Data Requirements

Biological starting material

The dossier must contain extensive details regarding the origin of the biological starting material and how it is handled between collection and arrival at the manufacturing site

- Donor material must be compliant with Therapeutic Goods Order (TGO) 108
  - If your product is manufactured from cell banks – obtain as much information as possible to demonstrate compliance to TGO 108
    - Donor selection
    - Medical and social history
    - Mandatory infectious disease testing
    - Mandatory deferral periods
    - Ongoing donor management and review
    - Gap analysis and additional testing may be acceptable through s14s
- **TGO 109(9)** – Australian std for Human cell & tissue products



➢ Are there any donor conditions that may affect product quality, safety, efficacy? How is this assessed?

Quality and Manufacturing Data Requirements

Manufacturer must demonstrate control and oversight of the collection process

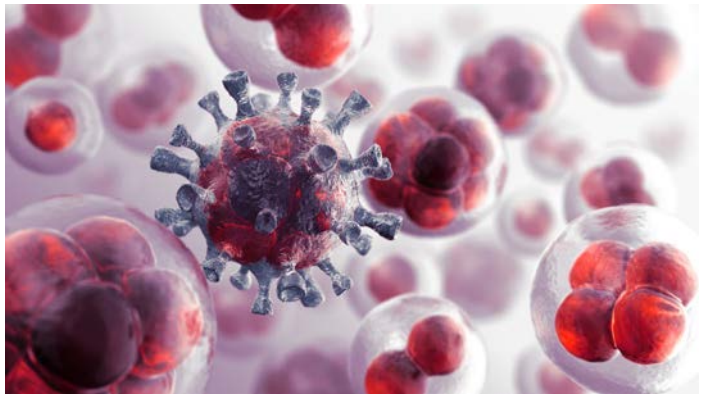
- In the evaluation of the dossier, we do not approve each individual collection site, but we approve a process by which the manufacturer is controlling the collection
    - Collection centre training programmes, site auditing and approval
    - Provision of SOPs for collection, control of critical materials and containers
    - Transportation – provision of validated shippers and SOPs
    - Does the collection centre conduct preliminary testing that will contribute to acceptance? Validation protocols and acceptance criteria required.
        - Quantitation of cells, FACS, bioburden testing
    - Validation of any post-collection processes (cryopreservation)
- We need to be shown how the Sponsor is:
    - Ensuring the starting material is of sufficient quality and consistency to manufacture a safe and effective product
    - Ensuring every incoming batch of starting material will meet their incoming materials specifications

Quality and Manufacturing Data Requirements

Viral Vectors for Ex-Vivo Genetic Modification

- Need full details of manufacture of viral vectors (a Drug Substance section)
  - Manufacturing process, controls points
  - Cell bank development and testing (ICH Q5D, ICH Q5A)
  - Critical materials – especially any human, animal or biotechnology-derived ingredients
  - Replication-Competent Virus (RCV) testing mandatory
  - Specifications
  - Release testing, validation of methods
  - Sterile process validation/media fills
  - Stability

➢ If you have manufactured with a contract manufacturer – we still need this information. Data package can be submitted to the TGA separately as a Drug/Biological Master File, questions raised directly with manufacturer



Quality and Manufacturing Data Requirements

Critical materials

- **TGO 109 (10)** - The critical materials used in the manufacture of a biological must:
  - not be contaminated with, or be likely to introduce, microorganisms or other infectious disease agents; and
  - not adversely affect the quality, safety or efficacy of the biological

- Provide a complete list of anything that comes into contact with the product at any stage of collection and manufacture

- For human/animal/biotech derived ingredients, demonstration of viral and TSE safety are critical
  - Demonstrating the safety of adventitious agents



Quality and Manufacturing Data Requirements

Characterisation

- What is your product?
- Establishes a baseline for your product through ongoing process development
- Detailed analysis of composition of multiple batches
- Evidence of biological activity (potency)
- Impurities, especially anything potentially dangerous to recipient

Process Validation

- Need to see multiple manufacturing runs (n=3) – evidence that product can be manufactured to meet in-process control points and release specifications within the manufacturing site to be used, using the process defined in the dossier
- Healthy donor material can be used for validation runs, if appropriate

