Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Biologicals

Part 1 - Introduction to the Australian Regulatory Guidelines for Biologicals

Version 1.0, June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating biologicals, medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of biologicals, medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with biologicals, medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a biological, medicine or medical device, please see the information on the TGA website.

Version history

Version	Description of change	Author	Effective date
V1.0	Original	BSS	June 2011

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Abbreviations and acronyms

ACB	Advisory Committee on Biologicals
ADME	Absorption, distribution, metabolism and elimination
AHMC	Australian Health Ministers' Conference
AQIS	Australian Quarantine and Inspection Service
ARGB	Australian regulatory guidelines for biologicals
ARTG	Australian Register of Therapeutic Goods
AS/NZS	Australian standard/New Zealand standard
BMF	Biological master file
BP	British Pharmacopeia
cGMP	Australian code of good manufacturing practice
CTN	Clinical trial notification
CTX	Clinical trial exemption
DMF	Drug master file
eBS	eBusiness
EMEA	European medicines agency
FAQ	Frequently asked questions
GM	Genetically modified
GMP	Good manufacturing practice
HBsAg	Hepatitis B surface antigen.
HBV	Hepatitis B virus
HCV	Hepatitis C virus.
HIV	Human immunodeficiency virus
HPC	Haematopoietic progenitor cell
HPC-A	Haematopoietic progenitor cells-apheresis.

HPC-C	Haematopoietic progenitor cells-cord.
HPC-M	Haematopoietic progenitor cells-marrow.
HREC	Human research ethics committee
HTLV-1	Human T-Lymphotropic Viruses type 1.
HTLV-2	Human T-Lymphotropic Viruses type 2.
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ISO	International organisation for standardization
IVD	*In vitro* diagnostic device
IVF	*In vitro* fertilization
NAT	Nucleic acid amplification test
Ph Eur	European Pharmacopeia
PMF	Plasma master file
RMP	Risk Management Plan
SAS	Special access scheme
TG Act	Therapeutic Goods Act 1989
TG Regulations	Therapeutic Goods Regulations 1990
TGA	Therapeutic Goods Administration
TGO/TG Order	Therapeutic goods order
TOC	Table of contents
USP	United States Pharmacopeia

About these guidelines

The *Australian Regulatory Guidelines for Biologicals* (ARGB) provide information for manufacturers, sponsors, healthcare professionals and the general public on the legal arrangements in Australia for the supply and use of human cell and tissue-based therapeutic goods. These products are collectively defined as 'biologicals' (see the information box below).

The Biologicals Regulatory Framework came into effect on 31 May 2011 with the amendment of the *Therapeutic Goods Act 1989* (Cwlth) (TG Act). Transition arrangements apply for up to three years to allow all biologicals to meet the new arrangements, which are administered by the Therapeutic Goods Administration (TGA).

See Section 1.5 for further details

The TGA recognises that many different people may use, or be interested in, biologicals; for example, sponsors and manufacturers, consumers and their families or guardians, healthcare professionals and advocacy groups. Therefore, these guidelines are written for a broad and general audience, where possible.

If you are a sponsor or manufacturer, this guide:

- explains whether the Biologicals Regulatory Framework applies to your products, or whether they are exempt, and why
- explains the Australian regulatory requirements for supplying biologicals
- sets out what is required for a marketing application to the TGA for biologicals, so they can be processed as quickly as possible
- allows you, along with healthcare professionals, regulators and consumers, to openly access information on biologicals, the TG Act, and related matters.

In this guide, the term 'supply' (in relation to biologicals) is used to mean importing biologicals into Australia, and supply in Australia and export from Australia. These activities are also collectively called 'marketing'

What are therapeutic goods?

Therapeutic goods are any products that are used in healthcare to treat, prevent or diagnose diseases, ailments, defects or injuries (therapeutic use). This includes a wide range of medicines for treating and preventing health conditions, as well as medical devices and diagnostic tests.

Since the introduction of the Biologicals Regulatory Framework, there are now three major categories of therapeutic goods:

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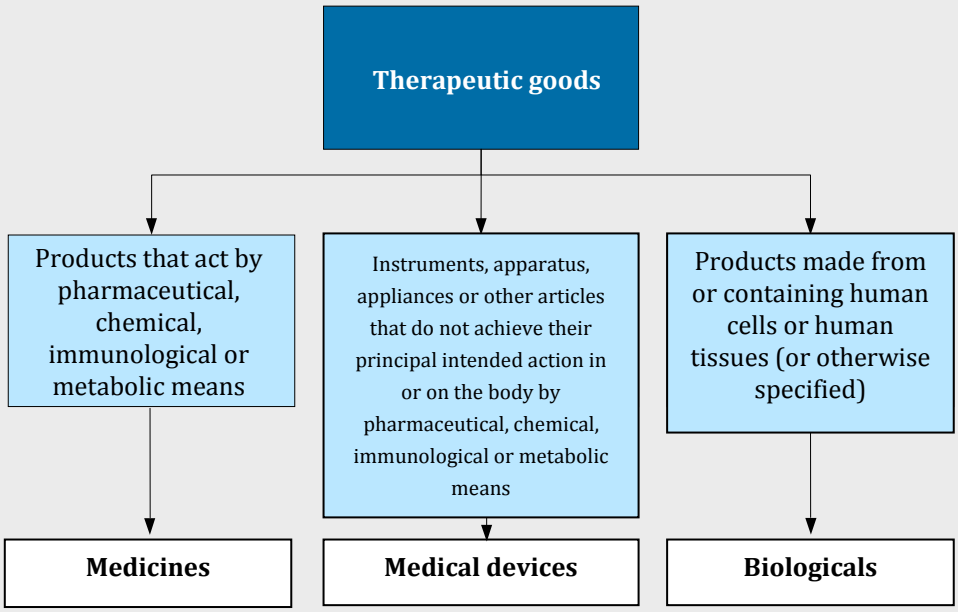


How are therapeutic goods regulated?

In Australia, the *Therapeutic Goods Act 1989* (Cwlth) (TG Act) provides a uniform national framework for import, export, manufacture and supply of therapeutic goods. The TG Act is supported by the Therapeutic Goods Regulations (TG Regulations) and various orders and determinations, which provide further details of the TG Act (see Section 1.5 of these guidelines).

Any product for which therapeutic claims are made by the manufacturer must be entered on the Australian Register of Therapeutic Goods (ARTG) before it can be imported, exported or supplied for use in Australia.

The Therapeutic Goods Administration (TGA), which is part of the Australian Government Department of Health and Ageing, administers the TG Act and the ARTG. A key focus of the TGA is to ensure that consumers have timely access to safe, good-quality and efficacious medicines, devices and biologicals. This also means ensuring that any new products are properly evaluated and assessed within an agreed timeframe.

The TGA regulatory framework is based on a risk-management approach. It is designed to ensure public health and safety while reducing the administrative burden and cost to industry of the regulatory process. This approach also contributes to the continued viability of industry by creating confidence in, and acceptance of, Australian therapeutic goods, both at home and overseas.

The TGA also manages a number of committees, which provide independent advice on different areas of therapeutic goods administration (e.g. Advisory Committee on Prescription Medicines, Advisory Committee on Medical Devices). The Advisory Committee on Biologicals will provide independent advice on biologicals.

These guidelines provide further information about the legislation and overall regulatory process for biologicals. Additional details about the regulatory arrangements for therapeutic goods are on the TGA website.

Structure of these guidelines

Part 1 (Introduction to the ARGB) provides a general introduction to the regulatory guidelines, including the way in which biologicals are classified, and how they are assessed for risks to human health.

