Available online on 15 June 2019 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Open Access to Pharmaceutical and Medical Research
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Open Access

Regulatory aspects for Biologic Product licensing in Australia

Sanjeev Kumar Maurya*, Vikesh Kumar Shukla, Sunny Kumar Maurya, Prachi Kaushik, Indu Maurya

Department of Drug Regulatory Affairs, Amity Institute of Pharmacy, Amity University, Sector-125, Noida (UP), India

Abstract

The TG Act defines biological as product made, from or containing, human cells or human tissues, lives animal organs, cells or tissues, and that is used to treat or prevent disease or injury, Diagnose a condition of a person and Alter the physiological processes of a person.

The Australian Regulatory Guidelines for Biologicals (ARGB) provide the keen information for manufacturers, sponsors, professionals in healthcare and also to public about the use of human cells and tissues based therapeutic goods, live animal cells, organs and tissues (1). These all products are Biologicals. This guideline is specially written for general public. If you are a sponsor or manufacture, this will:

- Explains the biological regulatory framework is applies to manufacturer's product and their exemption conditions (1).
- Explains the Australian regulatory requirements for supplying of Biologicals
- Explains what is required for the market authorization as per TGA especially for Biologicals.

Keywords: Biologicals, TGA, ARGB, Therapeutic Goods.

Article Info: Received 17 Mar. 2019; Review Completed 15 May 2019; Accepted 26 May 2019

Cite this article as:

Maurya SK, Shukla, Maurya SK, Kaushik P, Maurya I. Regulatory aspects for Biologic Product licensing in Australia. International Journal of Drug Regulatory Affairs [Internet]. 15 Jun 2019 [cited 15 Jun 2019]; 7(2):1-6. Available from: http://ijdra.com/index.php/journal/article/view/310

DOI: 10.22270/ijdra.v7i2.310
*Corresponding author Tel.: +91-8375937871;
E-mail address: sanjeevpkmskm@gmail.com (S.K. Maurya).

1. Introduction

Biologicals Regulatory Framework

The Biologicals Regulatory Framework is the term for legislation that came into force in 2011 for the regulation of human cells and tissue-based, or live animal organ, cell and tissue-based products as a distinct group of therapeutic goods called 'Biologicals'. The framework is administered by the Therapeutic Goods Administration (TGA), who has produced this document-the Australian Regulatory Guidelines for Biologicals (ARGB)-to inform manufacturers, sponsors, healthcare professionals and all other interested parties about the framework (2).

The Key features of the framework are listed below:

The Biologicals Regulatory Framework provides a comprehensive system of assessment and controls that must be completed before products are allowed to be marketed in Australia (premarket), and follow-up and further controls after they are marketed (post-marketed) (3).

Before Biologicals can be legally imported, exported, manufactured or supplied in Australia, they must be:

- Included on the ARTG (Australian Register of Therapeutic Goods)

  Or

- Otherwise exempted, approved or authorized.

The Biologicals regulatory framework allows for four classes of Biologicals based on the risk posed by the products, which are in turn related to:

- The methods used to prepare and process the product during their manufacture

  And

- Whether their intended use is the same as their usual biological function.

Key benefits of the Biologicals Regulatory Framework

- Minimize the risk of infectious disease transmission

- Ensure the level of regulation applied matches the level of risk
- Provide a more flexible framework to respond to changes in technology than has been the case under previous arrangements
- Increase International harmonization of therapeutic goods regulation
- Reduce the ambiguity about what was included or excluded from regulation through the use of consistent terminology (2).

Products Regulated as Biologicals under the Biologicals framework *(4)*

To be included in the Biologicals Regulatory Framework, products must:

- Be therapeutic goods (as defined in the TG Act)
- Not be an 'excluded good'
- Either meet the definition of a biological or are specified by legislative instrument to be a biological
- Not be specified in the Therapeutic Goods Determination 'Things that are not Biologicals'

Biologicals currently only refer to human cells and tissues, or live animal cells, tissues and organs, and not to:

- Tissues or cells from non-human or non-animal biological sources (e.g. bacteria)
- Medicines made using biological or biotechnology processes (e.g. non-cellular vaccines, insulin) *(4)*.

