Australian Government
Department of Health
Therapeutic Goods Administration

Australian regulatory guidelines for complementary medicines

ARGCM

Version 8.0, April 2018

TGA Health Safety Regulation

Contents

Abbreviations

Refer to the TGA acronyms & glossary for terms, definitions and acronyms used in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM).

Introduction to the ARGCM

The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) provide information for manufacturers, sponsors, healthcare professionals and the general public on the regulation of complementary medicines in Australia.

If you want to supply a complementary medicine in Australia, you may choose to employ a regulatory affairs consultant.

The ARGCM Version 7.0 is structured as follows:

- **Part A: General guidance on complementary medicine regulation in Australia**
  Part A provides an overview of the regulatory framework for complementary medicines in Australia. The guidance is provided for sponsors, healthcare professionals and the general public.
- **Part B: Listed complementary medicines**
  Part B provides guidance on the regulatory framework for 'low risk' listed complementary medicines. The guidance is mainly directed at sponsors and manufacturers of listed medicines.
- **Part C: New substance evaluation for use in listed medicines**
  Part C provides guidance on the evaluation process for a new complementary substance. This guidance is for applicants requesting the evaluation of a new substance for potential use in listed medicines.
- **Part D: Registered complementary medicines**
  Part D provides guidance on the evaluation process for registered complementary medicines. This guidance is for sponsors, applicants and manufacturers of proposed new registered complementary medicines.

ARGCM Part A: General guidance on complementary medicine regulation in Australia

Complementary medicines: what they are

In Australia, medicinal products containing such ingredients as certain herbs, vitamins and minerals, nutritional supplements, homoeopathic medicines and aromatherapy products are referred to as 'complementary medicines' and are regulated as medicines by the Therapeutic Goods Administration (TGA) under the *Therapeutic Goods Act 1989* (the Act) and the supporting Therapeutic Goods Regulations 1990 (the Regulations)—refer to Regulation basics.

Part 1(2) of the Regulations provides the following definitions:

> **Complementary medicine** means a therapeutic good consisting wholly or principally of 1 or more designated active ingredients, each of which has a clearly established identity and a traditional use.
>
> **Designated active ingredients**, for a complementary medicine, means an active ingredient, or a kind of active ingredient, mentioned in Schedule 14 (to the Regulations).

Schedule 14 to the Regulations provides a list of designated active ingredients:

> **Designated active ingredients**
> 1. an amino acid
> 2. charcoal
> 3. a choline salt
> 4. an essential oil
> 5. plant or herbal material (or a synthetically produced substitute for material of that kind), including plant fibres, enzymes, algae, fungi, cellulose and derivatives of cellulose and chlorophyll
> 6. a homoeopathic preparation
> 7. a microorganism, whole or extracted, except a vaccine
> 8. a mineral including a mineral salt and a naturally occurring mineral
> 9. a mucopolysaccharide
> 10. non-human animal material (or a synthetically produced substitute for material of that kind) including dried material, bone and cartilage, fats and oils and other extracts or concentrates
> 11. a lipid, including an essential fatty acid or phospholipid
> 12. a substance produced by or obtained from bees, including royal jelly, bee pollen and propolis
> 13. a sugar, polysaccharide or carbohydrate
> 14. a vitamin or provitamin

Regulation of complementary medicines in Australia

Australian Register of Therapeutic Goods (ARTG)

Unless exempt (refer to exempt goods) any therapeutic product for which indications are made must be entered on the Australian Register of Therapeutic Goods (ARTG) before it can be legally imported, exported, manufactured or supplied for use in Australia.

To supply a therapeutic good in Australia, sponsors must pay the following fees—refer to schedule of fees and charges:

- an initial application fee
- an annual charge to maintain the inclusion of their product on the ARTG.

Registered and listed complementary medicines

Within the regulatory framework, complementary medicines are either registered or listed on the ARTG (refer to Medicines and TGA classifications) based on their ingredients and the indications made for the medicine.

Most complementary medicines are listed (refer to ARGCM Part B: Listed complementary medicines), however, some are registered (refer to ARGCM Part D: Registered complementary medicines).

Regulatory requirements and guidance for complementary medicines

In Australia, the *Therapeutic Goods Act 1989* (the Act) is administered by the TGA and provides a uniform national framework for import, export, manufacture and supply of therapeutic goods. The Act is supported by the Therapeutic Goods Regulations 1990 and various Therapeutic Goods Orders (TGOs) and determinations, which provide details relevant to the various provisions in the Act.

All therapeutic goods must conform with applicable standards before they can be entered on the ARTG. The standards recognised under the Act are those made by the Minister under section 10 of the Act (TGOs) and the default standards. It should be noted that any matter specified in an order under section 10 of the Act has precedence over requirements of the default standards.

Refer to Legislation & legislative instruments for a list of relevant therapeutic goods legislation that sponsors are required to comply with. Sponsors should also be aware of:

- Medicines Advisory Statements Specification 2016
- The Permissible Ingredients Determination
- Compositional guidelines: Where there is no default standard available for a substance permitted for use in listed medicines, a TGA compositional guideline links formal descriptions and specifications with the Australian approved ingredient name.
- The European Medicines Agency (EMA) website provides information about medicine evaluation, including scientific guidelines on the evaluation of herbal medicines.
- The Evidence guidelines: Guidelines on the evidence required to support indications for listed complementary medicines assist sponsors to determine the appropriate evidence to support therapeutic indications made in relation to listable medicines.
- Australian Clinical Trials provides information for sponsors developing clinical trials for a medicine or a new complementary medicine substance.

Other legislation and requirements applicable to complementary medicines

Sponsors should be aware of other applicable Australian legislation and requirements, such as:

- *Environment Protection and Biodiversity Conservation Act 1999*
- *Food Standards Australia New Zealand Act 1991*
- *Customs Act 1901* and the Customs (Prohibited Imports) Regulations 1956
- *Industrial Chemicals (Notification and Assessment) Act 1989* and the National Industrial Chemicals Notification and Assessment Scheme
- *Gene Technology Act 2000* and the Gene Technology Regulations 2001
- *Competition and Consumer Act 2010* and the Australian Consumer Law
- *National Measurement Act 1960*
- Australian Dangerous Goods Code
- *Agricultural and Veterinary Chemicals Code Act 1994*.

In addition, sponsors should be aware of the requirements applicable under other Australian State and Territory legislation such as those concerning:

- weights and measures
- deceptive packaging
- quarantine
- state/territory therapeutic goods legislation
- state/territory drugs and poisons scheduling
- advertising
- genetically modified organisms or genetically modified products.

