Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Guidance on boundary and combination products

Medicines, medical devices, and biologicals

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Contents

About this guidance

The TGA regulates therapeutic goods as defined in Section 3 of the *Therapeutic Goods Act 1989* (the Act) which generally fall under the following categories:

- Medicines as defined under Section 3 of the Act,
- Biologicals as defined under Section 32A of the Act,
- Medical devices as defined under Section 41BD of the Act, and
- Other therapeutic goods (OTGs) which include goods like tampons and disinfectants.

Products that fall under these categories have different regulatory pathways and requirements.

See our webpage for more information about these categories and other products that we regulate.

Appendix A contains definitions and concepts used for regulating of therapeutic goods.

Using the online decision tool work out if your product is a therapeutic good, and if so, the category of therapeutic good.

Some products may have attributes of two or more categories with different intended actions or effects and the appropriate regulatory pathway is not immediately obvious. These are referred to as '**boundary products**'.

Some products contain more than one type of therapeutic good with more than one therapeutic action or effect and are referred to as '**combination products'.**

This guidance has been developed to help manufacturers and sponsors understand which requirements and regulatory pathways apply to boundary and combination products in Australia.

We discuss key concepts and provide examples and case studies to show how boundary and combination products are regulated.

This information is provided for guidance only. It should not be relied on to address every aspect of the relevant legislation.

You should get independent legal advice to make sure everything is legal.

Boundary products

'**Boundary products**' are therapeutic goods that:

- have some of the attributes of two or more categories of regulated goods, and
- are products for which the appropriate regulatory pathway is not immediately obvious.

Regulation of boundary products

We regulate boundary products depending on the:

principal therapeutic effect of the product,

the therapeutic claims and

intended use mentioned on the product information or advertising materials.

Based on the factors below, we regulate products that incorporate or administer medicinal substances as either medical devices or medicines:

- which component or ingredient of the product provides the most important therapeutic effect of the product,
- what the principal therapeutic effect achieved is, when used consistently with the manufacturer's intended use, and
- the primary mode of action of the product in achieving its therapeutic effect and how it relates to the definitions of medicine, biological and medical device.

Some factors can influence the determination of principal therapeutic effect, including:

- actual therapeutic effect of the product and scientifically demonstrated action, verifiable in humans through clinical study findings,
- therapeutic claims made for the product, including any made on:
    - websites
    - linked helplines
    - testimonials
    - publications
- the context in which the claims are made, and the overall presentation,

the labelling, packaging or package inserts, pamphlets and promotional literature including any pictures or graphics,

product names and branding can also be deemed to be implicit claims,

advertisements, including those appearing in "advertorials", on television, other media and the Internet, and

the product form (capsule, tablet, injection etc.) and how it is supposed to be used.

Medicinal products

The action of a **medicinal product** is typically achieved by pharmacological, chemical, immunological, or metabolic means.

For example, substances used for diagnostic purposes (in vivo diagnostics) usually act chemically and are regulated as medicines.

Appendix A explains the concept of pharmacological, immunological, and metabolic means.

Medical devices

The principal intended action of **medical devices** is typically achieved by physical means. This includes:

- mechanical action,
- impervious, physical barrier only protecting the surface it is directly applied to,
- replacement of, or support to, organs or body functions, and
- measurement or monitoring body or its physiological functions.

Therapeutic goods that are chemical substances and exert their therapeutic effect through local or systemic chemical means are generally not medical devices. In most cases, the principal mode of action is metabolic or pharmacological.

Examples of boundary products

A product can contain medicinal substances that act on the body in an ancillary way. This includes herbal material and plant extracts. Depending on the intended therapeutic action, these substances may be regulated as medicines.

Alcohol swabs

- Alcohol swabs with antiseptic claims will probably be regulated as medicines due to the claims.
- Swabs with no claims other than cleaning skin will likely be regulated as medical device.

Nasal decongestion

- Products that use physical means to penetrate, clear and wash nasal blockages and loosen mucus are likely regulated as medical devices.
- Nasal decongestion products that contain an active ingredient and clear the nasal blockages by pharmacological means will likely be regulated as medicines.