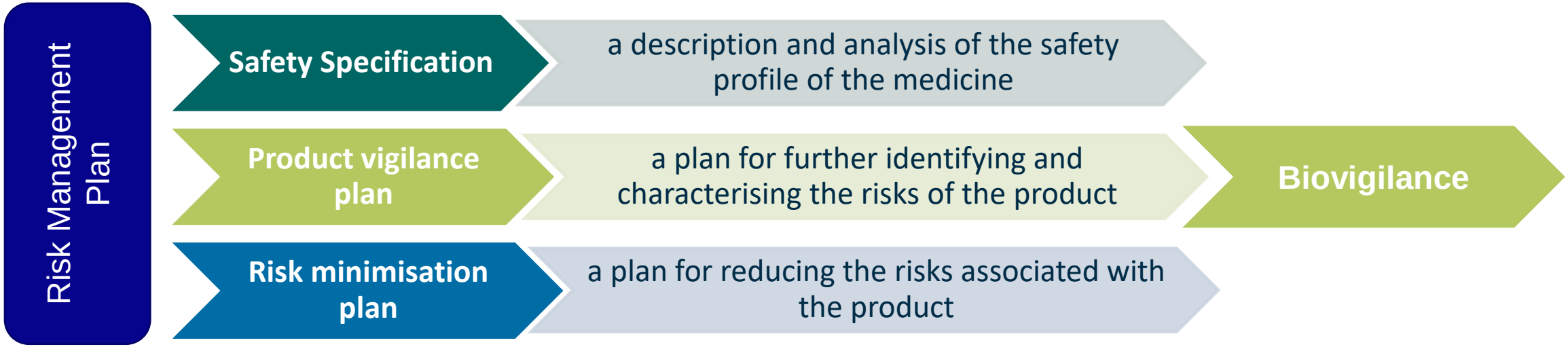
Specifications, release testing and assay validation

- List of product specifications and how they are tested
- Critical safety specifications – endotoxin, bioburden, RCL, residual pluripotent cells
- Details of all release test methods
- Assay validation – ICH Q2(R2)

Stability

- Class 3 & 4 products: Stability should measure more than just viability – some measure of product potency/activity should be included
- Evaluation of available real-time data and an ongoing long-term shelf-life validation protocol for approval for the proposed shelf-life

Post-market monitoring and RMPs



- Well maintained patient registries and consistent follow up key for monitoring for any adverse events or long-term implications from products
- Mandatory reporting of adverse events by sponsors
- Biovigilance responsibilities of sponsors of biologicals

Biologicals

- Class 3 and 4 Biologicals require RMP
- Class 2 Biologicals don't require RMP unless clinical evaluator requests

Post-market monitoring and RMPs

Periodic Safety Update Reports (PSURs)

- are also referred to as Periodic Benefit Risk Evaluation Reports (PBRERs)
- part of the Biovigilance systematic review of the global safety data that becomes available to the sponsor of a marketed product during a specific period (e.g. annually). Class 3 and 4 Biologicals as per RMP

Collection of Data and Reporting from Australian Patients

- data collection and reporting annually is a condition of approval of commercial CAR-T products
- crucial decision points, such as the date of product request, diagnosis for which product is prescribed, age of patient at treatment (infusion), duration from decision (product request)
- dose of product received, best overall response, duration of remission (if relevant), duration of survival, and adverse events
- Example - ANZTCT Registry

Useful resources for evaluation of cell therapies

Relevant Legislation and Guidance

Therapeutic Goods Orders

- TGO 108 - Standard for Human Cell or Tissue Products - Donor Screening Requirements
- TGO 109 - Standards for Biologicals-General and Specific Requirements
- TGO 107 - Standard for Biologicals - Labelling Requirements

International Guidance Documents (European Medicines Agency; EMA)

- EMEA/CHMP/410869/2006 – Guideline on human cell-based medicinal products
- EMA/CAT/GTWP/671639/2008 - Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
- EMA/CAT/80183/2014 - Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products
- EMA/CHMP/BWP/271475/2006 - Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer
- CHMP/BWP/2458/03 - Guideline on development and manufacture of lentiviral vectors

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration