Review Article

Navigating Biologics Regulation: A Deep Dive into Australian Compliance

Nayana Saji, Deeksha Kethareshwara Sujatha, Balamuralidhara Veeranna*

Department of Pharmaceutics, Center of Excellence in Regulatory Sciences, JSS College of Pharmacy, JSS Academy of Higher Education and Research, S.S. Nagar, Mysuru, Karnataka, INDIA.

Submission Date: 27-01-2024; Revision Date: 26-02-2024; Accepted Date: 12-04-2024.

ABSTRACT

Biologics are at the forefront of therapeutic breakthroughs, marking a paradigm change in medical therapies in an ever-evolving field. Complex biological products known as biologics are used to treat a variety of illnesses and disorders and both their development and marketing are governed by strict rules. Examples of biologic drug kinds include vaccines, the blood, cells, blood components, allergies, tissues, genes and recombinant proteins. Australia's regulatory agency, the Therapeutic Goods Administration (TGA), employs rigorous pre-approval assessments and post-marketing surveillance to guarantee the effectiveness, safety and quality of biologics. Detailed information on the safety and effectiveness of biologics, including information from preclinical and clinical research as well as details on the production process and quality control, must be provided by manufacturers. The TGA also collaborates extensively with foreign regulatory organizations to keep Australia's biologics regulations current and compliant with international norms. The article's conclusion states that Australia's regulatory guidelines for biologics are intended to safeguard the general public's health and guarantee that patients receive reliable medical care.

Keywords: Biologics, TGA, Post-marketing surveillance, Quality, Safety, Efficacy.

Correspondence:
Dr. Balamuralidhara V
Associate Professor and Head, Department of Pharmaceutics, Center of Excellence in Regulatory Sciences, JSS College of Pharmacy, JSS Academy of Higher Education and Research, S.S. Nagar, Mysuru-570015, Karnataka, INDIA.

Email: baligowda@jssuni.edu.in

ORCID ID: 0000-0003-3841-0710

INTRODUCTION

Biologics can be defined as a "thing made from, or that contains, human cells or human tissues, that is used to treat or prevent disease, ailment, defect or injury and diagnose a condition of a person to alter the physiological processes of a person and test the susceptibility of a person to disease and replace or modify a person's body parts". Proteins, carbohydrates, nucleic acids, or complex combinations of these components can make up biologics. Additionally, they may consist of biological entities such as tissues and cells. Biotechnology methods and other state-of-the-art technologies can be used to produce biologics. They can be separated from a range of natural sources, including human, animal and microbial ones. For example, biologics based on genes and cells are often at the forefront of medical research and may be able to cure a variety of diseases for which there are no other viable treatments.[1]

Products that meet the definition of biologicals represented in Figure 1:

SCAN QR CODE TO VIEW ONLINE

www.ajbls.com

DOI: 10.5530/ajbls.2023.13.2

PRODUCT TYPES CONTROLLED AS BIOLOGICALS

Among the items that are subject to regulation as biologicals are, but are not limited to:

- Goods made of tissue, such as skin, bone, eyes, hearts and amnion.
- Items made from cells (genetically modified, *in vitro* cell growth or depletion).
- Products for immunotherapy derived from human cells.

- Items in combination (such as cell treatment and medical devices);
- Goods made of or containing live animal cells, tissues, or organs, such as pig pancreatic islet cells.
- Human tissue, cells and stem cell products that is autologous.
- Faecal Microbiota Transplant (FMT) items (anything made from, originated from, or containing human faeces).[2]

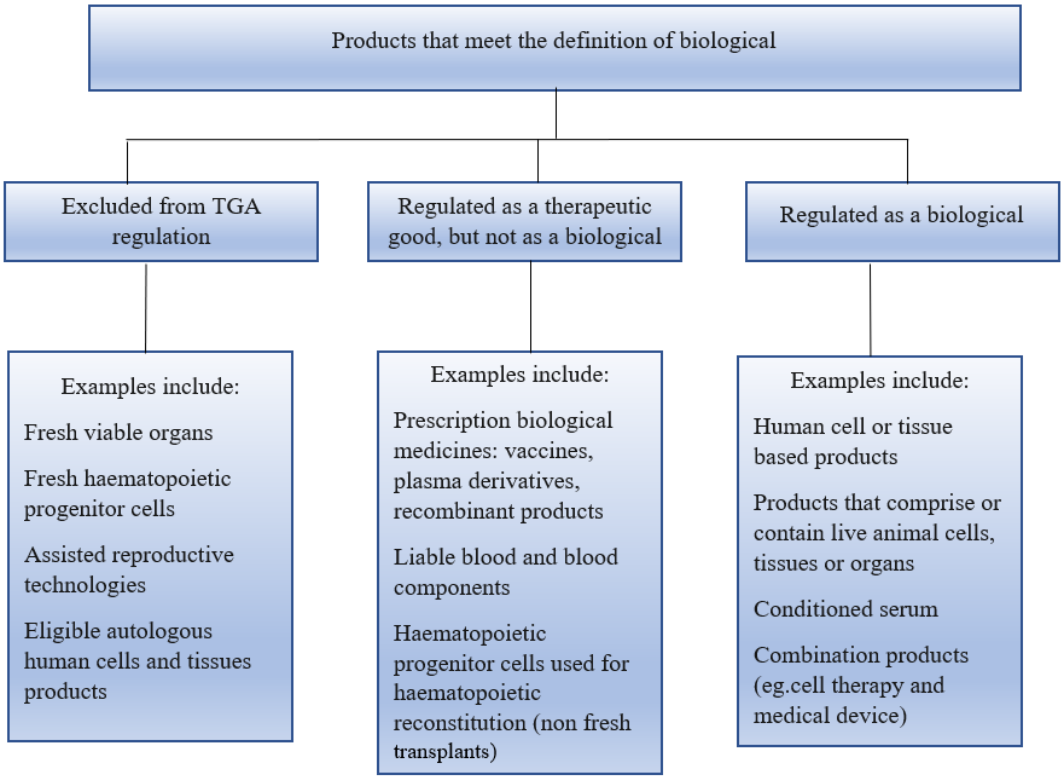

Figure 1: Products that meet the definition of Biologics.[3]

VALIDITY TIME PERIOD OF BIOLOGICS

The validity time period of biologics in Australia refers to the duration of their marketing approval by the Therapeutic Goods Administration (TGA). Biologics, like other therapeutic products, are granted marketing approval for a specific period of time, which is usually subject to renewal after thorough re-evaluation of their safety, efficacy and quality.