Eye lubricating products

- Products that are only intended to lubricate the eye are likely regulated as medical devices.
- Eye lubricating products that have pharmacological components intended for antiseptic effect are likely regulated as medicines.

Disinfectants

- Liquid, spray, wipe, or aerosol intended to be used for disinfecting medical devices are likely regulated as medical device.
- Commercial grade disinfectant for surfaces other than medical devices or skin with a specific claim of killing bacteria will be likely regulated as an OTG.

Combination products

Products with components that have more than one therapeutic effect can potentially fit within more than one category of therapeutic goods are commonly referred to as ‘combination products’.

Combination products can commonly be:

- medicine - medical device combinations - medical devices that incorporate, or are used to administer a medicine,
- biological – medical device combinations - biologicals presented as a combination product with a medical device component (i.e., integrated with the medical device), such as a metal stent coated with a matrix and endothelial cells,
- biological – medicine combinations - biologicals presented as a combination product with a medicine component.

Regulation of combination products

The ***principal*** therapeutic effect for the product determines what type of therapeutic good the product is and how it is regulated. Like boundary products, the regulation of combination products may also depend on other factors such as therapeutic claims and intended use mentioned on the product or in advertising.

Medicine – medical device combinations

Medical devices that incorporate or are used to administer medicine are regulated as either medical devices or as medicinal products, depending on the **primary intended purpose of the product**. These combinations may be in the form of:

- **Medical devices used to administer a medicine** that is supplied separately will be likely regulated as medical devices. For example, syringes marketed empty, medicine spoons, and droppers. These products are usually supplied empty.
- **Medicines co-packaged with or contained within the same pack as the medical device** where the medicine component is responsible for the primary intended purpose of the product will be likely regulated as medicines. The device component is intended to be used to measure or administer the medicine within the pack. For example, paracetamol oral liquid and its measuring syringe or a cup.
- **Medical devices used for administering medicines** where the device and the medicine component forms a single **integral product** will likely be regulated as medicines. The product must not be re-usable or refillable. For example, epinephrine auto-injectors, and pre-filled asthma inhaler.

‘Integral’ is usually taken to mean a single component product. However, there may be circumstances where this could apply to two elements that are packaged together and combined into one product immediately prior to administration to the patient.

The relevant Essential Principles of Schedule 1 of the Therapeutic Goods (Medical Devices) Regulations 2002 apply with respect to safety and performance for the device component (for example, a syringe component of a pre-filled syringe). The device component does not need a separate ARTG entry, unless supplied separately.

- Medical devices incorporating a medicine as an integral part will likely be regulated as medical device. These are products that:
    - meet the definition of a medical device, and
    - incorporate, as an integral part, a substance, that:
        - if used separately, would be considered a medicine, and
        - is liable to act upon the body with action ancillary to that of the other functions of the medical device.
- 'Medicine' in this context includes but is not limited to substances that may be medicines, including herbal medicines (herbal material and plant extracts) and substances derived from human blood or blood plasma. For example, heparin-coated catheter. The safety, quality, and efficacy of the medicinal substance may be assessed by the relevant Branch of the TGA.

Medicine device combinations may be covered by System or procedure packs. Refer to our webpage for further guidelines.

Biological combination products

Combination products will likely be regulated as biologicals when at least one of the components is biological and other components are therapeutic goods.

Combination products are biological products that are:

- combined or incorporated with another therapeutic good such that the other good may or may not act on the human body in addition to the biological,
- the goods are combined and supplied for use as a single product entity that is transplanted or injected, and
- not packaged individually to the therapeutic good.

See guidance on Biologicals packaged or combined with another therapeutic good.

Biological – medical device combinations

Biological products presented as combination with a medical device component (i.e., integrated with the medical device) are regulated under the Biologicals Regulatory Framework and included in the ARTG as a biological. It is the constituents of the combination product that define the product as a biological, rather than the mode of action or principal therapeutic effect.

For example, metal stent coated with a matrix and endothelial cells will be regulated Biologicals Regulatory Framework. The device (i.e., the metal stent itself) will be assessed according to medical device regulatory requirements but will not be included in the ARTG separately.