The following Biologicals are currently included in the regulatory framework:

- Human tissue therapy products (e.g. skin, tissues, bone for grafting)
- Processed human tissues (e.g. demineralised bone, collagen)
- Human cellular therapy products (e.g. cartilage cells, cultured skin cells)
- Immunotherapy products containing human cells
- Genetically modified human cellular products.
- Live animal cells, tissue and organs (e.g. pancreatic islet cells isolated from pigs)

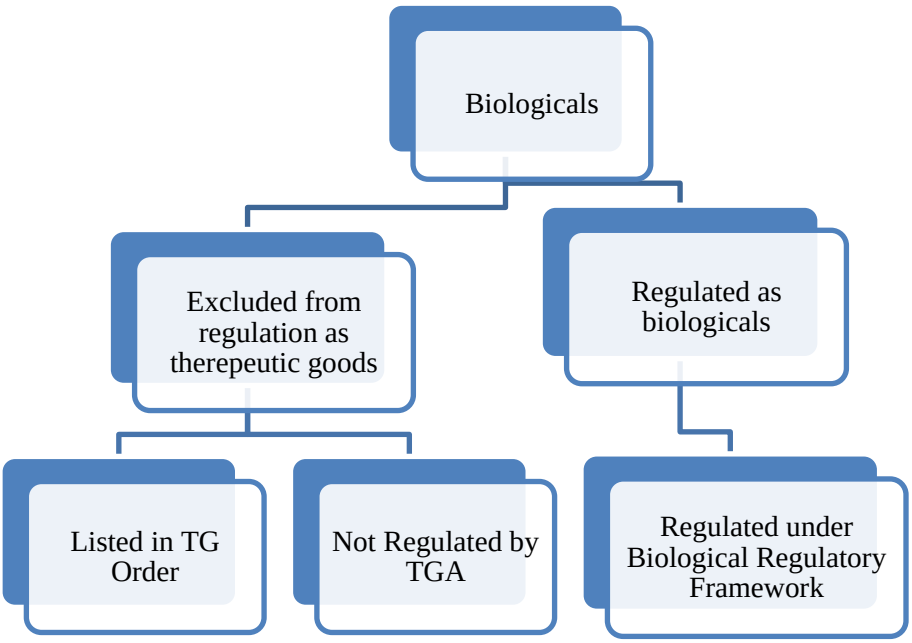

Figure 1. Biologicals Regulatory Framework

Products not covered by the Biologicals framework *(5, 6)*

- Fresh viable human organs, or parts of human organs, for direct donor-to-host transplantation and used in accordance with applicable laws and standards
- Fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution (e.g. bone marrow cells and cord blood)
- Reproductive tissue (e.g. sperm, eggs, embryos for in vitro fertilisation and other assisted reproductive technologies) that are 'unmanipulated' (i.e. they have not been processed in any way apart from freezing).

Australian regulatory guidelines for Biologicals (ARGB) *(7, 2)*: The ARGB:

- Explains legislative requirements outlined in the regulatory framework for Biologicals
- Provides information about the supply and use of human cell and tissue based therapeutic goods, living cells of animal based

2. Regulatory framework for Biologicals (4, 7)

It provides the legislative basis for the regulation of human tissue and also the cell derived products and living animal cells, tissue or organs that are supplied or exported in Australia. This was commenced on 31 may 2011, following a recommendation from Commonwealth, state, and Territory health ministers to improve the regulation of human tissues and cell based therapies. All products need to comply with the requirements made under this legislation (4). The framework applies different levels of regulation to products based on the risks associated with their use. It is designed to be flexible enough to accommodate emerging technologies (7).

