Australian Government
Department of Health
Therapeutic Goods Administration

# Quality Control of Biotechnological or Biological Medicines

## Manufacturing quality perspective

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TGA Health Safety Regulation

# The Therapeutic Goods Administration (TGA)

The TGA was established in 1990 and is part of the Health Products Regulation Group (HPRG) in the Australian Government Department of Health

- It is the national regulator responsible for regulating the quality, safety and efficacy of therapeutic products imported into, exported from, supplied or manufactured in Australia
- Regulation underpinned by the Therapeutic Goods Act 1989
- Uses risk-based regulatory framework
- Main offices in Canberra – satellite offices in Sydney, Melbourne, Adelaide and Brisbane

# 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**

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

The TGA does not regulate: veterinary medicines, food, health insurance, cosmetics, chemicals, healthcare professionals

# How do we fulfil this mission?

1. Good Manufacturing Practice or Manufacturing Principles: licensing Australian manufacturers and verifying compliance of overseas manufacturers
2. Premarket assessments: assessing therapeutic goods for quality and safety (the extent of the assessment depends on the type of product and level of associated risk), and for higher risk products also for efficacy or performance
3. Postmarket assessments: monitoring of therapeutic goods and enforcement of standards

# What are biological/biotechnological medicines?

## Therapeutic Goods Regulations definition

Are therapeutic goods derived from biological sources and are regulated as registered medicines. Include

- a medicine (other than an antibiotic) that is:

  (i) a vaccine, a peptide, a protein or polysaccharide-based; and

  (ii) derived from a human, animal or other organism, or produced through recombinant technology or biotechnology; and

  (iii) of a kind specified in item 1 of Part 1 of Schedule 10 (includes biotechnology medicines); or

  a medicine that is a human blood product of a kind mentioned in Appendix A in Part 5 of the Poisons Standard.

**Biotech medicines are a subset of Biological medicines.**

*Note that the term biologics, biologicals and biological medicines can have different interpretations in different countries/jurisdictions*

# Biological and Biological Medicines

Biological medicines are not biologicals as defined in the *Therapeutic Goods (Things that are not Biologicals) Determination No.1 of 2011* )

## Biological

- tissue-based products
- cell-based products
- immunotherapy products containing human cells
- autologous human cells and tissue products (including stem cells)
- gene-modified cell therapies
- Regulated under the Biological regulatory framework

Australian regulatory guidelines for biologicals (ARGB)

## Biological Medicines

- recombinant products
- plasma derived products (or that contain plasma derived products)
- vaccines (that do not contain viable human cells)
- gene-therapy vectors alone
- Regulated as prescription medicines
- Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

# Regulatory Framework: TGA's mandatory requirements

- Biological medicines are regulated as Prescription Medicines
- Approved under Part 3-2 (Section 25) of the *Therapeutic Goods Act 1989*
- Reviewed by the TGA in accordance with *Therapeutic Goods Regulations 1990*
- Several *Therapeutic Goods Orders* including:
  - TGO 91 Labelling
  - TGO 100 Microbiological Standards
  - TGO 89 (Standard for Water for Injections for Parenteral Medicines)
  - TGO 90 (Standard for Human Albumin)
- International standards – Ph. Eur., BP, USP

# TGA registration process for prescription medicines

**Standard Pathway- can take upto 255 working days**

- Ø Applications for new PM are to be supported by nonclinical, clinical and/or bioequivalence data (category 1 and category 2)
- Ø managed by milestones
- Ø dossiers prepared in accordance with common technical document (CTD) format and other TGA regulatory requirements
- Ø Legislative instruments made under section 9D and section 23 of the Act support this process.

- **Priority review pathway** for faster assessment of vital and life-saving prescription medicines for which a complete data dossier is available. The target timeframe of 150 working days- up to three months shorter than the standard prescription medicines registration process.
- **Provisional approval pathway** for provisional registration of prescription medicines on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients.

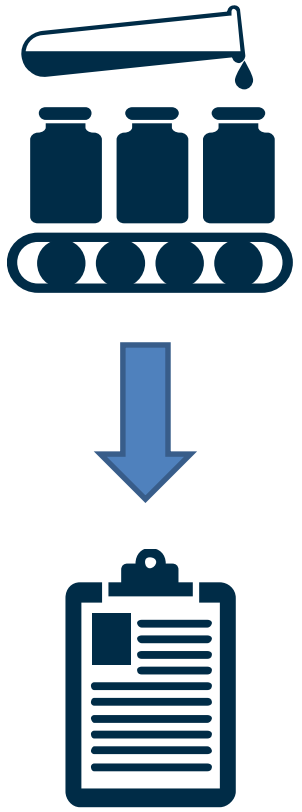
# Other pathways- International work-sharing