Biological – medicine combinations

Biological products presented as combination product with medicine component are regulated under the Biologicals Regulatory Framework and included in the ARTG as a biological. For example, a

human bone product mixed with purified active protein such as recombinant Bone Morphogenetic Protein (BMP). The medicine (BMP) is intended to enhance the osteoinductivity of the bone graft.

Adding a substance can change the product's principal therapeutic effect, changing the product's category of therapeutic good.

See Appendix B for case studies of regulatory pathways with multiple therapeutic effects.

Summary

This document focuses on boundary and combination products and how they are regulated in Australia.

The information in this document is for guidance only. It should not be relied on to address every aspect of the relevant legislation.

It is best to read this in conjunction with information on the TGA website such as guidance documents, decision making tools, and links to our assessment processes.

More information

You can consult the TGA if you are unsure about your product's category or regulatory pathway. Email the following areas for information:

- Prescription Medicines - info@tga.gov.au
- Over-the-counter medicines - OTC.Medicines@health.gov.au
- Medical Devices - devices@health.gov.au
- Biologicals - bloodandtissues@tga.gov.au
- TGA info - info@tga.gov.au

This guidance focuses on boundary and combination products. For information on related topics see:

- Food-Medicine Interface Guidance Tool
- Complementary medicine interface (includes guidance on cosmetic-medicine interface)
- Excluded goods orders, determinations and specifications
- Biological products regulated as a therapeutic good, but not as a biological
- Biological products that are exempt or excluded from TGA regulation
- Disinfectants, sterilants and sanitary products

Version history

Version	Description of change	Author	Effective date
V1.0	Original Guidance	Therapeutic Goods Administration	June 2004
V1.1	Updated to reflect alcohol swabs with no claims regulated as medical devices, alcohol swabs with antiseptic claims regulated as medicines (item 24). Inserted page numbers.	Therapeutic Goods Administration	November 2005
V2.0	Updated Guidance	Medical Devices and Product Quality Division	December 2023

Appendix A

Concepts and terms

Medicine

Medicines are defined in Section 3 of the Act as therapeutic goods that are represented to achieve or are likely to achieve their principal intended action by:

- pharmacological
- chemical
- immunological, or
- metabolic means
- in or on the body of a human.

Medical device

Medical devices are defined in Section 41BD of the Act. Medical devices:

- are used in, for, or in relation to humans
- have therapeutic benefits
- generally, have one or more of the following characteristics:
    - have a physical or mechanical effect on the body
    - are used to record patient images for diagnosis or monitoring
    - are used to measure or monitor functions of the body
    - are used for prediction, prognosis, diagnosis, or monitoring of diseases or conditions
    - are used to guide treatment.

They can include components with:

- pharmacological
- immunological
- metabolic means as ancillary (secondary and assistive) functions.

Additionally, certain types of products may be explicitly declared as being or not being medical devices. These declarations are used to clarify the status of particular therapeutic goods or a category of therapeutic goods.

Biological

Biologicals, defined in Section 32A of the Act, are therapeutic goods comprising, containing, or that are:

- derived from human cells or human tissues
- certain other products comprising or containing live animal cells, tissues, or organs.
- Biologicals entered into the ARTG are classified into one of four regulatory classes.

The Secretary may 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. Refer to Therapeutic Goods (Biologicals—Specified Things) Instrument 2021 for further information.

Other therapeutic goods

Other therapeutic goods are therapeutic goods that do not fit the definition of a medical device, medicine or biological. These products are either:

- regulated under Chapter 3 of the Act as listed therapeutic goods, or
- are exempt from entry in the ARTG.

Examples include sterilants, disinfectants, tampons, and menstrual cups.

Sterilants and disinfectants are regulated in a variety of ways depending on the intended purpose as detailed in:

- the instructions for use
- labelling
- promotional material.

Specific information and guidance are available at Disinfectants, sterilants and sanitary products.

Differentiating terms

The terms listed below are important to understand and help differentiate between product type.

A therapeutic good is likely to be a medicine if its principal intended action is by:

- pharmacological,
- immunological
- metabolic

means in or on the body of a human.

The term *in or on the body of a human* includes actions upon:

- all components of the human body itself
- microbial flora
- pathogenic organisms.