Consent to supply goods that are not compliant with prescribed standards

A sponsor can apply under sections 14 and 14A of the Act, to request consent to supply goods that do not comply with a prescribed standard or aspects of a prescribed standard.

Please refer to:

- Consent to import, supply or export therapeutic goods that do not comply with standards - information for industry on the TGA website.
- Application for consent to import, supply or export goods that do not comply with standards - section 14/14A available on the TGA website. Such requests incur an application fee.

Complementary medicines exempt/excluded from certain regulatory requirements

Excluded goods

Where there is some doubt as to whether a product may fall within the definition of a therapeutic good it may be declared not to be a therapeutic good under section 7 of the Act, where the Secretary has a reasonable basis for arriving at that decision. Refer to Declarations made under section 7 of the Act for more information. A consolidated list of excluded goods is provided in Therapeutic Goods (Excluded Goods) Order No. 1 of 2011.

Exempt goods

Some medicines do not need to be registered or listed on the ARTG as a result of a specific exemption or determination under the Act (refer to section 18 of the Act and Schedules 5 and 5A of the Regulations). These include, for example:

- Medicines (other than those used for gene therapy) that are dispensed or extemporaneously compounded by a practitioner for use by a particular person—refer to Complementary medicine practitioner medicines/exemptions.
- Certain homoeopathic preparations—refer to Homoeopathic medicines.
- Certain shampoos for the treatment/prevention of dandruff.
- Starting materials used in the manufacture of therapeutic goods, except when pre-packaged for supply for other therapeutic purposes or formulated as a dosage form.

These goods are exempt from Part 3-2 of the Act, relating to inclusion on the ARTG, however it is important to note that all other applicable requirements under the Act and the Regulations must be complied with.

Some medicines or persons are exempt from the manufacturing requirements set out in Part 3-3 of the Act. The criteria for manufacturing exemptions are provided in Section 34 of the Act, together with Schedule 7 (exempt medicines) and Schedule 8 (exempt persons) of the Regulations.

Schedule 7 of the Regulations provides the following as exempt from the operation of Parts 3-3 of the Act:

> 2. ingredients, except water, used in the manufacture of therapeutic goods where the ingredients:
> (a) do not have a therapeutic action; or
> (b) are herbs, bulk hamamelis water or oils extracted from herbs, the sole therapeutic use of which is as starting materials for use by licensed manufacturers

For example: the Australian manufacturer of a 'bulk' essential oil (the farmer extracting oil from lavender plants) does not need to be licensed for Good Manufacturing Practice (GMP). However, the Australian manufacturers who undertake steps in the manufacturing of the finished dosage form (such as filling, blending, testing, labelling and release for supply) are required to hold the appropriate GMP licence.

Complementary medicine practitioner medicines and exemptions

The TGA does not regulate health practitioners, we regulate therapeutic products. The Australian Health Practitioner Regulation Agency (AHPRA) is responsible for the implementation of the National Registration and Accreditation Scheme across Australia. Currently, only Chinese medicine practitioners are registered with the AHPRA.

In April 2015, Health Ministers agreed to the terms of the first National Code of Conduct for health care workers detailed in the COAG Health Council's Final Report: A National Code of Conduct for health care workers. The National Code, once implemented, will set minimum standards of conduct and practice for all unregistered health care workers. It will also set national standards against which disciplinary action can be taken including the issuing of a prohibition order.

There are a number of specific provisions in the Act which provide exemptions from the operation of certain parts of the Act, for example: the requirement for specific therapeutic goods to be included on the ARTG; the requirements for specific therapeutic goods to be manufactured under GMP; and advertising exemptions.

Exemptions for extemporaneously compounded and dispensed complementary medicines

Schedule 5, Item 6 of the Regulations provides exemption from inclusion on the ARTG for medicines that are dispensed or extemporaneously compounded by practitioners.

Schedule 8(4) of the Regulations provides an exemption for specified complementary medicine practitioners from the operation of Part 3-3 of the Act (Manufacturing of therapeutic goods) and therefore the requirement to manufacture certain medicines under GMP:

> where the preparation is for use in the course of his or her business and:
>
> a) the preparations are manufactured on premises that the person carrying on the business occupies and that he or she is able to close so as to exclude the public; and
>
> b) the person carrying on the business:
>
> i) supplies the preparation for administration to a particular person after consulting with that person; and
>
> ii) uses his or her judgement as to the treatment required.

The exemptions relating to extemporaneous compounding and dispensing apply where a health practitioner prepares a medicine for an individual patient either following consultation with that particular patient, or to fill a prescription for that particular patient. This allows health practitioners such as pharmacists, herbalists, naturopaths, nutritionists and homoeopaths, to prepare medicines for individual patients that do not need to be assessed or evaluated by the TGA for quality, safety or efficacy. The exemption recognises the one-off nature of such medicines and the professional training of the health practitioner to prepare a medicine for the specific needs of an individual patient.

Most herbal ingredients may be used for preparing medicines that are dispensed or extemporaneously compounded. However, access to some medicinal ingredients is restricted by State and Territory drug and poisons legislation. Depending on the level of access control, some ingredients are not available for dispensing or extemporaneous compounding by health practitioners, such as: ingredients included in Schedule 4 of the Poisons Standard which are available only on prescription from a practitioner registered under a law of a State or Territory.

Pre-packaged (manufactured) medicines made by practitioners

The exemption for extemporaneously compounded medicines does not cover situations where a health practitioner makes up medicines in advance, in anticipation of patients who may come onto the premises and ask for that medicine.

Ingredients that are either pre-packaged for other therapeutic purposes or formulated as a dosage form are subject to assessment for quality, safety and efficacy as appropriate, and are to be included on the ARTG. Unless exempt, medicines included on the ARTG need to be prepared by a person in accordance with Good Manufacturing Practice.

'For practitioner dispensing only' products

Sponsors may choose to supply their products in a dispensing pack solely to healthcare practitioners with the words 'for practitioner dispensing only', or words to that effect, included on the label. These medicines must meet the same statutory requirements relating to entry on the ARTG. This includes that labelling (apart from indications) must meet the requirements of the Therapeutic Goods labelling Order and the Therapeutic Goods Advertising Code (unless the appropriate exemption or approval to do otherwise has been granted).

Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92) commenced on 31 August 2016 and has a 4 year transition period. During this time, complementary (non-prescription) medicines must comply with either TGO 92 or Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69). Sponsors must specify which order they are compliant with. On and from 1 September 2020, these medicines must comply with TGO 92.