- **Comparable overseas regulators (CORs) for prescription medicines- report-based process open to prescription medicines that have received full overseas marketing approval following a de novo evaluation.**
  - Applications can relate to all types of new prescription medicines, including new chemical entities, new fixed dose combinations, generic medicines, biological medicines and biosimilars.
  - countries and jurisdictions from whom the TGA will accept reports for COR report-based process- Canada (HC), japan (PMDA), Singapore (HSA), Switzerland (SwissMedic) UK (MHRA), USA (FDA) and the EU (EMA).
- **Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium-**goal is to maximise international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products

# Data requirements for registration

Divided into three parts-

- **Quality data -** evaluated by chemists, biochemists, microbiologists, toxicologists and others working for the TGA.
  - The composition of the drug substance and the drug product
  - Batch consistency
  - Stability data
  - Sterility data (if applicable)
  - The impurity content
- **Nonclinical data -** evaluated by toxicologists.
  - Pharmacology data
  - Toxicology data
- **Clinical data** - usually evaluated by a medical doctor
  - Mostly results of clinical trials



# Regulatory challenges – Quality aspects

| | |
|---|---|
| **Size** | • Biological medicines are complex and diverse, size ranges from small peptides to large molecules |
| **Complexity** | • difficult or impossible to construct using chemical methods<br>• rely on shape for function that comes from interactions in 3-D<br>• complex structure results in lack of stability unless conditions are well-controlled |
| **Source** | • Living cells: bacteria, yeast, mammalian cells<br>• Biological source of the product makes it susceptible to contamination |
| **Product Quality & Process** | • Processing difficulties – common purification/decontamination methods are not suitable<br>• Methods adopted must be sensitive and protect protein integrity |
| **Technology** | • Technology involved in manufacture and characterisation is rapidly evolving |

# Evaluation of Biological Medicines

- Manufacturing quality of all Biological Medicines (except vaccines) is evaluated by the Biological Science Section, Scientific Evaluation Branch
- Secondary assessments are conducted for viral safety, endotoxin, sterility, containers by specialist areas
- Vaccines are evaluated and tested by Laboratories Branch. Survey testing of Biological Medicines is also conducted by LB

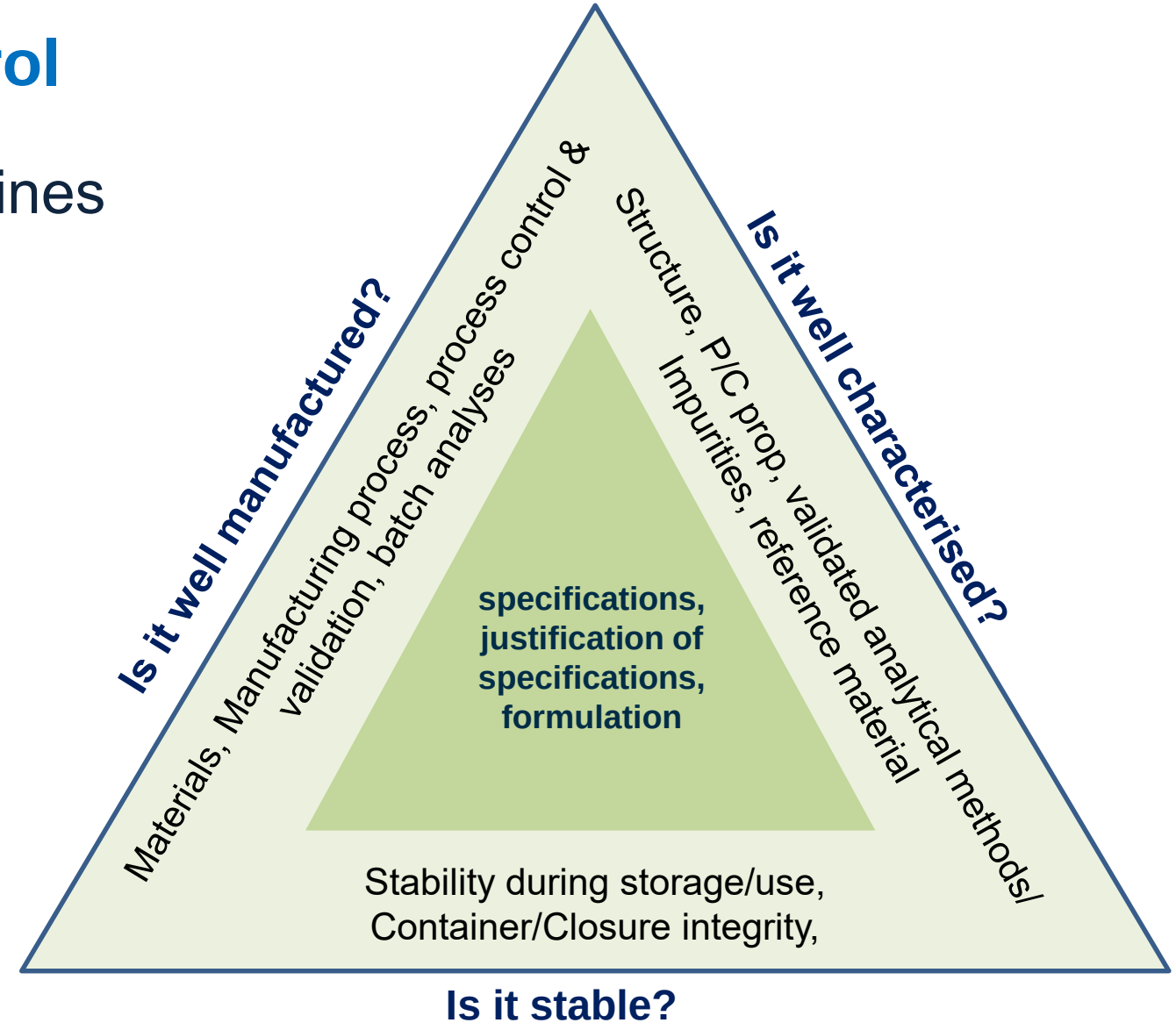
# Manufacturing Quality Evaluation- Key criteria