Extracorporeal blood that is in continuous circulation with the body is considered a part of the body.

Principal intended action refers to the main mechanism of how a product exerts its therapeutic effect. This allows discrimination between types of therapeutic goods. The principal intended action must be scientifically plausible, considering:

- the intended clinical indications for the product

- how physiological or pathological processes are affected.

The principal intended action must be a verifiable and desirable therapeutic effect.

Key therapeutic actions that discriminate between types of therapeutic goods are:

'**Pharmacological means**[1]' is an interaction between:

- a substance or its metabolites (typically at a molecular level), and
- a constituent of the human body
    - that results in initiation, enhancement, reduction or blockade of physiological functions or pathological processes.

Examples of constituents of the human body include, amongst others:

- cells and their constituents including:
    - cell membranes
    - intracellular structures
    - RNA
    - DNA
    - proteins, for example, membrane proteins
    - enzymes
- components of extracellular matrix, foreign objects and organisms that are within or on the body
- components of blood
- components of body fluids.

Examples of action via pharmacological means:

- interaction between a ligand (for example, agonist, antagonist) and a receptor
- interaction between a substance and membrane lipids
- interaction between a substance and components of the cytoskeleton
- interaction between a substance and a pathogenic organism.

[1] Based on EU borderline and classification guidance. MDCG 2022-5 - https://health.ec.europa.eu/system/files/2023-06/mdcg_2022-5_en.pdf

'Immunological means[1]' is:

- an action initiated by a substance or its metabolites on the human body
- mediated or exerted (that is, stimulation, modulation, blocking, replacement) by cells or molecules involved in the functioning of the immune system, such as:
    - lymphocytes
    - toll-like receptors
    - complement factors
    - cytokines
    - antibodies.

Examples of action via 'immunological means' include:

- modulation of an immune response (for example, suppressing, blocking, activating, enhancing)
- replacement, reconstitution or introduction of natural or modified immune cells or molecules
- triggering an immune response against the targeted tissues, cells or antigens by immune-specific recognition
- targeting action of other linked or coupled substances.

Examples of substances acting via immunological means:

- vaccine
- tetanus anti-serum
- monoclonal antibodies
- anti-venom
- C1 esterase inhibitor.

Products with immunological recognition as a principal intended action are medicines. This is because immunological recognition used to target or direct the effects of linked or coupled substances is not an ancillary[2] action.

'**Metabolic means**[3]' is an action of a substance or its metabolites that involves an alteration in the function of the human body by stopping, starting, changing the rate, extent or nature of a biochemical process.

The biochemical process can be physiological or pathological.

The term 'biochemical processes' refers to reactions in the human body such as:

- anabolic and catabolic reactions
- transport of substances between compartments.

An interaction with a known receptor is not a prerequisite for the metabolic means of action.

Examples of action via 'metabolic means' include:

- the movement of water due to active transport of electrolytes mediated by, for example, Na/K ATPase pumps

[2] Ancillary – an accessory, subsidiary or helping thing – Macquarie Dictionary

[3] Based on EU borderline and classification guidance. MDCG 2022-5 - https://health.ec.europa.eu/system/files/2023-06/mdcg_2022-5_en.pdf

- inhibition of endogenous enzymes, including the digestive enzymes
- inhibition of absorption of any substance in the alimentary or respiratory tracts
- altering the electrolyte balance, including pH and osmolality, of the serum or other body compartment or cavity.

The Australian Register of Therapeutic Goods (ARTG)

The ARTG is the public database of therapeutic goods that can be legally supplied in Australia. Medical device sponsors must have their product in the ARTG unless the product is exempt from ARTG inclusion, excluded from regulation by TGA or otherwise approved. The ARTG database is publicly accessible and includes the following:

- registered goods
- listed goods
- medical devices
- biologicals

Registrable and listable goods

Registrable and listable goods are regulated under Chapter 3 of the Act. Registrable goods undergo a more rigorous evaluation of their quality, safety and efficacy, before being entered into the ARTG, than listable goods.

Medical devices

Medical devices are regulated under Chapter 4 of the Act and can be entered into the ARTG if their manufacturers:

- comply with the Essential Principles for safety and performance
- have applied appropriate conformity assessment procedures or undergone comparable overseas regulator pathways
- meet certain other requirements.