The only difference between 'for practitioner dispensing only' products and other listed or registered complementary medicines is that the former do not need to include a statement of their purpose/therapeutic indication on the label [refer to TGO 69 Section 3(2) subsection (m) or TGO 92 Section 8(1)(n)]. These medicines should only be supplied to an individual after consultation with a healthcare practitioner at which time, the healthcare practitioner attaches a label to the medicine providing instructions for use for that individual.

Exemptions for advertising directed to health professionals

Section 42AA of the Act provides for sponsors to advertise directly and exclusively to health professionals[1] advertising material that is exempt from complying with the advertising requirements in the Act and the Regulations. Section 42AA of the Act also exempts those health professionals from the advertising rules when they give advice to their patients.

Some health professional associations provide their members with 'Therapeutic Goods Advertising exemption certificates', advising the member they may receive advertising material from sponsors that are exempt from complying with usual advertising requirements. Note that such certificates are not issued by the TGA.

Advertisements for therapeutic goods directed exclusively to healthcare professionals are governed by industry codes of practice and are not subject to the Therapeutic Goods Advertising Code. For more information, please refer to the CMA Codes of Practices on the Complementary Medicines Australia website and the Australian Self Medication Industry (ASMI) Code of Practice.

[1] Refer to paragraph 42AA(1)(a) and (c) of the Act and Schedule 1 of the Therapeutic Goods Regulations 1990 for the health professionals to which this applies

Approved terminology for complementary medicines

Guidance on Australian approved terminology is provided in the publication TGA approved terminology for medicines, available on the TGA website. The Ingredients Table (located on the TGA Business Services (TBS) website) is a searchable database of approved terminology for chemical, biological and herbal ingredients, including:

- active ingredients
- excipients
- components of herbal ingredients.

Types of names include:

- Australian Approved Name (chemical) (AAN)
- Approved Biological Name (ABN)
- Approved Herbal Name (AHN) (the Latin binomial of a herbal species).

A complete herbal ingredient name, to be used in ARTG applications and on medicine labels, consists of 3 components: the 'AHN' (identifies the herb species) plus the 'plant part(s) code' plus the 'plant preparation code'.

Instructions on searching the database are provided in ARGCM Part B: TGA Business Services ingredient database.

- **Approved Herbal Substance name (AHS):** An AHS is used for herbal materials described in a pharmacopoeial monograph. An AHS name is considered a complete name, as the plant part and preparation are described in the monograph.
- **Herbal Component Name (HCN):** HCNs are names for components that are found in herbal ingredients. A HCN will only be assigned to a component or group of components of a herbal species if it is either a therapeutic marker (where the component has known therapeutic activity) or a quality marker (a chemical marker used for quality control). Generally, a HCN will not be assigned for ubiquitous non-phytochemical components of herbal species, for example: compounds that commonly occur in plant materials. A HCN is not a stand-alone name and should only be used when expressing the herbal component equivalence for a herbal ingredient name.
- **Approved Food Name (AFN):** AFNs are allocated to substances that are food grade, for example: blackberry. AFNs can only be used as excipient ingredients in therapeutic goods. If the substance is to be included as an active ingredient in a product, the name of the ingredient must be expressed in AHN format, for example: *Rubus fruticosus* fruit + preparation.

The Code Tables (located on the TGA Business Services (TBS) website) provide terminology (for example: routes of administration, dosage forms) for use in product applications and on medicine labels, where relevant.

Applying for new Australian approved name

When submitting an application for evaluation of a complementary medicine substance (including a new substance in a proposed registered complementary medicine) that does not have an approved name, the applicant should submit a proposal for a new name with that application using the appropriate form—see Application forms for proposing names.

Note: Assignment of a name does not imply any recommendation for the use of the substance or that the ingredient has been approved for use in therapeutic goods.

Types of complementary medicines

Herbal medicines

Herbal medicines are therapeutic goods that are, or contain as the major active ingredient(s), herbal substances. Herbal substances are preparations of plants, and other organisms that are treated as plants in the International Code of Botanical Nomenclature, such as fungi, algae and yeast.

Traditional medicines

Traditional medicines include a diverse range of health practices, approaches, knowledge and beliefs incorporating medicines of plant, animal and/or mineral origin. Examples of traditional paradigms include: Traditional Chinese medicine, Ayurvedic medicine, Aboriginal and Torres Strait Islander medicine and Western herbal medicine.

Traditional use is defined in Part 1(2) of the Regulations:

> **traditional use**, for a designated active ingredient, means use of the designated active ingredient that:
> (a) is well documented, or otherwise established, according to the accumulated experience of many traditional health care practitioners over an extended period of time; and
> (b) accords with well-established procedures of preparation, application and dosage

An established tradition of use is considered to be three generations of human use, equating to approximately 75 years.

Homoeopathic medicines

In Australia, medicines containing homoeopathic preparations are considered to be low-risk medicines and are regulated under the Act.

Part 1(2) of the Regulations provides the following definition:

> **homoeopathic preparation** means a preparation:
>
> (a) formulated for use on the principle that it is capable of producing in a healthy person symptoms similar to those which it is administered to alleviate; and
> (b) prepared according to the practices of homoeopathic pharmacy using the methods of:
> (i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol; or
> (ii) serial trituration in lactose

A 'homoeopathic preparation' is based upon the central tenet of homoeopathy 'let like cure like' and the principles of homoeopathic pharmacy—'potentisation', being the serial dilution and succussion of a stock. Homoeopathic medicines are derived from a wide variety of natural source materials, mostly plants and minerals. Some of these source materials are poisonous, for example: *Atropa belladonna*. The highly diluted nature of homoeopathic preparations is considered to render starting materials non-toxic and therefore safe for therapeutic use.

The term 'mother tincture' means a preparation prepared by the process of solution, extraction or trituration. Homoeopathic medicines are manufactured to different medicinal strengths or 'potencies' according to manufacturing standards described in homoeopathic pharmacopoeias. The expressions of homoeopathic potencies are provided below:

- 'nX' (or 'D') potency: where each dilution of the mother tincture is a decimal or 10-fold dilution and 'n' is the number of dilutions, such that the total dilution is 10^n. For example: a 1X potency represents a 1:10 dilution; 2X a 1:100 dilution; 3X a 1: 1,000 dilution; 4X a 1:10,000 dilution.