- **Background Information**
  - Nomenclature, Product Name, Structure, Physicochemical properties, Overseas regulatory status
- **Manufacture**
  - Is it well manufactured?
  - Is it well characterised?
  - Is it stable?
  - Are specifications and limits adequate and justified
- **Presentation Issues – ARTG entry, Label, PI, CMI**
  - Consistency with evaluation and relevant parts of the TG Act, Regs and Orders.

# Key criteria for quality control

## Manufacture of Biological Medicines

Module 3 CTD



# Key criteria for quality control

**Manufacture**

- Is it well manufactured?
  - **Materials, control of materials:** Cell lines, full history and characterisation, animal & human ingredients, other raw materials for cell culture and purification
  - **In process tests**: ensures each step does what it is meant to do
  - **Manufacturing process**, development etc: clinical implications and changes in manufacturing process
  - **Validation of manufacturing steps**: ascertaining that a step performs as intended
  - **Batch analyses** – how many? which campaign? which sites? chosen from clinical and commercial batches
  - **GMP:** current (until approval time) and valid (claims match clearance/licence)

# Key criteria for quality control

**Manufacture**

Is it well manufactured? Risks related to adventitious agent contamination of the final product have been controlled to an acceptable level

Prion risks

Viral and mycoplasma risks

- **Qualification of starting material**
  - Ø Selection/testing of donors, cell lines, animals, human/animal-derived critical materials
- Manufacturing and **In-process testing**
  - Ø Testing of plasma pools, cell banks (MCB/WCB/EOP), pooled cell/culture media harvest
- **Clearance of adventitious agents via the manufacturing process**
  - Ø Validation of manufacturing process for ability to remove viruses/prions

TSE risk assessment- Control measures for bacterial contamination

# Key criteria for quality control

## Manufacture

Is it well characterised?

- **Structure/Characterisation** – analytical methods –validated, state of the art, orthogonal
- **Physical or chemical property** of an intermediate or DS related to safety, quality, integrity, purity or potency
- **Impurities –** Process/product related (not product-related substance) – use of stressors to determine expected breakdown products upfront and the capacity to detect them
- **Contaminants** – Secondary evaluations – microbiology/sterility, adventitious agents (viral/TSE/ mycoplasma), container safety, endotoxin safety
- **Reference material** – in-house, international standard, stringency of specs/ characterisation, traceability map

# Key criteria for quality control

**Manufacture**

- Is it stable?

**Stability**

- Most biological medicines are affected by temperature – shipping conditions, deviations, variations
- Degradation pattern & kinetics may not necessarily be linear
- Shelf life for new entity is based on real time data provided – NO EXTRAPOLATION
- Carried out in final DS/DP container and in the correct orientation
- For variations, consideration may be given to company's history/knowledge of the product

**Container/compatibility** – description, compatibility over shelf life

# Key criteria for quality control

**Manufacture**

- Are specifications and limits adequate and justified
  - Specification – part of overall control strategy
  - Justification of specifications
    - Ph. Eur. or BP Monograph
    - Linked to manufacturing process, IPT, process validation results and characterisation
    - Accounts for stability of DS and DP
    - Linked to preclinical and clinical studies
    - Linked to analytical procedure
    - Linked to batch analyses