The initial marketing approval for a biologic is typically granted for a certain number of years, which can vary depending on the specific biologic and the medical condition it is intended to treat. The validity period may range from several years to up to 5 to 10 years, depending on the regulatory pathway and the data submitted by the manufacturer during the approval process.[4]

Once the initial validity period is nearing expiration, the manufacturer needs to apply for renewal with updated safety and efficacy data. The TGA will reassess the biologic's benefits and risks to determine if it continues to meet the compulsory standards for safety and efficacy. If the biologic still meets the necessary criteria, the TGA may renew its marketing approval for another period.

Keep in mind that the information provided is based on the situation as of September 2021 and the regulatory landscape may have evolved since then. For the most current and accurate information about the validity time period of biologics in Australia, it is essential to refer to the latest guidelines and updates from the Therapeutic Goods Administration.[5]

PATENT EXCLUSIVITY

Patents can also provide protection for biologics in Australia, granting the patent holder exclusive rights to manufacture, use and sell the biologic for a specified period. Patents are crucial for incentivizing innovation and providing a period of exclusivity to the original developers of biologics, allowing them to recoup their investment in research and development.

The patent protection for biologics in Australia, as well as in many other countries, is usually granted for a fixed period from the date of filing the patent application. The

time period of patent protection can vary depending on the type of biologic and the specific patents involved. In general, patent terms for biologics can extend for 20 years from the filing date, but this may be adjusted based on factors such as regulatory delays during the approval process.[6]

It's important to note that the patent protection period and its potential extensions can vary due to certain factors, including:

Patent Term Extensions (PTE)

In some cases, the regulatory approval process for a biologic may take a considerable amount of time, cutting into the effective patent protection period. To compensate for this delay, some countries, including Australia, offer Patent Term Extensions (PTEs) or Patent Term Adjustments (PTAs) that can extend the patent's term to account for the regulatory review period.

Supplementary Protection Certificates (SPCs)

In some jurisdictions, including the European Union, Supplementary Protection Certificates (SPCs) may be available for certain biologics, providing additional protection beyond the regular patent term.[7]

Patent challenges and litigation

The duration of patent protection can be influenced by legal challenges, patent litigation, or settlements between the patent holder and generic/biosimilar manufacturers.

- Although the search results do not specify the exact patent exclusivity period for biologics in Australia, patent protection often lasts for a certain amount of time, generally 20 years from the date the patent application was filed.
- Patents provide a legal framework for protecting intellectual property and encouraging innovation by granting the patent holder a monopoly on their invention for a limited period of time.
- Unlike data exclusivity, patent protection covers the underlying invention itself, rather than the specific data submitted for regulatory approval.[8]

DISCUSSION

Overview of Regulatory Bodies in Australia

Australia's regulatory organization in charge of overseeing biologics is the Therapeutic Goods Administration. Sponsors and producers can get guidelines on biological legislation from the Australian Regulatory Guidelines for Biologicals (ARGB). The regulatory frameworks for biologicals' statutory requirements, including particular biological standards, are explained in the ARGB. For the safety, effectiveness and efficacy of therapeutic items in Australia, including biological products, the TGA is responsible. A vast array of items are classified as biological products, such as vaccines, tissues, blood and blood components, allergies, somatic cells, gene therapy and recombinant therapeutic proteins. The Australian Register of Therapeutic Goods (ARTG), a database including all therapeutic products that are permissible to offer in Australia, is used by the TGA to establish or monitor criteria. The quality, safety and effectiveness of therapeutic goods, including biologics, are governed by the TGA. The Australian Government has measures to lessen the administrative cost of switching for prescribers and to increase consumer confidence in biosimilars. The Schedule to Australia's Pharmaceutical Benefits Scheme (PBS) lists originator biologics and biosimilar brands.[9]

Navigation Pathway

Navigation pathway of biologics is represented as in Figure 2:

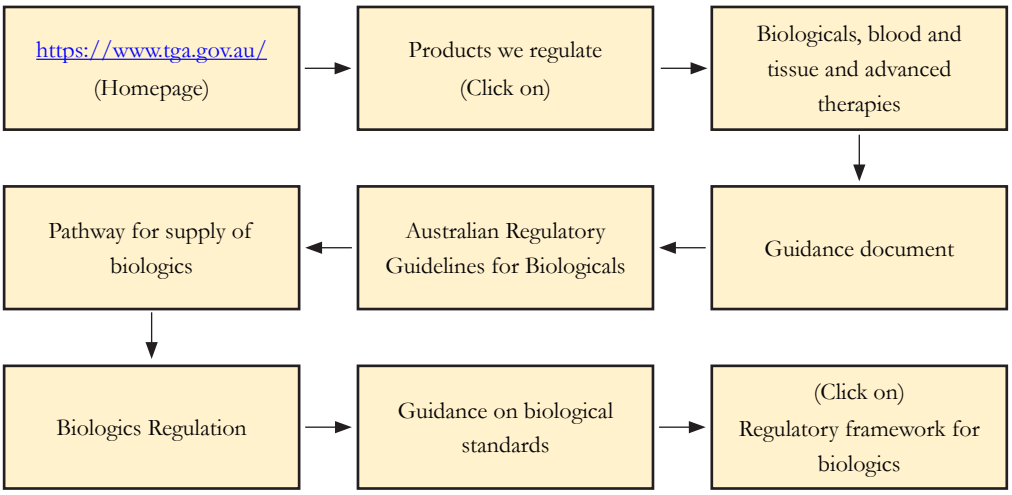

Figure 2: Navigation Pathway of Biologics.[10]

Regulatory Pathway of Biologics in Australia

The term "Biologicals Regulatory Framework" refers to legislation that went into effect in 2011 and regulates products made from human cells and tissue or live animal organs as a separate class of therapeutic commodities referred to as "Biologicals."

- The Therapeutic Goods Administration (TGA) is in charge of the Australian Regulatory Guidelines for Biologicals (ARGB), which it developed to provide information about the framework to sponsors, producers, healthcare providers and other interested parties. The regulatory pathway of biologics is represented in Figure 3.