- 'nC' potency: where each dilution of the mother tincture is a centesimal or 100-fold dilution and 'n' is the number of dilutions, such that the total dilution is 100^n. For example: a 1C potency represents a 1:100 dilution; 2C a 1:10,000 dilution.
- 'M' potency: refers to a homoeopathic preparation that has undergone 1,000 potentisation steps in the centesimal scale. For example: 1M potency represents a 1,000C dilution; 2M a 2,000C dilution.
- 'nLM' (or 'Q'): where each dilution from a mother tincture first potentised to a 3C starting material is a quinquagintamillesimal or 50,000-fold dilution and 'n' is the number of dilutions, such that the total dilution is $50{,}000^n$. For example: a LM/01 (or Q/01) potency represents a 1:50,000 dilution from a 3C starting potency; LM/02 (or Q/02) a 1:50,000 dilution from a LM/01 (or Q/01) potency, and so on.

Homoeopathic preparations exempt from inclusion on the ARTG

Where a medicine meets the definition of 'homoeopathic preparation' and meets the conditions set out under Item 8 of Schedule 5 to the Regulations it is exempt from the requirement to be included on the ARTG. Note that this does not apply where the homoeopathic preparation is part of a medicine containing other ingredients requiring inclusion on the ARTG.

> Schedule 5
>
> 8) the following medicines unless the indications proposed by the sponsor are in the treatment of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 to the Therapeutic Goods Advertising Code:
> (a) homoeopathic preparations more dilute than a one thousand fold dilution of a mother tincture and which are not required to be sterile, and which do not include an ingredient of:
> (i) human origin; or
> (ii) animal origin, if the ingredient consists of, or is derived from, any of the following parts of cattle, sheep, goats or mule deer:
> (A) adrenal;
> (B) brain;
> (C) cerebrospinal fluid;
> (D) dura mater;
> (E) eye;
> (F) ileum;
> (G) lymph nodes;
> (H) pineal gland;
> (I) pituitary;
> (J) placenta;
> (K) proximal colon;
> (L) spinal cord;
> (M) spleen;
> (N) tonsil.

That is, most homoeopathic preparations that are more dilute than a 1,000 fold dilution of a mother tincture (4X and above) are not required to be on the ARTG as they are considered to be sufficiently low risk. Some homoeopathic medicines however, are required to be on the ARTG—refer to Homoeopathic preparations required to be listed on the ARTG.

A homoeopathic medicine prepared by practitioners specifically for an individual patient, after consultation with that patient, does not need to be entered on the ARTG—refer to Exemptions for extemporaneously compounded and dispensed complementary medicines.

Homoeopathic preparations required to be listed on the ARTG

Items 4A of Part 1 of Schedule 4 to the Regulations state that the following therapeutic goods are required to be included in the part of the ARTG for listed goods:

> 4A. homeopathic preparations where:
> (a) the preparation consists of, or contains a dilution of, mother tincture that is a 1,000 fold dilution, or a lesser dilution, of that mother tincture; and
> (b) the preparation only contains ingredients that are specific in a determination under paragraph 26BB(1)(a) of the Act; and
> (c) if a determination under paragraph 26BB(1)(b) of the Act specifies requirements in relation to ingredients being contained in the preparation –none of the requirements have been contravened; and
> (d) the preparation is not required to be sterile; and
> (e) none of the ingredients in the preparation are included in a Schedule to the Poisons Standard or Appendix C of the poisons Standard (other than any ingredient that is more than a 1,000-fold dilution of mother tincture)

That is, mother tinctures and 1X, 2X and 3X homoeopathic preparations must be included on the ARTG to be supplied in Australia.

Homoeopathic medicines that contain a substance that is in a Schedule or Appendix C to the Poisons Standard may be able to be listed on the ARTG, provided that the ingredient is more dilute than a 1,000 fold dilution of the mother tincture (that is, 4X or above) and the medicine is not required to be sterile.

To be listed on the ARTG, homeopathic preparations must only contain ingredients specified in the Permissible Ingredients Determination and meet any requirements in relation to the ingredient.

Manufacturing requirements for homoeopathic preparations

In Australia, homoeopathic medicines that:

- are not required to be sterile
- only contain homoeopathic preparations that are more dilute than a 1,000 fold dilution of the mother tincture (4X or above)

are exempt from the Australian requirement that the manufacturer must hold a GMP license - refer to Item 7 of Schedule 7 to the Regulations.

Specific labelling requirements for homoeopathic preparations

All commercially supplied homoeopathic medicines in Australia, regardless of whether they are included on the ARTG, must:

- comply with advertising requirements set out in Schedule 2 of the Regulations
- be labelled in compliance with the general requirements for labels and the specific requirements for homoeopathic medicines in the Therapeutic goods labelling Order as current and in force), and any other applicable official standards.

Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92) commenced on 31 August 2016 and has a 4 year transition period. During this time, complementary (non-prescription) medicines must comply with either TGO 92 or Therapeutic Goods Order No. 69. General requirements for labels for medicines (TGO 69). Sponsors must specify which order they are compliant with. On and from 1 September 2020, these medicines must comply with TGO 92.

Guidance on indications for homoeopathic medicines

The Evidence guidelines: Guidelines on the evidence required to support indications for listed complementary medicines detail the requirements for making therapeutic indications for listed medicines, including homoeopathic medicines listed on the ARTG.

A homoeopathic product can carry claims specified in Part 1 or 2 of Appendix 6 of the Therapeutic Goods Advertising Code and be listed on the ARTG. This is provided the medicine is not displayed or advertised to the general public for purposes outside those permitted by the Therapeutic Goods Advertising Code and the Regulations, for example: it is supplied solely to practitioners. However, in accordance with the Therapeutic goods labelling Order as current and in force, the label on the container and on the primary pack must include a statement to indicate that the medicine is a homoeopathic medicine.

Anthroposophic medicines

Anthroposophic practitioners use a range of interventions including conventional therapies, remedies based upon homoeopathic principles, herbal medicine and external therapies.

Essential oils

The purpose of a product containing an essential oil determines which agency regulates it. That is, if the product makes only cosmetic claims it is considered a cosmetic and regulated by National Industrial Chemicals Notification and Assessment Scheme (NICNAS), but if the product makes a therapeutic claim it would be considered a therapeutic good and regulated by the TGA.

Sponsors of products containing essential oil(s), which are considered to be therapeutic goods must comply with all statutory requirements, including: the default standards, the Poisons Standard, Therapeutic goods labelling Order as current and in force and TGO No. 80 - Child Resistant Packaging Requirements for Medicines.