# Other considerations for Biotech products

- Vector design
  - Ø Elucidation of structure…sequencing…stability
  - Ø In vitro biological activity/potency…appropriate models
  - Ø level of transfer and gene expression
- Determine vector genome concentration – quantify the number of packaged genomes.
- Infectious titer assay – quantify the number of infectious particles
- Impurities
  - Ø packaging of non-viral nucleic acids/empty/non-infectious (ie Ratio of empty versus full vector particles – for eg Spectrometry assay)
- Genome mutants/recombinants
- Adventitious agents – multiple assays for detecting viral contaminants.
- Replication competence assay – for eg Wild type AAV2 contamination in medicines based on Adenovirus constructs

# Biosimilar Medicines

- A biosimilar is a version of an already registered biological medicine (the reference product) with demonstrated similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on a comprehensive comparability study.
- Regulated by the *Therapeutic Goods Act 1989* as prescription medicines
- No separate pathway for biosimilars
- Regulatory Framework-
  - TG Act, Regs, Orders and Monographs that apply to biological medicines are also applicable to biosimilars
- Relevant Guidelines
    - *Australian Regulatory Guidelines for Prescription Medicines (ARGPM)*
    - *Adopted EMA and ICH scientific guidelines*
    - *Specific EMA guidelines for biosimilars*
    - *Specific TGA Guideline for biosimilars- Biosimilar medicines regulation*
    - *CPMP/ICH/5721/03 ICH Topic Q 5 E: Comparability of Biotechnological/Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.*

# In summary: It's all about balance of controls

- Manufacturing controls
  - Raw materials
  - Validated manufacturing process
  - In-process testing
  - Critical Quality Attributes
  - Specifications
  - Stability testing
  - Analytical methods and validation
  - Consistency of lots (batch analyses)
  - Manufacturers- current licence/certification for appropriate manufacturing steps, GMP inspections
  - Packaging: Labelling and product information
- Conditions of Registration
- TGA Testing –batch release, survey, reactive testing
- Other post market activities and Risk Management Plan

# Guidelines for regulatory compliance

**Australian Regulatory Guidelines for Prescription Medicines (ARGPM)**
https://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm

**Biological medicines guidelines**
https://www.tga.gov.au/biological-medicines-guidelines

**International Council on Harmonisation Quality guidelines developed by European Medicines Agency (EMA)**
https://www.ema.europa.eu/human-regulatory/research-development/scientific-guidelines/ich/ich-quality

**Biosimilar medicines regulations**
https://www.tga.gov.au/publication/biosimilar-medicines-regulation

**Medicine Labels: Guidance on TGO 91**
https://www.tga.gov.au/sites/default/files/medicine-labels-guidance-tgo-91-and-tgo-92.pdf

**Minor variations to prescription medicines.  appendix 2: Variation change types – biological medicine**
https://www.tga.gov.au/sites/default/files/guidance-minor-variations-biological-medicines.pdf

# Relevant guidelines for registration of *in-vivo* Gene therapies

Information on prescription medicines that contain, or are produced by, genetically modified organisms (GMOs) is available in the ARGPM Guidance 21: *Medicines produced by genetic manipulation*

**Sponsors must:**

- consult the OGTR to determine any obligations under the Gene Technology Act 2000
- indicate whether an application has been lodged with the OGTR
- Refer to the
  - Australian Regulatory Guidelines for Prescription Medicines (ARGPM)
  - relevant European Union guidelines and pharmocopoeias, including:
    - Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)
    - Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells (pp. 275–286 of Rules 1998 (3A)–3AB6a)
    - Ph. Eur. 5.14 Gene Transfer Medicinal Products for Human Use
    - Other relevant European Union guidelines adopted by the TGA, listed on
      - https://www.tga.gov.au/guidance-21-medicines-produced-genetic-manipulation
      - https://www.tga.gov.au/ws-sg-index?search_api_views_fulltext=&field_ws_sg_category1%5B%5D=9098&sort_by=field_ws_sg_adopted&sort_order=DESC&items_per_page=60&=Search

# Guidelines for adventitious agent safety

- TGA TSE policy and Australian Regulatory Guidelines for Prescription Medicines (ARGPM) Guidance 10: Adventitious agent safety of medicines
- Ph. Eur. monograph 2034 ‘Substances for pharmaceutical use’ requires a risk assessment in accordance General Chapter 5.1.7 Viral Safety
- ICH Topic Q5A (R1): Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin.
- Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP/BWP/268/95)
- Ph. Eur. monograph 1483 ‘Products with risk of transmitting agents of animal spongiform encephalopathies’
- General Chapter 5.2.8 - Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents (**EMA/410/01 rev.3**)

# Thank You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