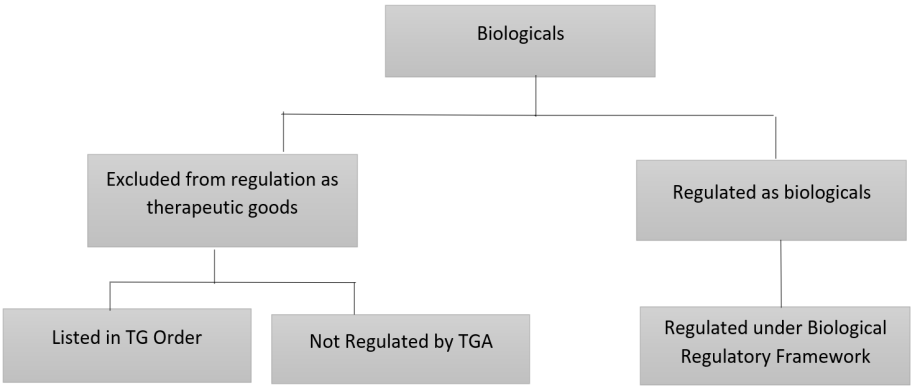

Figure 3: Regulatory Pathway of biologics.[11]

Classification of Biologics

Before being included on the Australian Register of Therapeutic Goods (ARTG), all biologicals must be categorized. Classification of biologics based on risk is represented in Figure 4:

Risk Basis for Classification

CLASSES OF BIOLOGICALS	RISK
CLASS 1 BIOLOGICALS	LOW RISK
CLASS 2 BIOLOGICALS	LOW RISK
CLASS 3 BIOLOGICALS	MEDIUM RISK
CLASS 4 BIOLOGICALS	HIGH RISK

Figure 4: Classification of Biologics.[12]

Method for classifying biologicals

Biologicals are categorized using one of the following criteria:

➢ Schedule 16 (Biologicals, Classes 1 and 4) mentions the way that Class 2 and 3 biologicals are prepared and how they will be used.

Schedule 16 (Biologicals, Classes 1 and 4) mentions Biologicals in Class 1

This low-risk designation is meant to ensure that a Class 1 biological product: poses little threat to public health and also possesses the proper controls, such as accreditation and strict practitioner supervision.

To provide a Class 1 biological, your product must:

- Meet all legal requirements be included in Schedule. You have to follow a compliance declaration on the ARTG.
- Doesn't need a manufacturer's certificate or GMP manufacturing license.
- Does not demand the evaluation of supporting data before market launch.

Biologicals in Class 4

Schedule 16 currently designates Class 4 biologicals as high-risk items. These biologicals include: a. biologicals comprising or containing live animal tissues, live animal cells, or live animal organs.

The biologicals are made up of, derived from, or contain human tissues or cells that have been intentionally modified to perform one or more activities that were not innate to the cells or tissues before their extraction from the donor.

Biology to which the two paragraphs that follow relate.

Stem cells with pluripotency.

Products derived from stem cells with pluripotency.[13]

Method of assembly and intended application

Classification matrix for class 2 and 3 biologicals based on the intended use and method of preparation is represented in Figure 5:

	Intended use: Homologous	Intended use: Non homologous
Method of Preparation Minimal Manipulation	Class 2 (LOW Risk)	Class 3 (MEDIUM Risk)
Method of Preparation More than minimal manipulation	Class 3 (MEDIUM Risk)	Class 3 (MEDIUM Risk)

Figure 5: Intended use and method of Preparation.[14]

GUIDELINES ON BIOLOGICS

TGA, Australia regarding the legal criteria and the application process for biologics approval, two fundamental principles is offered:

Routes for biological supply and Control over autologous human cells and tissues

The Australian approach to the procurement of biological products In Australia, a product may go via several distribution routes depending on whether it is pharmaceutical or biological.

1. Not subject to some TGA regulations,
2. An authorized biological that is deemed "unapproved" for supply and
3. A part of the ARTG.[15]

Exempt biologicals

See Exempt autologous HCTs to find out if your product qualifies and what rules you still need to abide by. Certain autologous human cell and tissue products may be excluded from some regulatory duties, but you must fulfill certain standards to be qualified.

Unapproved' biologicals

Because biologicals on the ARTG have completed evaluations for efficacy, safety and quality, their availability is encouraged. If you need to supply a biological that is not listed on the ARTG, there are a few different options available based on whether the biological is being used for a single patient (special access schemes), as part of a clinical trial (clinical trial schemes), or by a single practitioner for multiple patients (authorized prescriber schemes).

Biologicals included on the ARTG

It is your responsibility to request that your biology be included to the ARTG if it is not already exempt, permitted, or approved.

To be considered for inclusion on the ARTG, you must: Classify your biological systems.

Request to get the ARTG to include your biological data. Biologicals can also be combined with another medication or packaged with it. Biological kits, composite packs, system/procedure packs, combination goods, or packs are some categories for these.

Autologous human cells and tissue regulation

It may be possible to exempt some autologous human cell and tissue products from certain regulatory requirements:

When one or more requirements are not met, TGA enforces strict regulations for the following: samples taken from patients while they are receiving clinical treatment; minimally altered products for homologous use; preparations made by the practitioner for clinical care OR by someone working under their supervision; and use for a single indication in a single clinical procedure. The supply of biologics on the ARTG has been authorized after they underwent quality, safety and efficacy testing.[16]

Clinical Trial Requirements

To protect the safety of participants, clinical trials are subject to several regulatory requirements in Australia. Therapeutic goods legislation in Australia governs the provision of therapeutic products during clinical studies.[17]

Good Clinical Practice Inspection Program

The TGA's Good Clinical Practice (GCP) Inspection Program oversees clinical trials for drugs and biologicals controlled under the CTN or CTA schemes.

- To give sponsors more details on the Good Clinical Practice (GCP) Inspection Program's scope and operation, the TGA has provided guidance on the subject.