Part 2 (Regulatory lifecycle for approved biologicals) describes, in more technical detail, how biologicals are regulated, assessed, marketed and monitored, at all stages of their production and use, from original design to production and follow-up surveillance after they are released onto the market. Part 2 also includes information for sponsors on how to apply to have their product included on the Australian Register of Therapeutic Goods (ARTG).

Part 3 (Access to unapproved biologicals) explains the circumstances under which unapproved biologicals (those that are not included on the ARTG) can be used; for example, in clinical trials, in individual patients on a case-by-case basis, or in emergency situations.

If you are a consumer, healthcare professional, member of an advocacy group, or someone who is interested in biologicals but not an expert in the topic, Part 1 of these guidelines provides an overview of the Biologicals Regulatory Framework. Throughout the rest of the guidelines plain-English explanations and useful links have been provided with the technical information wherever possible.

Further information is available on the TGA website.

Part 1: Introduction to the Australian Regulatory Guidelines for Biologicals

1.1 Overview

1.1.1 What is the Biologicals Regulatory Framework?

The Biologicals Regulatory Framework is the term for legislation that came into force in 2011 to regulate human 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.

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 (pre-market), and follow-up and further controls after they are marketed (post-market).

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

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

or

- otherwise exempted, approved or authorised.

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 products during their manufacture

and

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

See Section 1.2 for further details

The TGA has been working with the biological sectors to develop new product standards and manufacturing principles that have direct relevance and application for biologicals. The standards have been harmonised with international standards, where possible and relevant.

See Section 1.5 for further details

Where it is required, the approval of a biological may be advised by a newly established independent expert committee, the Advisory Committee on Biologicals.

See Section 1.1.5 for further details

Approval of genetically modified biologicals will be overseen by the Gene Technology Regulator.

See Section 1.1.6 for further details

After biologicals have been approved for supply, ongoing (post-market) controls include manufacturing surveillance, targeted review and laboratory testing, reporting adverse events, investigations and recalls.

See Part 2 for further details

The Biologicals Regulatory Framework includes provisions for biologicals to be exempt from the TGA's usual requirements for inclusion on the ARTG to allow legal supply under certain circumstances (such as for clinical trials, emergency situations or use by individual patients).

See Part 3 for further details

The use of biologicals in clinical trials is regulated under similar arrangements to those for medicines and medical devices.

See Part 3 Section 3.1 for further details

The Biologicals Regulatory Framework also includes 'exceptional release' provisions to allow a biological that is included on the ARTG, but for which the specific item or batch does not meet required manufacturing or product standards for release, to be supplied under certain clinically urgent circumstances.

See Part 3 Section 3.3 for further details

The key benefits of the Biologicals Regulatory Framework

Regulating biologicals separately from other therapeutic goods under the framework will:

- minimise the risk of infectious disease transmission
- ensure the level of regulation applied matches the level of risk posed by specific biologicals by classifying them into four risk-based classes
- provide a more flexible framework to respond to changes in technology than has been the case under previous arrangements
- provide regulatory requirements that are unique for biologicals, because the arrangements for medicines or devices may not be appropriate, particularly in exceptional circumstances
- reduce the ambiguity about what was included or excluded from regulation through the use of consistent terminology
- increase international harmonisation of therapeutic goods regulation.

1.1.2 What is a 'biological'?

The amended TG Act defines a biological as an item made from, or containing, human cells or human tissues, and that is used to:

- treat or prevent disease or injury
- diagnose a condition of a person
- alter the physiological processes of a person
- test the susceptibility of a person to disease
- replace or modify a person's body part(s).

An item can also be specified as a biological by the Secretary.

The Secretary is the person who is the Secretary (i.e. the chief executive officer) of the Australian Government Department of Health and Ageing

The full definition from the amended TG Act is shown below.

Definition of a biological in the amended TG Act (Part 3-2A–Biologicals)

32A Meaning of *biological*

(1) Subject to subsection (3), a biological is a thing that:

(a) either:

(i) comprises, contains or is derived from human cells or human tissues; or

(ii) is specified under subsection (2); and

(b) is represented in any way to be, or is, whether because of the way in which it is presented or for any other reason, likely to be taken to be:

(i) for use in the treatment or prevention of a disease, ailment, defect or injury affecting persons; or

(ii) for use in making a medical diagnosis of the condition of a person; or

(iii) for use in influencing, inhibiting or modifying a physiological process in persons; or

(iv) for use in testing the susceptibility of persons to a disease or ailment; or

(v) for use in the replacement or modification of parts of the anatomy in persons.

(2) The Secretary may, by legislative instrument, specify things for the purposes of subparagraph (1)(a)(ii).

Note: For specification by class, see subsection 13(3) of the *Legislative Instruments Act 2003*.

(3) The Secretary may, by legislative instrument, determine that a specified thing is not a biological for the purposes of this Act.

1.1.3 What products are regulated as biologicals under the biologicals framework?

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'.

See Section 1.5 for further details about these criteria

Biologicals currently only refer to human cells or human tissues and not to:

- tissues or cells from nonhuman biological sources (e.g. animals, bacteria)
- medicines made using biological or biotechnology processes (e.g. noncellular vaccines, insulin).

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.

Combination products

Biologicals presented as a combination product with a medical device (i.e. integrated with the medical device), such as a metal stent coated with a matrix and endothelial cells, will be regulated under the Biologicals Regulatory Framework and included on the ARTG as a biological. The device (e.g. the metal stent itself) will be assessed according to medical device regulatory requirements, but will not be included on the ARTG separately. Clarification of this regulatory path is given in the Therapeutic Goods (Articles that are not Medical Devices) Order No. 1 of 2010, Item 3d. This states that the following articles are declared not to be medical devices:

> articles incorporating tissues, cells, or substances of human origin, other than medical devices incorporating stable derivatives of either human blood or human plasma that act on, or are likely to act on, the human body in a way that is ancillary to the device.

Kits, systems or procedure packs

Biologicals may also be included in a variety of packs designed to be used for preventing or treating diseases or conditions. Such packs contain individually packaged therapeutic goods (i.e. not combined or integrated as for the combination products described above), and may include combinations of medicines, medical devices and biologicals (e.g. because they must be used together to work). Such packs can contain different product combinations, including:

- a biological and a medicine
- a biological and a medical device

- a biological, a medicine and a medical device
- a biological and a biological.

Where a biological is packaged with a medicine, as in the first example above, the package will be known as a 'kit' and will be regulated as a 'listable' medicine.

Where a biological is packaged with at least one medical device, as in the second and third examples above, the package will be known as a 'system or procedure pack' and will be regulated as a medical device.

Where a biological is packaged together with other biological products, as in the fourth example above, the kit will be known as a 'biological kit' and regulated as a single biological under the Biologicals Regulatory Framework. This is because the combination of biological products might interact, thus posing a different risk from that of the individual biological products.

Any biological that is included in such a kit, system or pack must be individually included on the ARTG before the application for the kit, system or pack can be made, irrespective of whether the kit, system or pack will be regulated as a biological, a medicine or a medical device.

Sections 7B and 41 BF of the TG Act define kits, and systems and procedure packs, respectively

In vitro diagnostic devices (IVDs) that contain human cells or tissues will be regulated as IVDs, because these devices are used externally to the patients ('in vitro') and so any cells or tissues (biologicals) they contain are not in contact with the people being diagnosed.