Essential oils that are supplied solely as starting materials to practitioners are generally exempt from the requirement to be included on the ARTG before supply—refer to Exempt goods.

Vitamins and minerals

As with all complementary medicines, there are various legislative requirements which must be addressed in relation to medicines containing vitamins and minerals in order for them to be included on the ARTG. For example, the Therapeutic Goods Advertising Code states that an advertisement for vitamins must not imply that vitamin supplements are a substitute for good nutrition or a balanced diet. Other relevant legislative documents include: Therapeutic goods labelling Order as current and in force and Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules and Medicines Advisory Statements Specification 2016.

Many vitamins and minerals are scheduled in the Poisons Standard and in accordance with this scheduling, such things as pack size and container dimensions may be limited.

Nutritional substances

Some nutritional substances are regulated as foods and others are regulated as therapeutic goods. Refer to Food/complementary medicine interface. Examples of nutritional substances, if presented as therapeutic goods, that are considered to be complementary medicines include fish oils, shark cartilage and krill oil.

Essences (flower, shell, gem/crystal)

Essences (for example: flower, shell, gem/crystal) are not generally regulated as medicines in Australia, unless they have therapeutic indications.

Unless exempt goods, any product for which therapeutic indications are made by the sponsor must be entered on the ARTG before it can be legally imported, exported, manufactured or supplied for use in Australia.

Types of ingredients in listed and registered complementary medicines

Active ingredients in complementary medicines

The definition of an active ingredient is included in Regulation 2 of the Regulations:

> **'active ingredient'**, for a medicine, means a therapeutically active component in the medicine's final formulation that is responsible for its physiological or pharmacological action.

Excipient ingredients in complementary medicines

An excipient ingredient is not therapeutically active and does not contribute to the physiological or pharmacological action within the medicine's final formulation. Types of excipient ingredients include: a fragrance, flavour, preservative, printing ink, antioxidant, coating, binding agent, filler or an anticaking agent.

Sponsors of complementary medicines should ensure that the role of an excipient ingredient is appropriate and in an appropriate quantity for this purpose within the product formulation. Indications cannot be made for excipient ingredients.

Colourings permitted for use in complementary medicines

Colours used in oral products must be approved for such use—refer to 'Colourings used in medicines for topical and oral use'.

Incidental minor excipients in complementary medicines

Incidental minor excipients (IME) are substances that are added to certain raw material ingredients during the manufacture of that ingredient, for the purpose of increasing its stability, extending shelf-life or improving physical properties. IME are themselves substances that are approved for use in listed medicines and are present in the raw material at levels such that their concentration in the finished medicine is insignificant.

Note: an ingredient that is subject to any restriction or is required to be declared cannot be considered as an incidental minor excipient.

The TGA currently recognise specific instances where an IME included in the raw material may vary, for example:

- minor changes required to the type of anti-oxidant used in the manufacture of different batches of some oil raw material ingredients, such as fish oil
- the possible presence of silicon dioxide when used as an anti-caking agent in some ingredients.

In the above cases, the anti-oxidant or silicon dioxide ingredients are considered to be IME and applicants are not required to disclose details of these substances (used in the manufacture of an ingredient) in the listing application (for a medicine whose formulation includes that ingredient).

We will give consideration to recognising other IMEs, if suitable justification is provided. Please contact complementary.medicines@health.gov.au for such enquiries.

Proprietary ingredients in complementary medicines

Proprietary ingredients are entered into the TGA Business System (TBS) by the TGA, using details submitted by the supplier of the ingredient or by a medicine sponsor (on behalf of the supplier) using the Notification of a new proprietary ingredient form. This allows for the capture of complex formulation details and other relevant information, and the provision of a unique name and number. Sponsors may select proprietary ingredients using the assigned ingredient ID number for use in their application for a listed or registered medicine.

Proprietary ingredients may be excipient formulations or active pre-mixes. Proprietary ingredients consisting of excipient formulations include fragrances, flavours, colouring ingredients, trans-dermal patch adhesives and printing inks.

Active pre-mix proprietary ingredients can contain only one active ingredient to be included in listed medicines via the TGA Business Services system.

For any proprietary ingredient to be eligible for inclusion in a listed complementary medicine, all ingredients included in the proprietary ingredient's formulation must be permitted for use in listed medicines. Information about the eligibility of ingredients for use in listed medicines can be found in the Therapeutic Goods (Permissible Ingredients) Determination. The colourings contained in proprietary ingredients used in listed medicines are required to be only colourings used in medicines for topical and oral use.

The following limits apply to the concentration allowed in listed medicines for proprietary ingredients that are flavours, fragrances and inks:

- Flavours 5%
- Fragrances 1%
- Inks 0.1%

If an ingredient in the proprietary ingredient formulation is not permitted for use in listed medicines the ingredient must be evaluated, either as a new substance for use in listed medicines (see ARGCM Part C) or its safety must be established as part of the evaluation process for a registered medicine.

The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, and for its function and proportion in the finished product. For an active pre-mix, specifications must include tests for the identification and content of the active ingredient and impurity tests.

For further information on proprietary ingredients, refer to the Notification of a new proprietary ingredient page on the TGA website.

Proprietary ingredient commercially confidential information

Certain information supplied in relation to the inclusion of proprietary ingredients in TBS is treated as commercially confidential information. Commercially confidential information provided to us will be treated as follows:

- For treatment of sensitive information generally refer to: Treatment of information provided to the TGA.
- For commercially confidential information refer to: TGA approach to disclosure of commercially confidential information.

Labelling associated with proprietary ingredients in complementary medicines

If the label of a medicine that includes a proprietary ingredient includes a negative disclosure statement (for example: 'sugar free'), sponsors must ensure that the substance referred to in the negative disclosure statement is not contained in any proprietary ingredient in the product formulation. The onus is on the sponsor to obtain this assurance from the supplier.

Sponsors must also ensure that their medicine label complies with all the requirements of the Therapeutic Goods labelling Order as current and in force, including the declaration of excipient ingredients that must be declared on the medicine label.

Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92) commenced on 31 August 2016 and has a 4 year transition period. During this time, complementary (non-prescription) medicines must comply with either TGO 92 or Therapeutic Goods Order No. 69. General requirements for labels for medicines (TGO 69). Sponsors must specify which order they are compliant with. On and from 1 September 2020, these medicines must comply with TGO 92.