- Clinical trial sponsors need to be aware of Australia's standards for manufacturing, supplying and exporting medicinal items.
- The following channels allow for the importation of "unapproved" medicinal products into and supply in Australia for use in a clinical trial
- Clinical Trial Approval (CTA) and Clinical Trial Notification (CTN) schemes. [18]

CTA Scheme

The CTA Scheme is an approval process that entails the following:

- A sponsor requests authorization from us to provide "unapproved" pharmaceuticals for a clinical research. The application must be submitted with the necessary payment. The HREC must consider the trial design's ethical and scientific components. They go over the product's synopsis, which includes significant but constrained scientific facts (which might include preclinical and early clinical data).
- The Sponsor shall notify us of each study that makes use of the unapproved therapeutic good(s) permitted in the CTA application.[19]

THE CTN SCHEME

To fund a clinical study involving an "unapproved" medicinal product, the Australian clinical trial sponsor must first contact us. Before using the products, this must be done. The online notification form must be submitted together with the required cost. They have the option of providing the trial's sponsor with a formal letter requesting specific information about the products listed on the CTN form. At the time of submission, they do not assess any clinical trial-related data. The Human Research Ethics Committee (HREC) examines the trial's design for scientific validity, weighs the benefits of the therapeutic intervention against potential risks, determines if the trial's procedures are morally acceptable and then approves the protocol. The HREC is in charge of keeping an eye on the conduct of the trial.[20]

Manufacturing and Quality Control Requirements

- Biologicals that are formed of, contain, or originate from human cells and tissues, or that are identified as such by the Secretary, must adhere to the Australian code of GMP for human blood and blood components, human tissues and human cellular therapy products.
- Biologicals must adhere to the PIC/S guide to GMP (12), except annexes 4, 5, 14 and 16 (which include the identical production guidelines that apply to pharmaceuticals).

The Australian Code of Good Manufacturing Practice (GMP) for Blood and Blood Items, Human tissue products and Human Cellular Therapy Products, also known as the Code, applies to manufacturers who supervise the collection, processing, testing, storage, release for supply and quality assurance of human blood and blood components, human tissues and human cellular therapy products.[21]

The Therapeutic Goods Act of 1989's Part 3-3 outlines the prerequisites for manufacturing licenses, including compliance with both general and specific licensing criteria. As a condition of their licensing, manufacturers of goods for blood, tissue and cellular treatment must adhere to the production guidelines set out in Section 36 of the Act. To comply with the Manufacturing Principles, manufacturers of human tissues, human blood and blood components and human cellular therapy products must demonstrate their adherence to the Australian Code of Good Manufacturing Practice.

Therapeutic Goods Orders (TGOs) are created individually and contain specifications addressing the efficacy and safety of the products. Manufacturers must create product group dossiers to show that certain TGOs have been satisfied.[22]

The Code describes all of the Good Manufacturing Practice (GMP) guidelines that, when combined, ensure that human tissues, human cellular therapies and human blood and blood components m*eet all* requirements. Other approaches are acceptable as long as it can be demonstrated that the Code's goal is achieved quickly and effectively to meet quality criteria. The Code outlines best practices that have to be adhered to.

This Code covers every facet of manufacturing and quality assurance systems; nevertheless, it is not intended to impose any restrictions on the creation or use of novel ideas or techniques. It is understood that workable alternatives may exist that satisfy the same fundamental needs and achieve the same objective [23]

REGULATORY CHALLENGES-QUALITY

The regulatory challenge for quality is represented in Figure 6:

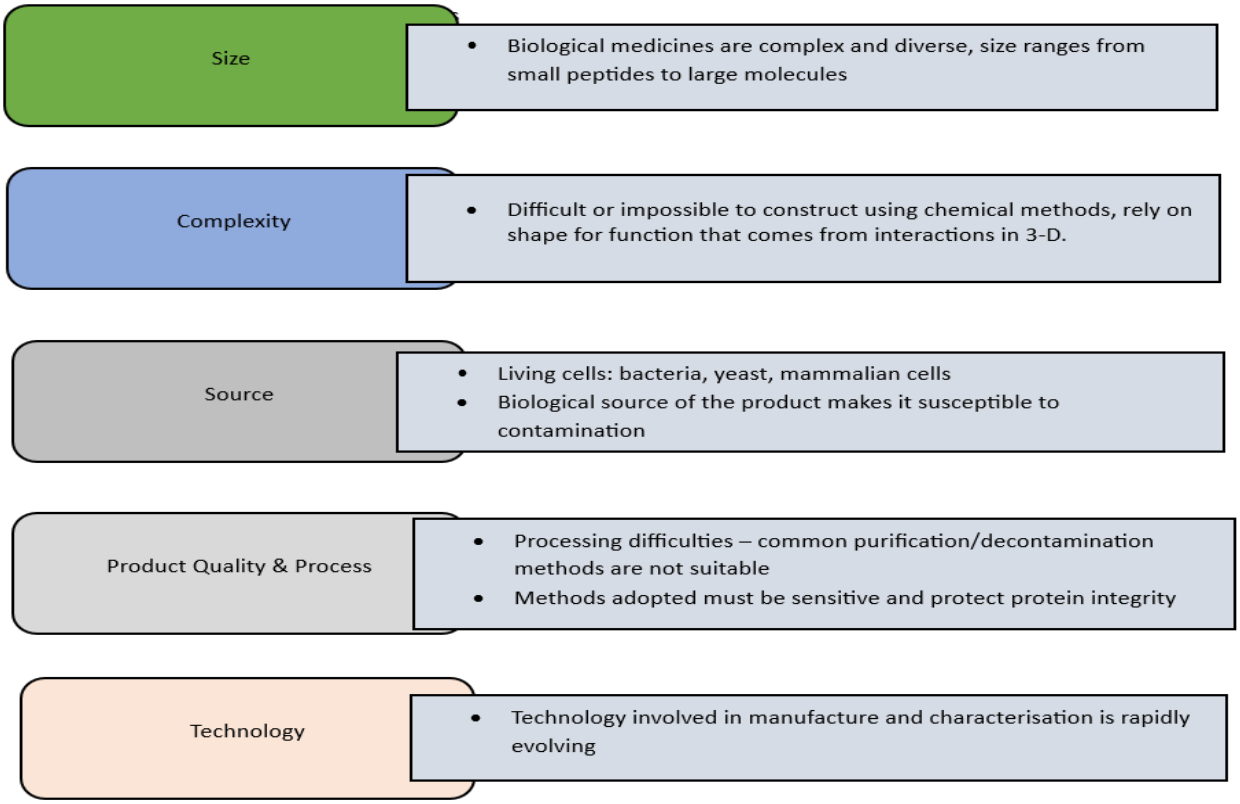

Figure 6: Regulatory Challenges for Quality.[24]

KEY CRITERIA FOR QUALITY CONTROL

Manufacturer

In Australia, material control is a significant factor in determining the quality of biological medicines. The history and characterization of cell lines should be complete and the use of human and animal substances as well as other raw materials for cell culture and purification should be regulated. The manufacturing process, development, etc., should be assessed for clinical implications and adjustments in the manufacturing process and in-process testing should ensure that each stage performs as intended. To ensure that a manufacturing procedure works as planned, it must be validated. The number, campaign and sites selected from clinical and commercial batches should be indicated after conducting batch analysis. GMP must be current (up until the time of approval) and legitimate (claims match clearance/license). The EMA offers recommendations on test techniques and acceptance criteria for biotechnological/biological products. Guidelines for the characterisation and quality of cellular substrate as well as additional biological materials used in the production of biologicals are provided by the FDA and WHO.