See Table 1.1 for further information on products that are included or not included in the Biologicals Regulatory Framework

Historical context

In Australia, before the introduction of the Biologicals Regulatory Framework, cell and tissue products were:

- not regulated (e.g. specified in the Therapeutic Goods [Excluded Goods] Order)
- regulated as either medicines or medical devices
- exempted from application of specific parts of the *Therapeutic Goods Act 1989* (TG Act) (e.g. banked tissues were exempted from Part 3-2 of the TG Act relating to the requirements for entry on the Australian Register of Therapeutic Goods [ARTG]), but still regulated on the basis of compliance with the other parts of the TG Act (including compliance with manufacturing principles).

Biologicals specified in the Therapeutic Goods (Excluded Goods) Order included:

- *fresh viable human tissue, other than blood; or*
- *human organs; or*
- *parts of human organs; or*
- *human bone marrow*

... intended for direct donor-to-host transplantation and used in accordance with applicable laws and standards.

Continued....

Blood and haematopoietic progenitor cells are regulated as medicines from a good manufacturing practice perspective and are exempt from registration on the ARTG.

Biological products that were not excluded from regulation were regulated as either medicines or medical devices. Neither of these regulatory frameworks was a good fit for biologicals, because biological products have unique properties and risks (such as infectious disease risks) that require special assessment. In addition, not all biological products or uses carry the same level of risk (depending on how much they have been modified compared with their natural counterparts, and how they are used in the recipients), and this needs to be taken into account in the regulatory process. This is in line with a global move to regulate biological products separately from other therapeutic goods.

In 2006, the Australian Health Ministers' Conference recommended that human cell and tissue therapies and other emerging biological therapies, except for solid organs and reproductive tissues, should be regulated as part of the therapeutic goods regulatory framework administered by the Therapeutic Goods Administration.

1.1.4 What products are not covered by the biologicals framework?

Biologicals that are excluded from regulation as therapeutic goods

Some biologicals that fall within the definition of a therapeutic good in terms of their use (i.e. they are used to treat, prevent or diagnose a disease or condition) have been declared not to be therapeutic goods. These are specified in the Therapeutic Goods (Excluded Goods) Order, and are therefore not regulated by the TGA. This is available at the TGA website

See Section 1.5 for further details about therapeutic goods orders

These excluded products include:

- 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)
- human tissue and cells that are:
  - collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and
  - manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner
- 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).

Products that are regulated as therapeutic goods but not as biologicals

Blood and blood components are not biologicals for the purposes of the TG Act; they are already regulated as medicines under Part 3-2 of the TG Act.

The legislation also allows the Secretary to declare specific therapeutic goods to either be or not be a biological. Goods declared to not be a biological are regulated by the TGA as either a medicine or a medical device, but are not included in the Biologicals Regulatory Framework at this time. These products are included in the Therapeutic Goods (Things that are not Biologicals) Determination No.1 of 2011, available on the TGA website.

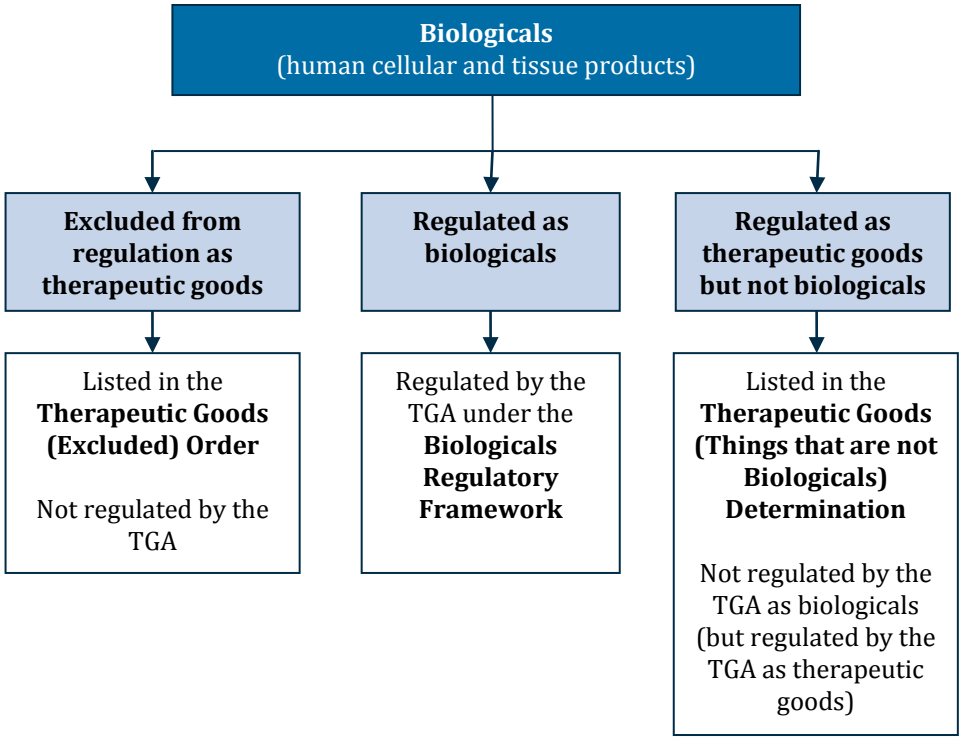
The following products are currently declared to not be biologicals:

- haematopoietic progenitor cells (used for haematopoietic reconstitution), other than those which are excluded from regulation (see above);
- samples of human cells or tissues that are solely for diagnostic purposes in the same individual
- blood, blood components
- in-vitro diagnostic devices (IVDs)
- biological medicines including
  - vaccines (that do not contain viable human cells)
  - recombinant products
  - plasma-derived products (or that contain plasma-derived products)

This provision also means that the types of products or therapeutic goods included in the Biologicals Regulatory Framework may change over time. Manufacturers, sponsors, health professionals and consumers will be consulted before the regulatory status of a product or therapeutic good is changed (including adding it to the Biologicals Regulatory Framework). Depending on the regulatory change, an agreement from the Australian Government, state and territory governments, and from the Australian Health Ministers' Council may also be required.

See 'Historical context' below for further information about the decision to exclude some products and declare others to not be biologicals

Figure 1.1 shows the relationship between products that are excluded as therapeutic goods, and those that are included and not included as biologicals. Table 1.1 provides further details and examples of excluded, included and not included biologicals.



TGA = Therapeutic Goods Administration

Figure 1.1 The relationship between human materials that are excluded from regulation as therapeutic goods, regulated as biologicals, or regulated as therapeutic goods but not as biologicals in the Biologicals Regulatory Framework

Table 1.1 Regulation of biologicals

Regulated as biologicals	Excluded from regulation as therapeutic goods	Regulated as therapeutic goods but not as biologicals
Human tissue therapy products, such as: • skin • musculoskeletal—bone, collagen • cardiovascular—heart valves • ocular—whole eye, cornea	Fresh, viable human organs or parts of organs Labile (fresh) blood and blood components (e.g. fresh frozen plasma) Unprocessed reproductive tissues (e.g. sperm, eggs, embryos for in vitro fertilisation and other assisted reproductive technology procedures)	Human tissues for diagnostic use Animal tissue products
Human cellular therapy products, such as: • stem cells and progenitor cells; e.g. – mesenchymal stem cells – haematopoietic progenitor cells for uses other than haematopoietic reconstitution – other stem cells (e.g. neural, epithelial) – other progenitor cells (e.g. nasal cells) • other human cell-based products, such as fibroblasts, epithelial cells, chondrocytes • immunotherapy products, such as – cell-based tumour vaccines – human cellular vaccines • genetically modified cells	Fresh viable haematopoietic progenitor cells (e.g. bone marrow, cord blood) used for blood regeneration Fresh viable human tissue or cells for a single course of treatment under the professional supervision of a single medical practitioner for a single patient	Haematopoietic progenitor cells used for haematopoietic reconstitution Fresh viable human cells for diagnostic use in the same person Blood and blood components Animal cells
No biological medicines are regulated as biologicals		Biological medicines: • products of genetically modified organisms (e.g. insulin) • vaccines (that do not contain human cells) • peptides (e.g. insulin, cytokines) • monoclonal antibodies Blood plasma products