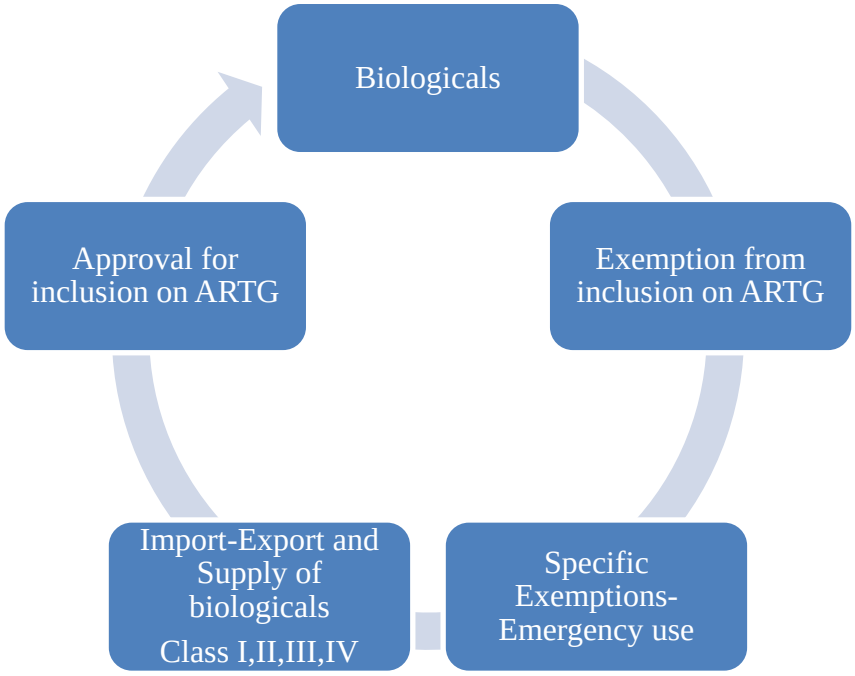

Figure 2. Classification of Biologicals

Table 1 Classification of Biologicals and their level of risk (8, 9)

Definitions from the TG Regulations	Meaning	Risk
Class 1 biological means a biological that is declare in regulations as a class 1 biologicals.	This has been designated Class 1 and is specified in Schedule 16 of the TG regulations.	Low
Class 2 biologicals means a biologicals that is: a. Both: • Processed using only one or more of the actions of minimal manipulation. • For homologous use. b. Declared in the regulations as a class 2 biologicals.	• It is prepared using simple methods, as stated for minimal manipulation method. • Used to repair, reconstruct or replace cells or tissues that have the same biological function in the recipient.	Low
Class 3 biologicals means a biological that is: a. Processed: • Using a method in addition to any of the minimal manipulation. • In a way that does not change in inherent biochemical or immunological property. b. Declared in the regulation as a class 3 biologicals.	• It is prepared using more complex methods, such as enzymatic dissociation. • These methods do not change the biological properties of the product.	Medium
Class 4 biological means a biologicals that is: a. Processed: • Using a method in addition to any of the actions of minimal manipulation. • In a way that changes an inherent biochemical, immunological property. b. Declared in the regulations as a class 4 biologicals.	• It is prepared using more complex methods, as for class 3. • The method have used have changed the biological properties of the product.	High