The Australian Regulatory Guidelines for Biologicals (ARGB) include instructions on post-market necessities, disclosing adverse occurrences, starting product recalls or hazard warnings and changing biological listings on the Australian Register of Therapeutic Goods (ARTG). The APVMA demands that applicants provide sufficient batch analysis and process control.[25]

Characterization

Australia relies heavily on analytical techniques for the structure and characterization of biological medicines for quality assurance. These techniques must be orthogonal, up-to-date and verified. They should be used to ascertain a drug substance's physical or chemical attributes that have to do with its safety, quality, integrity, purity, or potency. Impurities, whether linked to processes or goods, should be assessed utilizing stressors to identify anticipated breakdown products in advance and their detectability. By ethical and proper production, processing and storage procedures, the presence of contaminants and accidental elements should be reduced. Utilizing secondary assessments such as microbiology/sterility, adventitious agents (viral/TSE/mycoplasma), container safety and endotoxin safety, contaminants should be assessed. Reference materials

should be internal company standards or global norms, with exacting specifications, characterizations and a traceability chart. The Australian Regulatory Guidelines for Biologicals (ARGB) include instructions on post-market necessities, disclosing adverse occurrences, starting product recalls or hazard warnings and changing biological listings on the Australian Register of Therapeutic Goods (ARTG). Pharmaceutical drug research and manufacturing facilities must adhere to GxP rules, including GLP, GCP and GMP. Additionally, all drug products must undergo QC testing using reliable techniques that have been duly approved and validated under GxP guidelines.[26]

Stability

In Australia, stability is a significant factor for biological medicine quality control. The majority of biological medications may not degrade in a linear manner because to temperature changes during shipment, deviations and variances. Shelf life for a new entity is determined using the real-time data offered; extrapolation is not permitted. The final drug substance or drug product container and the proper orientation are used for stability testing. The history and product expertise of the organization may be taken into account while coming up with variants. The Australian Regulatory Guidelines for Biologicals (ARGB) offer guidance on post-market requirements, reporting adverse reactions, starting product recalls or hazard alerts and changing biological products entries on the Australian Register of Therapeutic Goods (ARTG). The Therapeutic Goods Administration (TGA) emphasizes the significance of stability testing and quality control during the manufacture of biological medicines. The Australian Government Department of Health and Aged Care evaluates medications for their safety and efficacy and regulates how they are supplied, working with state and territory governments and stakeholders. Laboratories involved in pharmaceutical drug development and manufacturing must comply with GxP regulations, including GLP, GCP and GMP.[27]

Labelling and Packaging Requirements

A biological will be graded according to the guidelines below:

All data in Part 1

If the biological is packaged in a sterile container, it must be on or attached to both the container and the biological; if not, it must remain on or affixed to the biological's primary pack and the first outer non-sterile layer of packing.

One of the following methods must be used to supply all Part 2 information:

On or affixed to the biological's principal pack or container; or

Accompanied by the biological container or main pack. If the information is contained in an electronic reference document, a link or QR code pointing to the document must be present in the container.

The information specified in item 1 of Part 1 of Schedule 2 must be labeled on or affixed to the main pack and container if the biological is packaged in a sterile container. The biological must be attached to the primary pack and the first external non-sterile layer of packaging if it is exported from Australia.

If one of the following circumstances is true, the information specified in each item in the table in Part 1 of Schedule 2 is referred to as "Part 1 information" while discussing a biological.

That item's column 3 contains the phrase "in all cases"; or

The biological conditions are those listed in that item's column 3.

Part 2 of Schedule 2 pertains to the information described in column 3 if the term "in all cases" appears therein, or if (a) the conditions listed in that item's column are true with regard to the biology.[28]

Details about the information which included in the basic packs and containers are represented in Table 1.

Table 1: Details about or affixed to basic packs and containers.[29]

Item	Information	Circumstances
1	Regarding the donor, either: an alphanumeric or unique identifying number; b) a machine-readable code.	Every time.
2	The number of batches.	There is a biological batch number associated with it.
3	The brand or kind of goods.	Every time.
4	The terms "autologous use only" and the intended recipient's name or identity, respectively.	Use of the biology is authorized.
5	The chosen patient's name or identification.	The use of the biological is intended to be allogeneic.
6	The identity of the biological sponsor.	Every time.

A Detail about the information which is affixed to or provided in primary packs or containers is represented in Table 2:

Table 2: Details about, affixed to, or provided with primary packs or containers.[30]