Regulated as biologicals	Excluded from regulation as therapeutic goods	Regulated as therapeutic goods but not as biologicals
Procedure packs containing multiple biologicals		Medical devices containing material of animal, microbial or recombinant (genetically modified) origin In vitro diagnostic devices (IVDs) containing human cells or tissues (e.g. human cell culture-based viral diagnostic IVD products) Procedure packs containing a single biological (e.g. spinal fusion system with bone paste)

See Apppendix 14 (Glossary) for definition of technical terms

1.1.5 What is the role of the Advisory Committee on Biologicals?

The Advisory Committee on Biologicals (ACB) advises and makes recommendations to the Health Minister or the Secretary of the health department on:

- which biologicals can be included on the ARTG
- variations to entries on the ARTG
- removal or continued inclusion of biologicals on the ARTG
- any other matters concerning a biological, or other matters referred to the ACB by the Minister or Secretary.

The Therapeutic Goods Regulations (1990) (TG Regulations) provide for the ACB to have up to 12 members, with expertise in a range of fields, including infectious diseases; cellular therapies and tissue engineering; organ, tissue and stem cell transplantation; blood products; clinical expertise; epidemiology and biostatistics; toxicology; and consumer issues.

The ACB can provide advice on issues other than biologicals, if necessary, and all recommendations must be published.

1.1.6 What is the role of the Gene Technology Regulator?

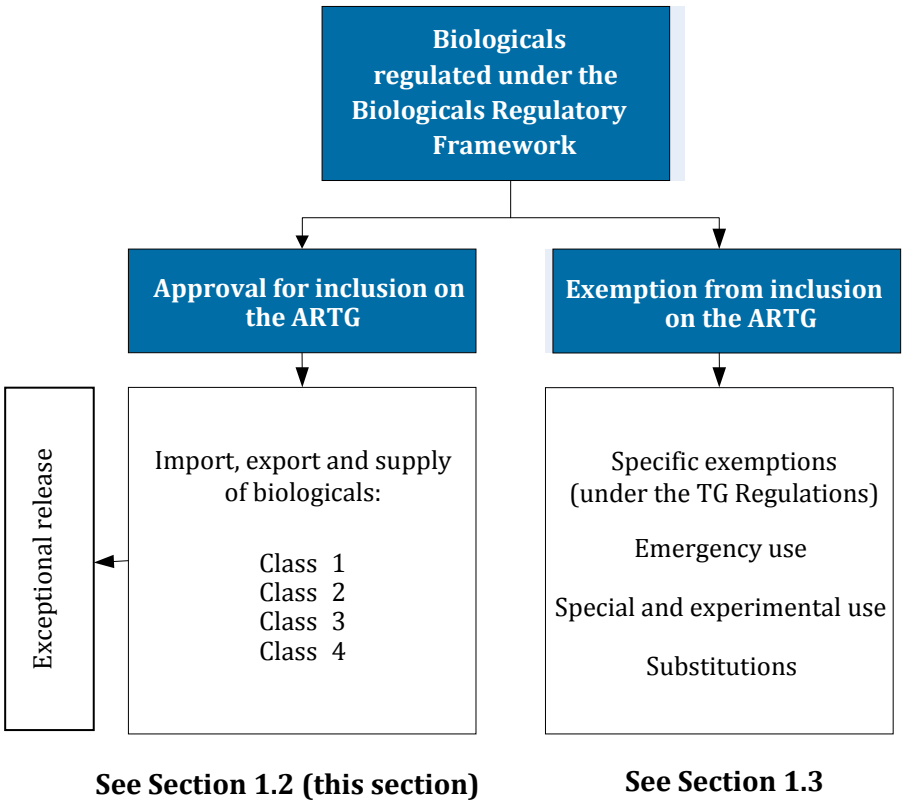
When a biological proposed for inclusion on the ARTG is, or contains, a genetically modified (GM) product or a GM organism, the TGA must notify the Office of the Gene Technology Regulator (OGTR) and request advice about the application. The OGTR may give written advice to the TGA, and the TGA must ensure that this advice is taken into account when making a decision about whether the product will be included on the ARTG.

For information please see the website of the Office of the Gene Technology Regulator.

1.2 Classification of biologicals

Figure 1.2 shows an overview of the regulation of biologicals under the Biologicals Regulatory Framework. Biologicals that are included in the framework cannot be legally supplied in Australia unless they are either approved for inclusion on the ARTG or are exempt from inclusion on the ARTG.

This section describes the classification of biologicals that are to be included on the ARTG; exempt biologicals are described in Section 1.3.



ARTG = Australian Register of Therapeutic Goods; TG Regulations = Therapeutic Goods Regulations

Figure 1.2 Overview of biologicals regulation under the Biologicals Regulatory Framework

Biologicals that are to be included on the ARTG must be classified into one of four classes, according to their level of risk.

The TG Regulations allow two methods of classifying a biological:

- classification based on
  - how far removed they are from their naturally occurring state (that is, how much they have been manipulated during the extraction and production process, and how altered they are)
  - how closely their intended use matches their original biological function
- classification based on inclusion in Schedule 16 of the TG Regulations.

Schedule 16 of the TG Regulations is where all Class 1 biologicals are specified. Class 2, 3 and 4 biologicals can also be specified in Schedule 16 if they are declared as belonging to a specific class for a reason not directly related to their preparation and use.

The classes are described in detail in Table 1.2.

See Section 1.4 for further information on risk-management

See Part 2 Section 2.2.2 for further information about how to apply to have a biological classified

Table 1.2 Classes of biologicals and their level of risk

Definition from the TG Regulations	Meaning	Risk
Class 1 biological means a biological that is declared in the Regulations as a Class 1 biological.	**A *Class 1* biological is any biological that has been designated Class 1 and is specified in Schedule 16 of the TG Regulations.**	Low
Class 2 biological means a biological that is: a. both: i. processed using only one or more of the actions of minimal manipulation; and ii. for homologous use; or b. declared in the Regulations as a Class 2 biological.	**A *Class 2* biological is a biological that is ...** **... prepared using simple methods, as stated for minimal manipulation methods in the information box below and ...** **... used to repair, reconstruct or replace cells or tissues that have the same biological function in the recipient as in the donor (replacing like with like); or ...** **... is specified in Schedule 16 of the TG Regulations as a Class 2 biological for another reason.**	Low
Class 3 biological means a biological that is: a. processed: i. using a method in addition to any of the actions of minimal manipulation; and	**A *Class 3* biological is a biological that is ...** **... prepared using more complex methods, such as enzymatic dissociation, that have potential to alter the cells or tissue, but ...** **... these methods do not change the biological properties of the product; or ...**	Medium

Definition from the TG Regulations	Meaning	Risk
ii. in a way that does not change an inherent biochemical, physiological or immunological property; or b. declared in the Regulations as a Class 3 biological.	**... is specified in Schedule 16 of the TG Regulations as a Class 3 biological for another reason.**	
Class 4 biological means a biological that is: a. processed: i. using a method in addition to any of the actions of minimal manipulation; and ii. in a way that changes an inherent biochemical, physiological or immunological property; or b. declared in the Regulations as a Class 4 biological.	**A *Class 4* biological is a biological that is ...** **... prepared using more complex methods, as for Class 3, and ...** **... the methods used have changed the biological properties of the product; or** **... is specified in Schedule 16 of the TG Regulations as a Class 4 biological for another reason.**	High

TG Regulations = Therapeutic Goods Regulations

Terms used in the classification of biologicals

Minimal manipulation includes centrifugation, refrigeration, freezing, trimming, flushing, washing; processing steps related to preserving function or minimising contamination, including using additives such as cryopreservatives, anticoagulants, antimicrobial agents and irradiation; and freeze drying (of structural tissues only).