Good manufacturing requirements for proprietary ingredients

Australian manufacturers who are involved in the manufacture of active ingredients, mixtures containing active ingredients and any other step taken to bring therapeutic goods to their final state (for example: intermediate manufacturing steps, testing, packaging/labelling and release for supply) are required to have a licence under Part 3-3 of the Act, unless specifically exempted.

Where a proprietary ingredient comprises multiple active ingredients or 'excipient plus active' ingredient formulations, manufacture of the proprietary ingredient may be considered a significant step in the manufacture of the finished product and evidence of licensing or approval of the manufacturer may be required.

However, where a proprietary ingredient is used in an excipient role within the medicine (for example: colours, printing inks, flavours, fragrances, and preservatives) evidence of Good Manufacturing Practice (GMP) is not required.

Active Herbal Extracts

An 'Active Herbal Extract' is a herbal extract or concentrate for which a supplier intends specific information on the extraction method, steps and/or solvent details, to remain confidential from sponsors who include the extract as an active ingredient in a medicine. The formulation can contain only one active herbal ingredient, but may also contain excipient ingredient(s). To be a permitted ingredient in listed medicines, the active ingredient must comply with the definition of a herbal substance (as defined in Regulation 2 of the Regulations).

For more information refer to the Guide to the completion of the 'Notification of selective non-disclosure of Active Herbal Extract details' form and the Notification of selective non-disclosure of Active Herbal Extract details form.

In relation to Good Manufacturing Practice requirements for Active Herbal Extracts see Good manufacturing practice requirements for proprietary ingredients.

Amino acid chelates

The TGA defines a metal amino acid chelate as a complex consisting of a metal ion with one or more proteinogenic amino acid ligands bound to it in such a way that the metal ion is part of a ring within the molecule.

Currently a number of metal amino acid chelates are included in the Permissible Ingredients Determination and are therefore eligible for inclusion in medicines listed on the ARTG. We have determined a number of specific names for these ingredients to enable sponsors to identify ingredients accurately—refer to new ingredient names for metal amino acid chelates.

Ingredients in listed complementary medicines

Listed medicines may only contain low risk (active and excipient) ingredients that are permitted for use in listed medicines—refer to Ingredients permitted for use in listed complementary medicines. When listing a medicine the sponsor must certify that all ingredients in their medicine are eligible for listing.

Australian native and endangered species in complementary medicines

In Australia, the export and import of wildlife, wildlife specimens and products made or derived from wildlife is regulated under the *Environment Protection and Biodiversity Conservation Act 1999* (the EPBC Act). This includes the movement of endangered species listed under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and of Australian native species.

For queries regarding the importation of restricted/endangered species and the general importation of plant material, please refer to the following authorities:

- Department of the Environment and Energy
- Department of Immigration and Border Protection
- Department of Agriculture and Water Resources

The TGA does not have the legislative power to reject listing or registration applications on the grounds that they contain a substance derived from a species that is subject to State or Australian Government environmental regulation. This may result in the situation where therapeutic goods that are listed or registered on the ARTG may be seized at Customs if they are exported or imported.

It is the responsibility of sponsors of therapeutic goods containing substances that are derived from Australian native or endangered species to be aware that controls on the trade of these goods may exist and comply with those requirements.

Genetically modified substances in complementary medicines

The nationally consistent legislative scheme for regulating gene technology comprises the Commonwealth *Gene Technology Act 2000*, the Gene Technology Regulations 2001 and corresponding State and Territory legislation—refer to the Office of the Gene Technology Regulator website. It is the responsibility of sponsors including genetically modified substances in their complementary medicine to ensure they comply with the provisions of all relevant legislation.

For applications for new complementary medicine substances and new registered complementary medicines, the applicant must advise us if the proposed substance is, or is obtained from, a genetically modified organism. We will assess the safety, quality and, where relevant, efficacy of the genetically modified organism or material in the same way as for any other new complementary medicine substance or new registered medicine.

Complementary medicine presentation

Section 3(1) of the Act provides the following definition:

> **'Presentation'** in relation to therapeutic goods, means the way in which the goods are presented for supply, and includes matters relating to the name of the goods, the labelling and packaging of the goods and any advertising or other informational material associated with the goods

Sponsors should be aware that the overall 'presentation' of a medicine includes such things as (but is not limited to):

- medicine name
- medicine label
- packaging
- promotional/advertising material
- graphics
- package inserts
- dosage form
- indications.

Complementary medicine labels

A product's 'label' includes the label attached to the container (for example: bottle, tube, sachet or blister pack) and the primary pack (for example: carton). Sponsors must ensure the product label and any printed information supplied with the medicine (for example: a package insert) complies with all relevant legislation before it can be supplied in Australia, including advertising requirements. Specific documents relating to medicine labelling requirements include:

- The Therapeutic goods labelling Order as current and in force Part 5-1 (Advertising and generic information) of the *Therapeutic Goods Act 1989*
- The Therapeutic Goods Advertising Code
- The Therapeutic Goods Regulations 1990
- The Therapeutic Goods (Permissible Ingredients) Determination
- The Medicines Advisory Statements Specification 2016
- The Poisons Standard (the SUSMP) (note: Australian states and territories vary in the way they adopt the Poisons Standard)
- The TGA approved terminology for medicines

Complementary medicines must also comply with any standard and specific conditions applying to registered or listed therapeutic goods under Section 28 of the Act.

Medicine labels for listed medicines are not submitted at the time of listing and are therefore not approved by the TGA. However, listed medicine labels may be reviewed as part of random and targeted compliance reviews—see Compliance reviews of listed complementary medicines.

Medicine labels for registered complementary medicines are evaluated. In evaluating a new registered complementary medicine (and in a listing compliance review of listed complementary medicines) all aspects of the medicine presentation, including proposed labelling and package

inserts, are assessed for compliance with the various legislative requirements (including advertising requirements). This is to ensure clarity is provided for consumers in relation to the medicine and its proposed use.