Item	Information	Circumstances
1.	The words "autologous usage only" and the recipient's name or other distinctive identifier.	Utilizing autologous tissue is the purpose of the biologic.
2.	The name of the selected patient or another distinctive identifier.	Biological is intended for specific allogeneic usage.
3.	The name of the biological's sponsor	Every time
4.	Regarding the sponsor's primary Australian company location address, phone number and other information. the cyber address (c).	Every time.
5.	An outline of the biological.	Every time.
6.	The biological indicators that have been authorized.	The biological is registered as either a Class 3 or Class 4 biological.
7.	The biological agent's authorized intended clinical usage.	In the Register, the biological is categorized as either a Class 1 or Class 2 biological.
8.	An overview of the medicinal applications of biology.	Biological is not listed on the Register.
9.	The biological material's use-by date	Every time.
10.	The biological materials' appropriate storage conditions.	Every time.
11.	The biological's dimensions, weight, volume, or concentration, as appropriate.	There is a biological entity having a certain shape, measurement, weight, or concentration.
12.	"Single patient use" is a phrase.	The biological is only meant for usage by one patient.
13.	The term "sterile" or similar expressions.	The biological is sterile.
14.	The brand of the ingredients or antimicrobials, where appropriate.	The biological has undergone a process including additions or antimicrobials.
15.	The name of the sterilizing or, if appropriate, bioburden reduction procedure	Sterilization or bioburden reduction has been applied to the biological.
16.	The brand of the suspension agent.	A suspended solution holds the biological.
17.	The preparation guidelines.	Precise preparation instructions are needed for the biological.
18.	The use instructions.	Every time.
19.	The safety instructions and specific warnings.	Every time.
20.	The contraindications.	Every time.
21.	A breakdown of the different interactions.	The intended recipient's physiological system, medications, or other biologicals may interact with the biological agent.
22.	An explanation of the conflicts.	Biological incompatibility might exist.
23.	A caution about the potential effects on nursing, pregnancy, or fertility, as appropriate.	The biology could affect nursing, pregnancy, or conception.
24.	A caution about the possible effect on allergies.	Allergies may be impacted by biological
25.	An explanation of the impact on personal actions as well as a warning about those impacts.	The intended recipient's actions may be impacted by the biological.
26.	A statement outlining the negative or unwanted impacts.	Biology might have negative or unwanted impacts.
27.	The rules for disclosing adverse events.	In all cases.
28.	The guidelines for returning biological materials.	It is possible to give the sponsor back the biological
29.	A description of any relevant biochemical, biodynamic, or biokinetic qualities.	There is knowledge of the biological's biochemical, biodynamic, or biokinetic qualities and it is a Class 3 or Class 4 biological.
30.	The details and results of the clinical studies.	Clinical investigations have been conducted on the biological under evaluation, which is classified as a Class 3 as well as Class 4 biological.
31.	The data and findings from preclinical safety studies about the dangers associated with: (a) usage during pregnancy; (b) effects on fertility; (c) Genotoxic effects; and (d) Carcinogenicity.	The biological has undergone preclinical safety investigations and is a Class 3 as well as Class 4 biological.

POST-MARKET REQUIREMENTS

Adverse event reporting

Reports of major and nearly significant adverse occurrences in Australia, as well as substantial threats to public health, are required.

Whether they are anticipated or not

- You don't agree with the reporter's conclusion that there could be a causal link
- The biological was administered as prescribed or by the authorized indications (e.g., overdose, abuse, off-label use, error in administration, or occupational exposure).[31]

The timeframes for reporting of adverse events is represented in Table 3.

Table 3: Time frames for Reporting of Adverse Events.

Reporting deadlines	
Type of Report	**Timeframe**
Grave risk to the public's health	≤48 hr
Major unfavourable incident (in Australia)	≤10 calendar days.
Almost severe bad event	≤30 calendar days.

The trade name, Internationally Non-proprietary Name (INN), as well as Australian Cell and Tissue Name (ACN) of the biological product, together with further information

Ingredients in use

- For combination biologicals with several ingredients and a delivery system, each active component should be mentioned. The report should include information if the primary source believes one of the elements may have a causal impact.
- Lot or batch number,
- ARTG code;
- The reason(s) the biological was applied;
- Dose type;
- Dosage (if applicable, mention units) and regimen;
- The administration path (or, in instances involving a parent-child or parent-foetus, the parent route of administration);
- The beginning time and date;
- If applicable, the length of the therapy and the time and date it ended. Acts conducted with the biological, such as the withdrawal of an implant;
- When the adverse event is believed to have been caused by a biological interaction with another substance or object, such as another biological, a pharmaceutical, food, alcohol, illegal drugs, or medical equipment.[32]

Periodic Safety Update Reports (PSURs)

The sponsor of a marketed product receives a Periodic Safety Update Report (PSUR), which is a methodical analysis of worldwide safety data that becomes available over a certain time frame is a methodical examination of global safety data that becomes accessible over a certain period. PSURs are created using a format that has been universally accepted. Periodic Benefit-Risk Evaluation Reports (PBRERs) are another name for PSURs.

A PSUR's main goal is to present a thorough and critical examination of a pharmaceutical product's benefit-risk balance while considering new and developing information in connection to previously established risks and benefits.

PSURs must be filed at predetermined time intervals for:

- Class 4 biologicals
- Class 3 biologicals
- Certain Class 2 biologicals as stipulated by the Therapeutic Goods Act of 1989 section 32ED.

The frequency of PSURs is specified in both the requirements of inclusion in the ARTG for Class 2 biologicals and the non-standard standards of approval for Class 3 and Class 4 biologicals. The report needs to be sent to us within ninety days following the data lock point, which is the day when no further data is posted to the PSUR.[33]

Online Portals and Software with Regulatory Approval

The Australian Therapeutic Products Administration (TGA) provides a variety of tools and online portals to simplify key steps in the regulatory approval process for biologics and other therapeutic products. The TGA and stakeholders including pharmaceutical firms, healthcare professionals and the general public are aiming to expedite communication, application submissions and information dissemination with the use of these digital technologies.

The TGA's eBusiness Services (eBS)

It is an online platform that sponsors (pharmaceutical firms) can use to submit electronic applications for the registration of therapeutic products, including biologics. It facilitates the filing of several application types, such as announcements of clinical trials and registrations for new products as well as amendments to already registered products.

Australian Public Assessment Reports (AusPAR)

An online database made available by the TGA, AusPAR provides comprehensive public summaries of TGA

evaluations of prescription drugs, including biologics. It gives details on the quality, efficacy and safety of the items that have been authorized.

Database of Adverse Event Notifications (DAEN)

The DAEN is an online reporting tool for adverse events and side effects associated with therapeutic products, including biologics. It is accessible to consumers and healthcare professionals. The TGA uses this data to keep track on the safety of certified items.

4. The Australian Register of Therapeutic Goods (ARTG) is a comprehensive database that includes data on all therapeutic products that have been given Australian approval for distribution. This covers biologics and other medications, as well as healthcare equipment and other things. To confirm a given biologic's registration status, one can do an online search of the ARTG.[34]

Intellectual property (Ip) and Market Exclusivity

Intellectual property enables a suitable window of exclusivity for the marketing of an invention, helping to offset the expenses of the initial outlay and the inherent risks of innovation. Future innovation is threatened by Australia's support of the World Trade Organization's (WTO) trade-related features of the Intellectual Property Rights (TRIPS) waiver for COVID-19 vaccines.