Homologous use means the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with a biological that performs the same basic function in the recipient as in the donor. This definition is internationally consistent and relates to the use of the product independent of whether the recipient is the same as the donor (autologous) or different from the donor (allogeneic).

Complex methods of modification include processes that are not listed under 'minimal manipulation', including such processes as demineralisation or enzymatic dissociation. Genetic modification is also a complex method and genetically modified biologicals are likely to be classified as Class 4.

1.2.1 Class 1 biologicals

For a biological to be classified as Class 1, it will need to be included as a Class 1 biological in Schedule 16 of the TG Regulations. This will require a justification that the biological should not be classified as Class 2, 3 or 4 and that the manufacturer complies with relevant mandatory standards to ensure the quality, safety and efficacy of the biological. These standards will be developed in consultation with each relevant sector. The risks associated with the use of a Class 1 product should be very low, with the risk satisfactorily managed by a high level of oversight e.g. the manufacture is under expert medical supervision.

To be included on the ARTG for supply in Australia, sponsors of Class 1 biologicals must submit a statement of compliance with the mandatory standards. The TGA will review the statement of compliance, but does not need to further evaluate the product before it is included on the ARTG. Furthermore, manufacturers of Class 1 biologicals do not need a manufacturing licence.

See Part 2 Section 2.2.3 for further details

At the time of implementation of the Biologicals Regulatory Framework, there are no Class 1 biologicals specified in Schedule 16 of the TG Regulations.

1.2.2 Class 2 biologicals

Class 2 biologicals are products that have undergone no or only simple methods of processing (called 'minimal manipulation') and are for homologous use (see the box above for definition of these terms). Class 2 biologicals include, for example, frozen bone, human heart valves and corneas.

To be included on the ARTG for supply in Australia, Class 2 biologicals must be evaluated by the TGA for their compliance with relevant standards.

Guidelines for Class 2 dossier submissions are provided in Appendix 1 of these guidelines

Manufacturers must also show that they comply with the manufacturing principles equivalent to the *Australian Code of Good Manufacturing Practice (GMP) for human blood and tissues*.

Alternatively, sponsors can apply for a biological to be declared a Class 2 biological and included in Schedule 16 of the TG Regulations.

See Part 2 Section 2.2.4 for further details

Examples of Class 2 biologicals

PRODUCT 1

Milled bone for allograft

Method of manufacture

The femoral head is collected from a living donor under aseptic conditions, and stored frozen until serology retest results are available. The femoral head is defrosted, debrided of extraneous tissue, milled and washed in sterile buffer, dispensed into sterile pouches and then sealed in a sterile jar. The allograft is then terminally irradiated.

Method of use

Musculoskeletal restoration or repair during orthopaedic surgery.

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs), product-specific standards (in this case, TGO 83 – Standards for human musculoskeletal tissue) and TGO 87 (labelling). The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 2 biological because it only undergoes minimal manipulation in the manufacturing process and the final product is used in a homologous manner; that is, to repair bone.

PRODUCT 2

Dental pulp-derived stem cells for tooth regeneration

Method of manufacture

Impacted third molars are removed from patients undergoing dental surgery, treated with an antimicrobial agent, cut open to reveal the dental pulp and the pulp removed. The pulp is then filtered aseptically through a nonactivated 70 nm mesh filter, mixed with a cryopreservative and cryopreserved (frozen) in a dental pulp bank.

Method of use

Banked dental pulp, including stem cells, is defrosted and inserted into a damaged tooth. The tooth is then surgically sealed and the stem cells in the pulp help to regenerate the tooth.

Continued ...

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs) and TGO 87 (labelling). The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 2 biological because it only undergoes 'minimal manipulation' in the manufacturing process; that is, treatment with an antimicrobial agent, cutting the tooth, filtration, mixing with a cryopreservative and freezing. The inherent biochemical, physiological or immunological properties are not altered, and the dental pulp containing the stem cells performs the same basic function in the recipient as in the donor (that is, the repair of tooth tissue).

1.2.3 Class 3 biologicals

Class 3 biologicals have been processed using methods that are considered to alter the cells or tissue beyond minimal manipulation, and may be either for homologous use (replacing like with like), or for functions other than their original, natural function. Class 3 biologicals include, for example, demineralised bone, cultured fibroblasts for skin repair, and chondrocytes for cartilage repair.

To be included on the ARTG for supply in Australia, Class 3 biologicals must be evaluated by the TGA for safety, quality and efficacy. This evaluation will be based on the information supplied to the TGA in the product dossier.

Guidelines for Class 3 dossier submissions are provided in Appendix 2 of these guidelines

Manufacturers must also show that they comply with the manufacturing principles equivalent to the *Australian Code of GMP for human blood and tissues*.

Alternatively, sponsors can apply for a biological to be declared a Class 3 biological and included in Schedule 16 of the TG Regulations.

See Part 2 Section 2.2.4 for further details

Examples of Class 3 biologicals

PRODUCT 1

Demineralised bone prepared with antibiotic

Method of manufacture

The femoral head is collected from a cadaveric donor under aseptic conditions, washed in sterile buffer, immersed in ethanol, frozen in liquid nitrogen and freeze-dried. The bone then undergoes a chemical demineralisation process and is prepared into a paste consisting of a carrier substance (inert excipient) and an antibiotic. The antibiotic is registered on the Australian Register of Therapeutic Goods. The final product is packaged in sterile vials.

Method of use

The demineralised bone paste is used in orthopaedic surgery to stimulate the healing of bone fractures, and for repairs.

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs), standards (in this case, TGO 83 – Standards for human musculoskeletal tissue) and TGO 87 (labelling). Compliance with all other dossier requirements for a Class 3 biological is assessed, which includes sections on nonclinical and clinical development. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 3 biological because it undergoes manufacturing processes above and beyond those defined as 'minimal manipulation'; that is, the chemical demineralisation process and the preparation into a paste with the addition of the carrier substance. However, the inherent properties of the biological are not changed and the manufacturing process has not altered any biochemical, physiological or immunological property of the biological. In addition, the final use of the biological is homologous, because it still performs the same basic (structural) function in the recipient as it did in the donor.

PRODUCT 2

Mesenchymal stem cells for treatment of graft-versus-host disease

Method of manufacture

Bone marrow is collected from a donor under aseptic conditions and washed in sterile buffer. The cells are cultured and expanded in vitro, and then frozen in liquid nitrogen. Cells are thawed before infusion into the recipient.

Method of use

The mesenchymal stem cells are infused into the patients to modulate recipient immuune response to allogeneic haematopoietic progenitor cell transplant.

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs) and TGO 87 (labelling). Compliance with all other dossier requirements for a Class 3 biological is assessed, which includes sections on nonclinical and clinical development. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 3 biological because it undergoes manufacturing processes above and beyond those defined as 'minimal manipulation', including in vitro expansion of the cells. However, the manufacturing process does not alter an inherent biochemical, physiological or immunological property, nor is the use considered non-homologous, as the mesenchymal stem cells have a natural immunosuppressive function that is performed in the donor as it is in the recipient.