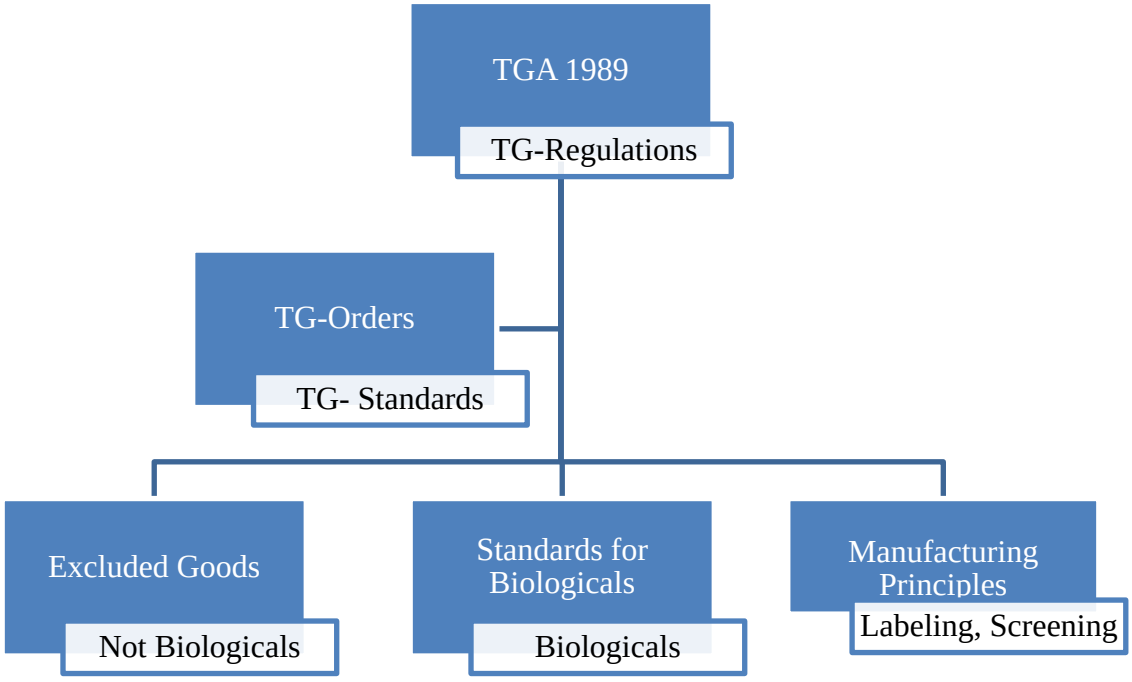

Figure 3. Regulatory process of Biologicals (10, 2)

Different forms for the Biologicals industry *(2)*

Followings are the forms for Biologicals industry:

- **Exceptional release of a biological**: Access to the request form and instructions are within guidance document.
- **Request for advice on Biologicals**: Information required to be submitted when requesting advice on the classification of Biologicals.
- **TGA business service forms**: Forms for sponsors, agents, manufactures to apply for access to TGA business services.
- **Notification of a change in sponsorship**: Use to notify of a change in sponsorship of ARTG entry.
- **Proposal for new Australian cell & Tissue Name (ACN) application form**: Use this form when applying for new cell and tissue name is Australia.
- **Biologicals, human blood and blood components report form:** Use to report recalls of human blood and biological products that are derived from human or live animal materials (2).

Legislation of Biologicals *(2, 3, 9)**:*** The regulations of Biologicals are specified in:

- Therapeutic goods act 1989
- Therapeutic goods regulations 1990
- Therapeutic goods (human cells, tissues and organs) determination 2018
- Therapeutic goods (charges) regulations 1990

Post market requirements for Biologicals *(3,7)*

- ADR reporting
- Product recall initiation
- Hazard alert
- Australian regulatory guidelines for advertising therapeutic goods

3. Standards for Biologicals (2, 11)

- **Default standards**: The Biologicals must comply with the any default standards. Default standards are publicly available standards that are mandated through the Therapeutic Goods Act 1989 and provided by the:
  - ❖ British pharmacopoeia
  - ❖ European pharmacopoeia
  - ❖ U S pharmacopoeia
- **Manufacturing principles**: Different manufacturing principles apply to different kinds of Biologicals:
  - ❖ Biologicals that contain human cells and tissues, must comply with the Australian code of GMP for human blood and blood components.
  - ❖ Biologicals that contain living animal cells, tissues or organs should be complying with PIC/S guide to GMP (2).
- **Product specific standards**: Product specific standards refer to Therapeutic Goods Orders (TGOs) that specify the legal requirements for the different product types, including labelling:
  - ❖ Human skin
  - ❖ Human ocular tissue
  - ❖ Human cardiovascular tissue

- ❖ General requirements for labeling of Biologicals
- ❖ Human musculoskeletal tissue

- **Standards for infectious disease minimization**: Unless exempt, sponsors and manufacturers of blood, blood components, and haematopoietic progenitor cells (HPCs) and Biologicals, must meet the requirements of:
  - ❖ Therapeutic order no. 88 – standards for donor selection, and minimizing infectious disease transmission via therapeutic goods that are human blood and blood components, human tissue and human cellular therapy products (2).