In relation to medicine labels, sponsors should also note the following:

- Graphics, logos and symbols: Non-corporate graphics, logos or symbols on labels should be consistent with the product's approved details, including being appropriate for the claimed therapeutic use of the product. For example: an illustration of a baby would be inappropriate for a product with a dose range starting at 2 years.
- Statements of comparative advertising, professional recommendations, endorsements, sponsorship must all be compliant with the Therapeutic Goods Advertising Code.
- Reference to other products: Reference in labelling to a sponsor's other products may be permitted, provided that the products are included on the ARTG (or exempt).
- Negative disclosure statements such as 'gluten free' or 'sugar free' must be true of all ingredients in the medicine, including proprietary ingredients. The statement 'sugar free' is acceptable where no sugars (such as fructose or sucrose) are included.
- Internet addresses: The inclusion of internet addresses on labelling is only acceptable where the information on the website (including any direct links from that website) is consistent with the information included in the ARTG for that product. Websites are considered advertising and are subject to the Therapeutic Goods Advertising Code.
- Label flashes: As a general guideline, label flashes such as 'New Formulation' or 'Now with …' should not be used to describe any product, presentation or therapeutic indication/claim which has been available and promoted in Australia for more than 12 months.
- Excipient ingredients on medicine labels: An excipient ingredient need not be nominated on a medicine label, unless it is a restricted ingredient, for example: included in the Poisons Standard; or included in the First schedule of Therapeutic Goods Labelling order, as current and in force (which lists excipient ingredients required to be mandatorily declared on medicine labels). Where a sponsor chooses to disclose a (non-mandatory) excipient on a medicine label, then all excipients must be disclosed, that is: declaration of excipients on a medicine label cannot be selective.
- Products that are supplied in Australia and also exported to another country may include international product registration numbers (in addition to the ARTG number) required by the importing country.

Advertising of complementary medicines

The objective of the regulation of therapeutic goods advertising in Australia is to ensure that the marketing and advertising of therapeutic goods, including complementary medicines, is conducted in a manner that promotes the quality and safe use of the product, is socially responsible and does not mislead or deceive the consumer.

Advertisements for complementary medicines are regulated by both co-regulatory and self-regulatory arrangements under the Act and Regulations, and involve the TGA, the Therapeutic Goods Advertising Code Council (TGACC), the Australian Self-Medication Industry (ASMI) and the Complementary Medicines Australia (CMA).

To ensure that the standards developed for the public benefit are met, advertisements for complementary medicines directed at consumers on specified media require prior approval by a Delegate of the Secretary of the Department of Health.

Australian based websites promoting use or supply of therapeutic products are considered advertising and must comply with all aspects of the Therapeutic Goods Advertising Code.

Refer to the TGACC website for further information on advertising for therapeutic goods, including details of the approval process for advertisements, the Complaints Resolution Panel and the Complaints Register.

Prohibited and restricted representations in advertising for complementary medicines

An advertisement for a complementary medicine (including information on the label and in the package of the medicine) must not contain, expressly or by implication, a prohibited representation specified in Part 1 of Appendix 6 of the Therapeutic Goods Advertising Code.

In addition, an advertisement for a complementary medicine must not refer, expressly or by implication, to a restricted representation specified in Part 2 of Appendix 6 of the Therapeutic Goods Advertising Code, unless prior approval is given under the Act. A restricted representation is any reference expressly or by implication, to a serious disease, condition, ailment or defect which is generally accepted to be:

- not appropriate to be diagnosed and/or treated without consulting a suitably qualified health professional and/or
- beyond the ability of the average consumer to evaluate accurately and to treat safely without regular supervision by a qualified health professional.

If you, as the sponsor of a complementary medicine, wish to advertise a restricted representation, including on the label of your medicine, you must obtain prior approval from the Secretary under Section 42DE of the Act. The application must be in writing and you must provide justification why the representation is necessary for the appropriate use of your medicine. In making a decision on your application, the Delegate for the Secretary will take into consideration matters specified under Section 42DF of the Act, including any recommendations from the TGACC and any advice from TGA advisory committees.

Notices of approved and permitted restricted representations are published on the TGA website.

Complementary medicines presented as composite packs or kits

Some medicines are put together and presented as a kit or composite pack. The definitions of these as per 7B of the Act are provided below:

(1) A package and therapeutic goods in the package together constitute a kit for the purposes of this Act if:
- (a) the package and the therapeutic goods are for use as a unit
- (b) each item of the therapeutic goods consists of goods that are registered or listed, are exempt goods in relation to Part 3 2, are included in the Register under Part 3 2A or are exempt under subsection 32CA(2) or section 32CB
- (c) the package and therapeutic goods do not constitute a composite pack or a system or procedure pack.

(2) A package and therapeutic goods in the package together constitute a composite pack if:
- (a) the therapeutic goods are of 2 or more kinds
- (b) the package does not contain any medical devices or therapeutic devices
- (c) the therapeutic goods are for administration as a single treatment or as a single course of treatment
- (d) it is necessary that the therapeutic goods be combined before administration or that they be administered in a particular sequence.

(3) To avoid doubt, it is declared that a kit constitutes therapeutic goods.

Medicines presented as kits

Kits are where two or more (listed, registered or exempt) goods are supplied in a single package, usually share a common therapeutic use and are intended for use as a unit. However, the individual goods can be used independently and do not need to be combined or administered in a sequence for the product's therapeutic purpose, for example: a sunscreen lotion and lip balm presented in a single package or a first aid kit.

Individual therapeutic goods in a kit must be listed (or registered) on the ARTG separately (unless the individual good in question is exempt from this requirement) and the packaged kit must also be listed on the ARTG and have its own AUST L number. As the components of a kit are already on the ARTG with a separate AUST L or AUST R, they are also regulated individually. Where a kit contains a device and a medicine (for example: hair lice kits with a comb) it is regulated as a device.

Medicines presented as composite packs

In a composite pack it is necessary for the therapeutic goods to be combined or used in a particular sequence, for a single treatment or course of treatment.

An example of this sort of product is 'night and day cold medication', which consists of tablets that are required to be taken in a particular order. A composite pack is required to be listed (or registered) on the ARTG, but the individual components do not require individual listing or (registering) on the ARTG. The primary pack must comply with all of the labelling requirements for containers/primary packs in the Therapeutic goods labelling Order as current and in force.

Complementary medicines for export

Refer to Exporting medicines from Australia for commercial supply for information relating to the export of medicines from Australia.

Generally, any complementary medicine exported for commercial purposes is either:

- intended for supply in Australia as well as overseas; or
- intended exclusively for export.

Complementary medicines intended for supply in Australia as well as overseas

Complementary medicines that are:

- registered or listed (under the provisions of section 26A of the act); or
- exempt from the requirement to be on the ARTG; and
- are supplied in Australia

can automatically be exported by the sponsor or their agent, providing other applicable export legislation is complied with, for example: State poisons legislation, legislation covering trademarks, patents, wildlife protection, customs and quarantine.