PRODUCT 3

Mesenchymal stem cells for the repair of myocardial ischaemia

Method of manufacture

Autologous bone marrow is collected from a donor under aseptic conditions and washed in sterile buffer. The stem cells are purified from the marrow using mechanical disruption, subjected to density gradient centrifugation and antibody-mediated enrichment for mesenchymal stem cells, and expanded in vitro.

Method of use

Injected directly into the site of cardiac ischaemia.

Continued ...

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs) and TGO 87 (labelling). Compliance with all other dossier requirements for a Class 3 biological is assessed, which includes sections on nonclinical and clinical development. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 3 biological because it undergoes manufacturing processes above and beyond those defined as 'minimal manipulation', including cellular isolation procedures and cell selection. The manufacturing process does not alter an inherent biochemical, physiological or immunological property, but the cells do not perform the same basic function in the recipient as in the donor; therefore, the use is non-homologous.

1.2.4 Class 4 biologicals

Class 4 biologicals have been processed in a way that alters their original function and state. They may or may not be for homologous use. Class 4 biologicals include, for example, genetically modified cells.

To be included on the ARTG for supply in Australia, Class 4 biologicals will require additional supporting data, and must be evaluated by the TGA for safety, efficacy and quality (as for Class 3), but with further assessment and analysis of the supporting data.

Guidelines for Class 4 dossier submissions are provided in Appendix 3 of these guidelines

Manufacturers must also show that they comply with the manufacturing principles equivalent to the *Australian Code of GMP for human blood and tissues*.

Alternatively, sponsors can apply for a biological to be declared a Class 4 biological and included in Schedule 16 of the TG Regulations.

See Part 2 Section 2.2.4 for further details

Examples of Class 4 biologicals

PRODUCT 1

Stem cells for cardiac muscular repair: stem cells isolated from bone marrow

Method of manufacture

Bone marrow is collected from a donor under aseptic conditions and washed in sterile buffer. The mesenchymal stem cells are purified from the marrow using mechanical disruption, and expanded and differentiated in vitro under the influence of growth factors into cells that phenotypically resemble cardiac myocytes.

Method of use

The differentiated mesenchymal stem cells are injected directly into the cardiac muscular tissue.

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs and TGO 87 (labelling). Compliance with all other dossier requirements for a Class 4 biological is assessed, including sections on nonclinical and clinical development. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 4 biological because it undergoes manufacturing processes above and beyond those defined as 'minimal manipulation', including in vitro expansion and differentiation. The cells have been differentiated in vitro, which has changed their biochemical, physiological or immunological properties. Finally, because the cells do not perform the same basic function in the recipient as in the donor, their use is non-homologous.

PRODUCT 2

Dermal fibroblasts for skeletal muscle repair in primary myopathy (e.g. Duchenne muscular dystrophy)

Method of manufacture

Adult human dermal fibroblasts are collected from skin. The skin is minced and undergoes enzymatic digestion to produce a single cell suspension. The dermal fibroblasts are then expanded using selective cell culture and transformed with an adenovirus vector carrying the *myoD* gene. The resulting cells express a myocyte-like phenotype.

Continued ...

Method of use

Transformed dermal fibroblasts expressing a myocyte-like phenotype are injected directly into the affected muscles, where they regenerate skeletal muscular tissue.

Method of TGA evaluation

A dossier submission is evaluated to ensure compliance with any default standards (such as pharmacopoeial monographs), TGO 87 (labelling). Some requirements of TGO 86 (Standards for human skin) may also apply. Compliance with all other dossier requirements for a Class 4 biological is assessed, including sections on nonclinical and clinical development. The level of detail in the dossier should correspond to the potential risk that the product poses to the recipient.

Manufacturing requirements

Compliance with manufacturing principles, including the *Australian Code of GMP for human blood and tissues*. This is demonstrated by a current TGA manufacturing licence or clearance.

Explanation of classification

This product is a Class 4 biological because it undergoes manufacturing processes above and beyond those defined as 'minimal manipulation', including enzymatic digestion, expansion in selective cell culture, and transformation with an adenoviral vector. The transformation of the fibroblasts results in them becoming myogenic and expressing a myocyte-like phenotype. This means that an inherent physiological property has been altered. Finally, because the myogenic dermal fibroblasts do not perform the same basic function in the recipient as they did in the donor, their use is non-homologous.

1.2.5 Requirements or conditions for biologicals to have separate entries on the Australian Register of Therapeutic Goods

The TG Act (section 32AB) and TG Regulations (regulation 11A) set out characteristics that need to be used to distinguish which products are considered to be separate biologicals (i.e. those that need a separate entry on the ARTG).

Class 1 or Class 2 biologicals will be considered separate and distinct, and will have separate ARTG entries, if different standards apply to them, if they have different intended clinical uses, or if they are manufactured by different principal manufacturers.

Class 3 or Class 4 biologicals will be considered separate and distinct, and have separate ARTG entries, if they have a different product name, dosage formulation or composition, different therapeutic indications, different types of containers, or different principal manufacturers.

The principal manufacturer means the person who carries out the total manufacture of a product or, if more than one manufacturer is involved, the person who takes overall responsibility for manufacturing the product, including releasing the product for supply.

This is an important aspect of regulation for biologicals, because a single biological (e.g. musculoskeletal tissue) may be sourced from many donors (living and cadaveric); however, each sample does not require a separate entry on the ARTG because they all have the same clinical use, applicable standards or principal manufacturer.

Table 1.3 summarises how these principles are applied.

Table 1.3 Characteristics of separate and distinct biologicals

Class of biological	Characteristics that define separate and distinct biologicals	Examples
Class 1 and Class 2	Applicable standards	TGO 86 (Standards for human skin) versus TGO 83 (Standards for musculoskeletal tissue)
	Intended clinical use	For dermatological repair versus musculoskeletal repair
	Principal manufacturer	Manufacturer A versus manufacturer B
Class 3 and Class 4	Product name	Mesenchymal stem cells versus dentritic stem cells
	Dosage form	Suspension versus paste
	Formulation or composition	Any differing active or excipient ingredient
	Therapeutic indication	For Parkinson's disease versus for coeliac disease
	Type of container	Bag versus vial
	Principal manufacturer	Manufacturer A versus manufacturer B

Examples of biologicals that have a single and separate ARTG entry

Biological products are included under a single ARTG entry when they have been manufactured to the same applicable standards, have the same intended clinical use and are manufactured by the same principal manufacturer. Examples of how this works for Class 2 biologicals, and Class 3 and Class 4 biologicals, are shown below.

Class 2 biologicals

Single entry

The following Class 2 musculoskeletal tissues are manufactured by the same manufacturer to the same standard (TGO 83) and have the same clinical use:

- femoral head, frozen, nonirradiated
- milled femoral head, frozen, irradiated.

These tissues are treated as the same biological and included in the same ARTG entry under a single product.

Overall, the TGO 83 (Standards for human musculoskeletal tissue) applies to a range of musculoskeletal tissues sourced from living and cadaveric donors, processed and not processed

after collection, and where bioburden is reduced or not. All of these tissues and products would be included under a single ARTG entry because they have been manufactured under the same standard, provided they have the same intended clinical use and the same manufacturer.

Similarly, TGO 85 (Standards for human ocular tissue) applies to a range of ocular tissues (e.g. eye globe, cornea, sclera) collected from living or deceased donors. All these products would be included as a single ARTG entry, with the specific tissues and products listed under that one entry, provided the principal manufacturer and intended use are the same for each product.

Separate entries

Milled femoral head, frozen, irradiated is manufactured under the same product specific standard, and has the same intended use, but the sponsor represents two 'principle manufacturers' (as defined in the Act), one in Perth and one in Brisbane. These products would require separate ARTG entries, as they have different principle manufacturers.