When a new pharmaceutical product is registered with the regulator, data exclusivity, sometimes referred to as Regulatory Data Protection (RDP), starts and continues simultaneously with any patent period. The policy of data exclusivity incentivizes innovative enterprises to allocate resources towards the generation and distribution of the copious amounts of data required for the endorsement of novel products. Compared to other countries like the US and EU, Australia has a shorter data exclusivity period (5 years), particularly for biologics.

Managing biological risk

The TGA will regulate biologicals in Australia using a risk-management strategy, based on the same risk-management principles now used to pharmaceuticals and medical devices. Each application for placement on the ARTG will undergo varying levels of inspection, which will be decided by a risk-management procedure [35]

The following papers ought to be employed in the creation and upkeep of a framework for risk management:

The TGA's method of regulating medicinal products uses risk management.

- DIS 13022 from the ISO (International Organization for Standardization). Draft international standard: Risk management application and processing techniques for medical goods containing live human cells.
- ISO 14971. Evaluation of medical device risk.
- ISO 22442:1. Application of risk management in medical devices using animal tissues and their derivatives-Part 1.

International Conference on Harmonization (ICH) Q9: Effective risk management.

Agency for European Medicines (EMEA). Guidelines for medications based on human cells EMA. Guidelines for the risk management, safety and efficacy monitoring of medications used in advanced medical treatments.[36]

LIFE CYCLE MANAGEMENT OF BIOLOGICS IN AUSTRALIA

The life cycle of biologics in Australia from IND application to PMS (post-marketing surveillance) can be broken down into the following stages:

IND (Investigational New Drug) application: Before a biologic can be tested in humans in Australia, the sponsor must submit an IND application to the Therapeutic Goods Administration (TGA) for approval.

Clinical trials: Following approval of the IND application, the sponsor can move forward with clinical trials aimed at determining the biologic's safety as well as efficacy in human subjects.

Registration: Following the conclusion of clinical trials, the sponsor may apply for registration with the TGA to have the biologic approved for sale.[37]

Approval: The TGA evaluates the registration application and approves the biologic for marketing in Australia if it meets the necessary safety, efficacy and quality standards.

Launch: Once the biologic is approved, it can be launched in the Australian market and made available to patients.

Post-marketing surveillance: After the launch of the biologic, the TGA continues to monitor its safety and efficacy through Post-Marketing Surveillance (PMS).

This involves ongoing monitoring of adverse events and other safety concerns associated with the use of the biologic.

Patent and data exclusivity: During the life cycle of the biologic, the sponsor may hold patents and data exclusivity rights that prevent other manufacturers from making, using, or selling the biologic without permission.

In summary, the life cycle of biologics in Australia from IND application to PMS involves several stages, including IND application, clinical trials, registration, approval, launch, post-marketing surveillance and

patent and data exclusivity. The TGA plays a key role in evaluating and approving biologics for marketing in Australia and monitoring their safety and efficacy through PMS.[38]

SUMMARY

In the context of Australian regulatory frameworks, "Navigating Biologics Regulation: A Deep Dive into Australian Compliance" provides a thorough examination of the life cycle management of biologics. The article explores a number of topics, starting with the categorization of biologics and moving on to a thorough analysis of production procedures and standards. Examine the particular manufacturing criteria and recommendations provided by regulatory bodies, such as the Good Manufacturing Practice (GMP) standards that are specific to the manufacture of biologics. Discuss about the significance of stability testing, including procedures for carrying out stability studies and creating shelf-life criteria, in guaranteeing the effectiveness, safety and quality of biologic products throughout their shelf lives. The paper further clarifies the significance of post-market surveillance in observing the security and effectiveness of biologic goods in actual use. Readers will obtain important insights into the complexities of Australian biologics regulation and the importance of compliance across the product life cycle from this in-depth analysis.

CONCLUSION

In conclusion, Australia has created regulatory frameworks for the evaluation and supervision of biologics that are based on global norms and best practices. These oversight organizations strive to protect the general public's health as well as the quality, efficacy and safety of biologics. The Therapeutic Goods Administration (TGA), which evaluates the quality, safety and efficacy of biologics before approving them for commercialization, is the regulatory body in charge of them in Australia. Once biologics are on the market, the TGA continues to monitor their safety and is prepared to act if any safety issues are discovered. Manufacturers are required by regulatory bodies to submit substantial data on the safety and effectiveness of biologics, including information on the production procedure, control of quality and outcomes of preclinical and clinical studies. Post-marketing surveillance is another need set out by the agencies for continuous safety and effectiveness monitoring. Overall, Australia's strict regulatory guidelines for biologics are intended to guarantee their patients' safety and efficacy.

ACKNOWLEDGEMENT

I would like to thank Dr. Balamuralidhara V**,** Associate Professor and Head, Department of Pharmaceutics, Center of Excellence in Regulatory Science, JSS College of Pharmacy, JSS Academy of Higher Education and Research, S S Nagar, Mysuru-570015, Karnataka, India and Deeksha K S for useful discussion during the studies and support in research.

CONFLICT OF INTEREST

The authors declare that there is no Conflict of interest.

ABBREVIATIONS

TGA: Therapeutic goods administration; **FMT:** Faecal microbiota transplant; **PTE:** Patent Term Extensions; **PTAs:** Patent Term Adjustments; **SPCs:** Supplementary Protection Certificates; **ARGB:** Australian Regulatory Guidelines for Biologicals; **ARTG:** Australian Register of Therapeutic Goods; **PBS:** Pharmaceutical Benefits Scheme; **CTA:** Clinical Trial Approval; **CTN:** Clinical Trial Notification scheme; **HREC:** Human Research Ethics Committee; **GMP:** Good Manufacturing Practice; **TGOs:** Therapeutic Goods Orders; **FDA:** Food and Drug Administration; **WHO:** World Health Organisation; **APVMA:** Australian Pesticides and Veterinary Medicines Authority; **GxP:** Good x Practice; **INN:** Internationally non-proprietary name; **ACN:** Australian Cell and Tissue Name; **PSUR:** Periodic Safety Update Report; **PBRERs:** Periodic Benefit-Risk Evaluation Reports; **eBS TGA's:** eBusiness Services Therapeutic Goods Administrations; **AusPAR:** Australian Public Assessment Reports; **DAEN:** Database of Adverse Event Notifications; **WTO:** World Trade Organization; **TRIPS:** trade-related features of the Intellectual Property Rights; **RDP:** Regulatory Data Protection; **DIS:** Draft international standard.