Exempt goods

Some therapeutic goods can be made exempt from selected regulatory requirements. For example, a therapeutic good could be made exempt from requiring entry in the ARTG. Exemptions are detailed in legislation and can include associated conditions.

Example conditions:

- notification to the TGA before supply
- reporting of adverse events after supply
- allowing of inspection of manufacturing facilities by the TGA.

Exemptions from the inclusion provisions of medicines and biologicals are published in Schedules 5 and 5A of the Regulations (exempt goods). Exemptions for medical devices are published in Schedule 4 of the MD Regulations.

Sponsors can identify applicable exemptions for products once the type of therapeutic good is known:

- medicine
- medical device

- biological
- other therapeutic good.

Note: Sponsors must comply with all conditions of applicable exemptions.

Excluded goods

The Secretary may declare that particular goods are not therapeutic goods. These goods are called Excluded goods and are not regulated by TGA. Information on Excluded Goods is available at Excluded goods orders, determinations and specifications.

Supply of 'unapproved' therapeutic goods not in the ARTG

Products not included in the ARTG are referred to as unapproved therapeutic goods and these can be legally supplied in Australia through several different pathways. These unapproved products may include medicines or medical devices, including medical cannabis and vaping products containing nicotine, and can be accessed under the following pathways depending on various factors including the needs of particular people or circumstances of use.

- Special access scheme
- Authorised prescribers
- Personal Importation Scheme
- Clinical trials
- Accessing medicines during a medicine shortage

These schemes cannot be used to facilitate the commercial supply of therapeutic goods.

Appendix B

Case studies of products with more than one therapeutic effect

Patches of bandages

A medicine-impregnated patch that adheres to healthy skin to deliver the medicine trans dermally in itself is not intended to have any therapeutic effect on the skin, although it could cause a local reaction. The therapeutic claims made only relate to systemic effects of the medicine.

The product is a **medicine**. This is because the principal therapeutic effect could only relate to the medicine. The adhesive patch provides the mode of administration of the active therapeutic ingredient. An antimicrobial medicated wound dressing intended principally for use as a barrier to protect a wound or damaged skin and hence promote healing is a **medical device**.

An irrigation solution with an added microbicide

A sterile, physiological solution with an added microbicidal substance that is intended to be used for irrigation of a part of the body is a **medicine**. In this case, the principal therapeutic effect is to reduce the clinical risk of infection at the site of a contaminated or infection-prone wound.

A similar solution that does not include a microbicide is a **medical device**. This is because its principal therapeutic effect is achieved through facilitating physical removal of objects and substances at the site of use.

A substance to fill a space between bone fragments that contains a medicine to stimulate bone growth

A matrix (not of human cell or tissue origin) principally used as a bone void filler achieves its effect by acting as a scaffold for bone formation, without physiological stimulation of bone growth or cellular infiltration is a **medical device**.

Adding a substance that stimulates bone growth changes the product's principal therapeutic effect. In this case, the matrix administers a medicine to the anatomical site. This medicine helps with fusion of bones. The principal intended action is achieved pharmacologically through stimulation of bone growth making this product a **medicine** rather than a medical device.

A matrix of human cell or tissue origin is a **biological**.

A bone cement incorporating an antibiotic

A cement for fixation of joint replacement systems in bone is a **medical device**.

Incorporation of an antibiotic to reduce the risk of infection does not alter the principal therapeutic effect of the cement, which is to fix a prosthesis to bone, thereby reducing pain or increasing functionality; the antibiotic has an important, but clearly ancillary effect in reduction of the risk of local infection.

This product is a **medical device**. The addition of an antibiotic does not affect the product’s principal therapeutic action of acting as a physical adhesive mechanism.

Should a similar product, incorporating an antibiotic, be intended to be used to treat or prevent an infection, whilst not being used to fix a prosthesis to bone, its principal therapeutic effect has changed and consequently, the product is a **medicine**.

Decisions on whether and how to enter products in the ARTG are made by the lead program although assessments may take place across the TGA.

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Reference/Publication #