This example should be clearly distinguished from a sponsor of a 'principal manufacturer' (e.g. a company) that may have multiple manufacturing sites that all could manufacturer milled femoral head, frozen, irradiated, where the entries do not have separate ARTG entries.

Class 3 and Class 4 biologicals

Single entry

The biological described in the Class 3 case study product 2, above (mesenchymal stem cell therapy for the treatment of graft-versus-host disease) is packaged into three different doses: vials containing 1×10^6 cells designed for recipients under 30 kg, vials containing 2.5×10^6 cells designed for recipients between 30 kg and 50 kg, and vials containing 5×10^6 cells designed for recipients over 50 kg. All other characteristics of these vials are identical (see Table 1.3).

These three products are treated as the same biological, and included under a single ARTG entry.

In some circumstances Class 3 and Class 4 biologicals may be defined as ‘separate and distinct’ products, but the Secretary may allow certain subsets to be grouped within a single ARTG entry. These specific circumstances will be defined in a gazetted order.

Separate entries

For the biological detailed in the Class 3 case study, product 2 (mesenchymal stem cell therapy for the treatment of graft-versus-host disease), all manufacturing steps are the same but two versions of the final product are produced. Version one contains 5×10^6 cells in saline and version two contains 5×10^6 cells in saline with an antibiotic included in the excipient solution. As these two versions of the biological differ in the formulation, they would require separate ARTG entries.

1.2.6 Additional provisions

Export-only biologicals

Biologicals that are intended for export only are classified using the same rules for the other classes of biologicals. The premarket evaluation process for Class 3 and Class 4 export-only biologicals is the same as for Class 2 biologicals that are intended for domestic supply. Further evaluation may be required by the importing country.

Exceptional release (post-market)

The new legislation also allows the use of an approved biological in the situation where a biological does not meet mandatory requirements, such as when there are no alternative tissues or cells to treat a life-threatening condition. Such products are called 'nonconforming products' and their use is called 'exceptional release'. An example of such a case is shown below.

Exceptional release for a biological that does not meet mandatory requirements

A paediatric patient with a congenital heart valve defect is critically ill and in intensive care. The patient's physician predicts she has a life expectancy measured in weeks without a transplant. A paediatric heart valve becomes available at a heart valve bank; however, according to the Cardiovascular Order, the tissue must be sampled for bioburden, and when tested must demonstrate no microbial growth. The microbial testing process will take 10 days, but the physician considers there to be a serious risk of death within this period if the transplant does not take place immediately.

Therefore, under the exceptional release arrangements in the Therapeutic Goods Regulations 1990, the transplant can be carried out even though the heart valve is nonconforming (in this case, microbial testing results have not been returned).

Exceptional release refers to a situation when, after a product has been included on the ARTG and is imported or supplied in Australia (i.e. post-market), a specific product does not meet the required standards or current cGMP. In certain situations (such as a life-threatening emergency), such a nonconforming product may be required for use because an alternative conforming biological is not available.

The exceptional release provisions recognise the varying and unique nature of biological products, which means that, in exceptional circumstances, biologicals that would otherwise not be approved for use because they do not meet the applicable safety or manufacturing standards may be clinically the best option available in critical circumstances.

1.3 Access to unapproved biologicals

In some circumstances, biologicals are exempt from having to be included on the ATRG before being supplied on the market. For example, this may apply in emergencies or other high-need circumstances, when access and availability is of the utmost importance.

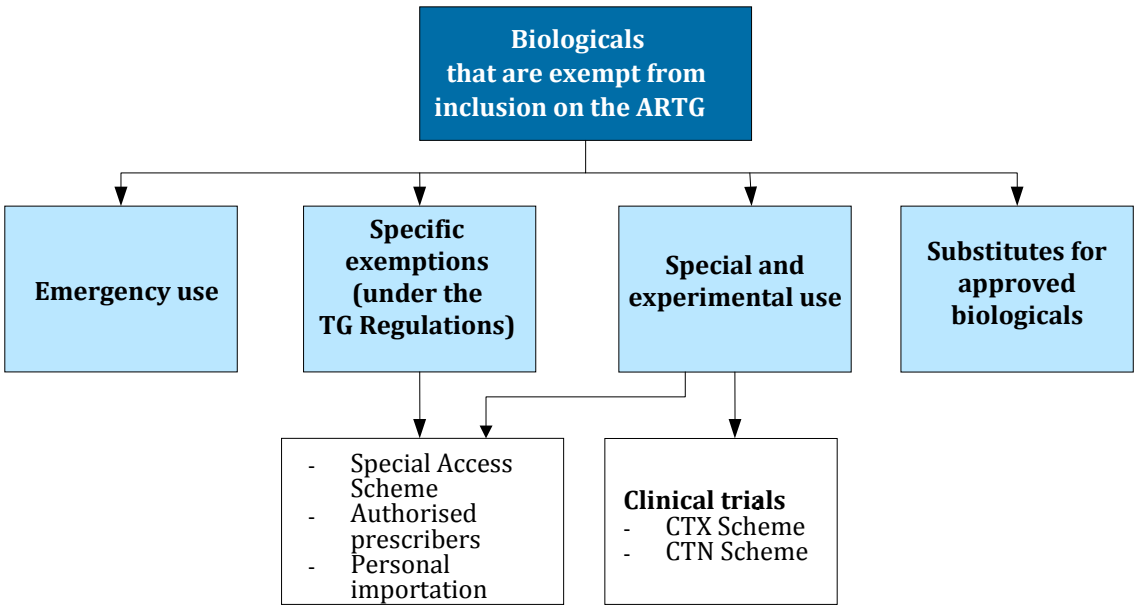
There are four types of exemptions:

- biologicals that are exempt under the TG Regulations
  - for example, unapproved biologicals that are imported or supplied for a single patient (on a case-by-case basis) under a scheme called the Special Access Scheme (SAS), or biologicals that are exempted for a single medical procedure or for personal importation
- biologicals that are needed in emergencies (e.g. in cases of national interest); for example
  - to stockpile particular biologicals as quickly as possible to prepare for a potential threat to public health that may be caused by a possible future emergency situation
  - to make biologicals available urgently in Australia to respond to an actual threat to public health caused by an emergency that has occurred
- biologicals for special and experimental use
  - access to biologicals for use in clinical trials under the Clinical Trial Notification (CTN) Scheme or the Clinical Trial Exemption (CTX) Scheme
  - access to unapproved biologicals under the SAS, allowing them to be used in particular circumstances (similar to special access to medicines or medical devices), such as for people who are critically ill, or who face premature death in the absence of early treatment
  - access to particular unapproved biologicals, as deemed necessary by authorised prescribers (under the Authorised Prescribers Scheme), for certain patients or classes of patients
- unapproved biologicals for use as substitutes for approved biologicals
  - to allow the use of unapproved biologicals (i.e. not included on the ARTG) when their approved equivalent is unavailable or in short supply (and it is in the public interest).

Figure 1.3 shows an overview of these exemptions.

See Section 1.4 for a discussion of the principles of risk management for unapproved biologicals

See Part 3 for further details about the regulatory arrangements for exempt (unapproved) uses



ARTG = Australian Register of Therapeutic Goods; CTN = Clinical Trial Notification; CTX = Clinical Trial Exemption; TG Regulations = Therapeutic Goods Regulations

Figure 1.3 Overview of biologicals that are not included on the ARTG

1.4 Biologicals risk management

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. Further information on the risk management process is available in ARGB Appendix 11 – Risk Management.

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 unforseen biological reactions.