License guidance (2)**:** License and overseas GMP certification applications:

- GMP decision tree
- Australian manufacturing license and overseas GMP certification
- Declaration of intent to supply the Australian market
- Transfer of a manufacturing license
- Requesting variations to your manufacturing license

4. Biologicals risk management (8, 9)

The TGA will use a risk-management approach to regulate Biologicals in Australia, based on the same principles of risk management currently used for medicines and medical devices. A risk-management system will take into account the level of scrutiny applied to individual applications for inclusion on the ARTG.

The following documents should be used to guide the development and maintenance of a risk-management framework:

- The TGA risk management approach to the regulation of therapeutic goods
- ISO (International Organization for Standardisation)/DIS 13022. Draft international standard: Medical products containing viable human cells—application of risk management and requirements for processing practices
- ISO 14971. Risk assessment for medical devices
- ISO 22442:1. Medical devices utilizing animal tissues and their derivatives—Part 1: application of risk management
- ICH (International Conference on Harmonisation) Q9. Quality risk management
- EMEA (European Medicines Agency). Guideline on human cell-based medicinal products
- EMEA. Guideline on safety and efficacy follow-up risk management of advance therapy medicinal products.

To ensure product quality and safety and to minimise risk, a risk-management system must be applied through all stages of the product's life, from concept or collection to release and clinical use. The risk-management system should guide manufacturers to identify and analyse risks, and to evaluate and control the risks at all stages of the biological product's life (9). The nature of Biologicals means that they can pose risks that do not apply to other therapeutic goods, such as the risk of infectious disease transmission, or other unforeseen biological reactions (8).

In addition, the diverse range of starting materials and processes used in the manufacture of Biologicals leads to differing levels of risk (11). Consequently, to approve a Class 2, Class 3 or Class 4 biological for inclusion on the ARTG, the TGA will need to determine that risk has been appropriately managed by taking into account the risks specific to the biological, as well as the level of risk imposed by the manufacturing materials and process (5).

5. Conclusion

After the study of Regulatory Aspects for Biologic Product Licensing in Australia, I have come to know about the various regulatory requirements, product licensing and different kinds of applicable forms that are necessary to taken into considerations for the biologic product in Australia.

Acknowledgements

We would like to express our sincere gratitude to Dr. Tanveer Naved and Dr. Balvinder Shukla (Vice chancellor), Amity University for their continuous support and motivation.

Financial Disclosure statement: The authors received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Therapeutic Goods (Excluded Goods) Order [Internet]. TGA; 2019 [cited 2019 Jan 23]. Available from: https://www.tga.gov.au/excluded-goods-orders
2. TGA [Internet]. TGA; 2019 [cited 2019 Feb 11]. Available from: https://www.tga.gov.au
3. EMEA (European Medicines Agency) [Internet]. EMEA; 2019 [cited 2019 Jan 10]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp@jsenabled=true
4. Therapeutic Goods (Things that are Biologicals) Specification 2017 (No. 1) [Internet]. TGA; 2017 [cited 2019 Jan 12]. Available from: https://www.tga.gov.au/therapeutic-goods-determinations
5. Therapeutic Goods (Things that are not Biologicals) Determination [Internet]. TGA; 2019 [cited 2019 Jan 25]. Available from: https://www.tga.gov.au/therapeutic-goods-determinations
6. ISO (International Organization for standardisation) [Internet]. ISO; 2019 [cited 2019 Jan 11]. Available from: https://www.iso.org/home.html
7. Current TG Act and TG regulations [Internet]. TGA; 2019 [cited 2019 Jan 19]. Available from: https://www.tga.gov.au/legislation-legislative-instruments

8. TGA risk management approach to the regulation of therapeutic goods [Internet]. TGA; 2011 Sept 12 [cited 2019 Jan 24]. Available from: https://www.tga.gov.au/tgas-risk-management-approach
9. ICH (International Conference on Harmonization) [Internet]. ICH; 2019 [cited 2019 Jan 15]. Available from: http://www.ich.org/home.html
10. Therapeutic goods act [Internet]. TGA; 1989 [cited 2019 Feb 10]. Available from: https://www.legislation.gov.au
11. Office of the Gene Technology Regulator [Internet]. TGA; 2019 [cited 2019 Jan 25]. Available from: http://www.ogtr.gov.au/