REFERENCES

1. What is regulated as a biological | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/what-regulated-biological
2. What is regulated as a biological | Therapeutic Goods Administration (TGA) [Internet]. [cited 2024 Mar 4]; Available from: https://www.tga.gov.au/resources/resource/guidance/what-regulated-biological
3. What is regulated as a biological | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/what-regulated-biological#types-define
4. Gleeson D, Lopert R, Moir HVJ. Proposals for extending data protection for biologics in the TPPA: Potential consequences for Australia Submission to the Department of Foreign Affairs and Trade. 2014 [cited 2023 Nov 21];

Available from: http://www.citizen.org/documents/biologics%20final%20draft1.pdf
5. Biologics and Biosimilars Regulations and Registration in Australia (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.artixio.com/post/biologics-and-biosimilars-regulations-and-registration-in-australia-tga
6. Intellectual property-Medicines Australia [Internet]. [cited 2023 Nov 21]; Available from: https://www.medicinesaustralia.com.au/publications/issues-briefs/intellectual-property/
7. Australia: patent-term extension developments and challenges - IAM [Internet]. [cited 2023 Nov 21]; Available from: https://www.iam-media.com/guide/global-life-sciences/2023/article/australia-patent-term-extension-developments-and-challenges
8. TPP outcomes: biologics | Australian Government Department of Foreign Affairs and Trade [Internet]. [cited 2023 Nov 21]; Available from: https://www.dfat.gov.au/trade/agreements/not-yet-in-force/tpp/Pages/outcomes-biologics
9. BIOLOGIC AND BIOSIMILAR MEDICINES 2020: MAKING THE MOST OF THE OPPORTUNITIES.
10. How we regulate | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/how-we-regulate
11. Maurya SK, Shukla VK, Maurya SK, Kaushik P. Regulatory aspects for Biologic Product licensing in Australia. International Journal of Drug Regulatory Affairs [Internet] 2019 [cited 2023 Nov 21];7(2):1-6. Available from: https://www.researchgate.net/publication/333969370_Regulatory_aspects_for_Biologic_Product_licensing_in_Australia
12. Classification of biologicals | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/classification-biologicals
13. Classification of biologicals | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/classification-biologicals#approach-method
14. Classification of Biological Agents - Health and Safety Authority [Internet]. [cited 2023 Nov 21]; Available from: https://www.hsa.ie/eng/topics/biological_agents/biological_agents_introduction/classification_of_biological_agents/
15. Australian regulatory guidelines for biologicals (ARGB) | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/australian-regulatory-guidelines-biologicals-argb
16. Pathways for supply of biologicals | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/pathways-supply-biologicals
17. Legislation and legislative instruments | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/about-tga/legislation/legislation-and-legislative-instruments
18. SLHD RPA - Research Ethics and Governance Office - Good Clinical Practice (GCP) [Internet]. [cited 2023 Nov 21]; Available from: https://www.slhd.nsw.gov.au/RPA/Research/gcp.html
19. Clinical trials | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/clinical-trials
20. Clinical trials | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/clinical-trials#ctn-scheme
21. Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products | Therapeutic Goods Administration (TGA) [Internet]. [Cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/australian-code-good-manufacturing-practice-human-blood-and-blood-components-human-tissues-and-human-cellular-therapy-products
22. Wright C, Velickovic Z, Brown R, Larsen S, Macpherson JL, Gibson J, *et al*. Raising the standard: changes to the Australian Code of Good Manufacturing Practice (cGMP) for human blood and blood components, human tissues and human cellular therapy products. Pathology. 2014;46(3):177-83. Available from: https://pubmed.ncbi.nlm.nih.gov/24614714/
23. Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/australian-code-good-manufacturing-practice-human-blood-and-blood-components-human-tissues-and-human-cellular-therapy-products
24. Bharadwaj M. Quality Control of Biotechnological or Biological Medicines Manufacturing quality perspective. 2021;
25. Health. Therapeutic Goods (Manufacturing Principles) Determination 2018.
26. Biologics and Biosimilars Regulations and Registration in Australia (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.artixio.com/post/biologics-and-biosimilars-regulations-and-registration-in-australia-tga
27. Goods Administration T. Stability testing for prescription medicines. 2017;
28. ARGB Appendix 11 - Guidance on TGO 107: Standard for Biologicals - Labelling Requirements | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/argb-appendix-11-guidance-tgo-107-standard-biologicals-labelling-requirements
29. Care H and A. Therapeutic Goods (Standard for Biologicals—Labelling Requirements) (TGO 107) Order 2021.
30. ARGB Appendix 11 - Guidance on TGO 107: Standard for Biologicals - Labelling Requirements | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/argb-appendix-11-guidance-tgo-107-standard-biologicals-labelling-requirements
31. Adverse event reporting | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/adverse-event-reporting
32. Reporting adverse events | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/reporting-adverse-events
33. Klepper MJ. The periodic safety update report as a pharmacovigilance tool. Drug Saf [Internet] 2004 [cited 2023 Nov 21];27(8):569-78. Available from: https://pubmed.ncbi.nlm.nih.gov/15154828/
34. Australia [Internet]. [cited 2023 Nov 21]; Available from: https://www.aabb.org/regulatory-and-advocacy/regulatory-affairs/regulatory-for-cellular-therapies/international-competent-authorities/australia
35. Intellectual property-Medicines Australia [Internet]. [cited 2023 Nov 21]; Available from: https://www.medicinesaustralia.com.au/publications/issues-briefs/intellectual-property/
36. ARGB Appendix 11 - Risk management | Therapeutic Goods Administration (TGA) [Internet]. [cited 2023 Nov 21]; Available from: https://www.tga.gov.au/resources/resource/guidance/argb-appendix-11-risk-management
37. Therapeutic goods: a quick guide-Parliament of Australia [Internet]. [cited 2023 Nov 21]; Available from: https://www.aph.gov.au/About_Parliament/Parliamentary_departments/Parliamentary_Library/pubs/rp/rp1819/Quick_Guides/TherapeuticGoods
38. Australia's TGA Post Market Surveillance for Medical Devices Manufacturers and Sponsors [Internet]. [cited 2023 Nov 21]; Available from: https://www.freyrsolutions.com/blog/ensuring-product-safety-post-market-surveillance-pms-in-australia

Cite this article: Saji N, Sujatha DK, Veeranna B. Navigating Biologics Regulation: A Deep Dive into Australian Compliance. Asian J Biol Life Sci. 2024;13(1):9-21.