In addition, the diverse range of starting materials and processes used in the manufacture of biologicals leads to differing levels of risk. 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.

1.5 Regulatory process

Figure 1.4 shows the relationship between the different legislation and other instruments that make up the Biologicals Regulatory Framework. Each of these components is described in more detail in the remainder of this section.

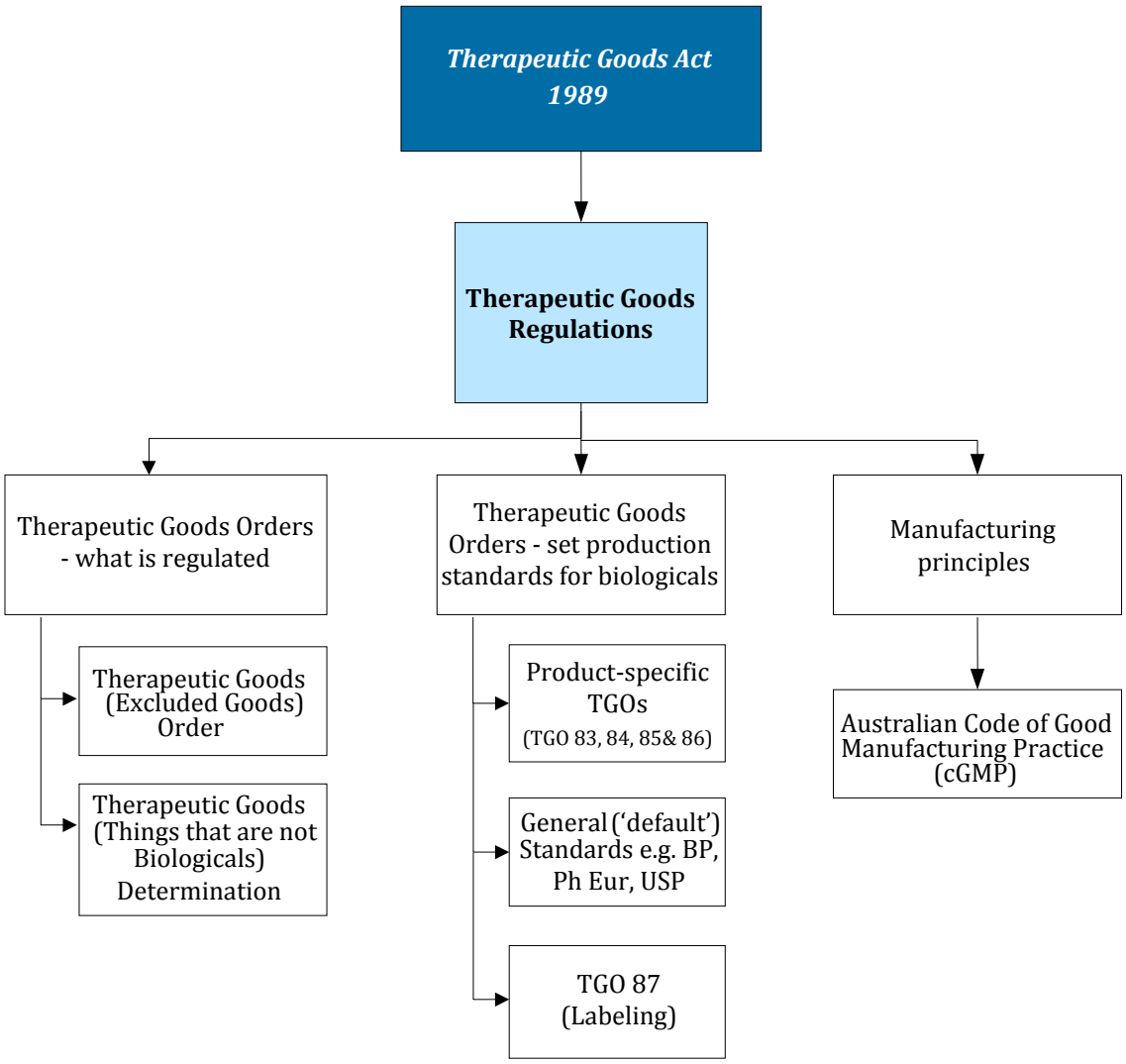


Figure 1.4 Overview of the Biologicals Regulatory Framework

1.5.1 Therapeutic Goods Act and Regulations

The TGA regulates therapeutic goods, including biologicals, via the TG Act and the TG Regulations.

Biologicals are included in Chapter 3 of the TG Act as Part 3-2A—Biologicals.

The current TG Act and Regulations can be accessed from the TGA website.

1.5.2 Therapeutic goods orders

The Biologicals Regulatory Framework is further supported by a number of therapeutic goods orders, which mandate how certain products are regulated, as well as product standards and other technical product requirements.

Some of these orders relate to which biologicals are regulated under the Biologicals Regulatory Framework. Other orders set standards on a wide range of quality and manufacturing issues.

Orders that relate to which biologicals are regulated

Therapeutic Goods (Excluded Goods) Order

This order specifies a range of products that are excluded from the definition of therapeutic goods and therefore not regulated by the TGA. This includes a number of biological products.

The TG (Excluded Goods) Order can be accessed from the TGA website.

Therapeutic Goods (Things that are not Biologicals) Determination

This order specifies a range of biological products that are included in the definition of therapeutic goods but are not regulated under the Biologicals Regulatory Framework.

See Section 1.1.4 for further details about articles that are not biologicals

The TG (Things that are not Biologicals) Determination can be accessed from the TGA website.

Orders that set standards

Section 10 (Part 3-1) of the TG Act allows the minister to make an order determining that matters specified in an order constitute a standard ('ministerial standards'). These standards can relate to a wide range of issues, including the quality of the goods (alone or in containers) and manufacturing procedures.

The Biologicals Regulatory Framework includes a number of standards. These are described below.

Product-specific standards

There are four therapeutic goods orders that set product-specific standards:

- TGO 84 (Standards for human cardiovascular tissue)
- TGO 83 (Standards for human musculoskeletal tissue)
- TGO 85 (Standards for human ocular tissue)
- TGO 86 (Standards for human skin)

These standards specify the minimum technical requirements for the safety and quality assurance for the specified biological.

General ('default') standards

In addition to the ministerial standards, manufacturers or sponsors are obliged to ensure that their products comply with all other standards (referred to as 'default' standards) that are applicable to biologicals. The current default standards are statements and monographs in the latest editions of the British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopeia.

Labelling

TGO 87 includes standards for the labelling of biologicals.

The standards can be accessed from the TGA website

1.5.3 Manufacturing principles

The manufacturing principles for biologicals mandate the cGMP. The cGMP sets out the manufacturing and quality system requirements for biologicals and operates in conjunction with the product standards.

The current (amended) cGMP can be accessed from the TGA website

1.6 References

Resource	URL
TGA website	http://www.tga.gov.au/
Therapeutic Goods (Excluded Goods) Order	http://www.tga.gov.au/industry/legislation-excluded-goods.htm
Therapeutic Goods (Things that are not Biologicals) Determination	http://www.tga.gov.au/industry/legislation-determinations.htm
Office of the Gene Technology Regulator	http://www.ogtr.gov.au/
TGA risk management approach to the regulation of therapeutic goods	http://www.tga.gov.au/industry/basics-regulation-risk-management.htm
ISO (International Organization for Standardisation)	http://www.iso.org/iso/home.html
ICH (International Conference on Harmonisation)	http://www.ich.org/
EMEA (European Medicines Agency)	http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp&jsenabled=true
Current TG Act and TG regulations	http://www.tga.gov.au/industry/legislation.htm

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