Complementary medicines intended exclusively for export

Medicines solely for the purpose of export are required to be listed (not registered) on the ARTG before export is commenced. These products can be listed under section 26 of the Act (referred to as Export-only products) or under section 26A of the Act (referred to as Solely for Export products). Both type of products are exclusively for export purpose and cannot be supplied within Australia including Duty Free outlets.

Sponsors of medicines intended exclusively for export are required to submit an application using the Export Electronic Lodgement (EEL) System which is part of the TGA Business Services.

Purchasing complementary medicines over the internet

Products available on international websites are not regulated by the TGA. We advise consumers not to order medicines, including dietary supplements and herbal preparations, over the Internet unless the consumer knows exactly what is in the preparation and has checked the legal requirements for importation and use in Australia. For more information refer to: Buying medicines and medical devices over the internet.

Complementary medicine interface issues

It is recognised that there can be a regulatory 'interface', or potential overlap, between certain foods, medicines, devices and cosmetics. Some examples are described below.

Complementary medicine/device interface

The Australian medical devices guidelines: 35. Device-medicine boundary products assists sponsors in determining the status of therapeutic goods that are not readily identified as medicines or devices, for example: a medicine impregnated dressing or barrier protectants.

Cosmetic/medicine interface

Most cosmetic products are generally not considered therapeutic goods, as they tend not to be for a therapeutic use. Such goods are not regulated by the TGA. However, a cosmetic may be a therapeutic good (medicine), depending on its ingredients, route of administration and if therapeutic claims are made on the product label or in advertising. In addition:

- Order that Goods are Therapeutic Goods No 2 of 1999 made under section 7 of the Act (see below) declares that products labelled or promoted for cosmetic purposes when promoted for oral consumption are, for the purposes of the Act, therapeutic goods
- Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 made under section 7 of the Act (see below) declares a number of products that are covered by the Cosmetics Standard 2007 made under the *Industrial Chemicals (Notification and Assessment) Act 1989* not to be therapeutic goods.

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) regulates cosmetic products under the Industrial Chemicals (Notification and Assessment) Act. That Act underpins the Cosmetics Standard 2007 and this Standard is supported by the NICNAS Cosmetic Guidelines 2007. Further information on the regulation of cosmetics is available from NICNAS.

Claims on cosmetic labels are regulated by the Australian Competition and Consumer Commission.

Food/complementary medicine interface

While products that are classed as therapeutic goods (including medicines) are regulated by the TGA at the federal level, foods (including many that make health claims) are predominantly regulated by state and territory food regulatory bodies. Food Standards Australia New Zealand (FSANZ) is the Commonwealth statutory authority responsible for developing food standards which make up the Australia New Zealand Food Standards Code (the Food Standards Code). The Food Standards Code is enforced by the states and territories which regulate the sale and supply of food within their respective jurisdictions. The importation of food is regulated by the Commonwealth Department of Agriculture under the *Imported Food Control Act 1992*.

The TGA's Food-Medicine Interface Guidance Tool can be used to work out whether particular products are likely to be therapeutic goods or not. It is designed to take the user though the relevant definitions in the Act.

Further information can be found on the TGA website at Food and medicine regulation.

Declarations made under section 7 of the Act

Section 7 of the Act enables the Secretary of the Department of Health (through the TGA) to declare that particular goods or classes of goods are therapeutic goods where satisfied they are therapeutic goods. The Secretary can also declare that particular goods or classes of goods are not therapeutic goods where satisfied they are not therapeutic goods.

When making a declaration that particular goods or classes of goods are therapeutic goods, the Secretary can disregard the fact that the goods are:

- goods for which there is a standard under the *Food Standards Australia New Zealand Act 1991*; or
- goods which, in Australia or New Zealand have a tradition of use as foods for humans in the form in which they are presented.

The following orders have been made under section 7 of the Act:

- Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 declares certain goods not to be therapeutic goods.
- Orders that Goods are Therapeutic Goods, including Order that Goods are Therapeutic Goods No. 1 of 2009 and Order that Goods are Therapeutic Goods Nos. 1, 2, 3 and 4 of 1999 and Order that Goods are Therapeutic Goods No. 1 of 1998, which declare that particular goods are therapeutic goods.

Determinations made under section 7AA of the Act

The Minister for Health is able, by making a determination under section 7AA of the Act, to exclude goods from regulation under the Act. The Minister, before making a determination will consider the following matters:

- whether it is likely that the goods might harm the health of members of the public if they were not regulated under the Act
- whether it is appropriate in all circumstances to apply the national system of controls relating to the quality, safety, efficacy and performance of therapeutic goods established by the Act to regulate the goods
- whether any risks to which the public might be exposed from the goods could be more appropriately managed under another regulatory scheme.

Any determination by the Minister excluding goods will be preceded by consultation with affected industry and other stakeholders and will be disallowable by the Parliament.

Removal of products from the ARTG if not therapeutic goods

The Secretary of the Australian Government Department of Health (through the TGA) can, under section 9F of the Act, remove a product from the ARTG if satisfied that the goods are not 'therapeutic goods' as defined in the Act. The sponsor of the product will be notified of the proposed action and any submissions made by the sponsor will be considered before the product is removed from the ARTG. Particulars of a decision to remove a product from the ARTG will be published on our website. Refer to Food and Medicine Regulation on our website for more information.

A decision to remove the goods from the ARTG is an initial decision within the meaning of section 60 of the Act and sponsors may seek reconsideration by the Minister. Refer to Mechanism for review of decisions made under the Act.

Changes to complementary medicines

Following the inclusion of a medicine on the ARTG, a sponsor may wish to change certain details held by the TGA for that medicine.

For Changes that result in 'separate and distinct' goods you are required to submit a new medicine application and a new ARTG number (AUST L or R) will be issued. However, where eligible, the new medicine will be 'grouped' under the ARTG entry of the existing medicine and assigned the same ARTG number—see the Therapeutic Goods (Groups) Order.

For other medicine changes, there are provisions in the legislation for certain variations to be made to a medicine's existing ARTG entry—refer to Variations to complementary medicines permitted under section 9D of the Act.

Please be aware that legislation is subject to change and should always be referred to for the most up to date regulatory requirements.

Changes to complementary medicines that result in 'separate and distinct' goods

Where the proposed change to the medicine will result in goods that are considered 'separate and distinct' from the existing goods, sponsors are required to submit an application for a new medicine. In certain circumstances, the new medicine may meet the criteria for grouping under the existing medicine ARTG entry.

For listed complementary medicines

Section 16 (1A) of the Act outlines those criteria which make medicines that are listed goods (other than export only medicines) separate and distinct from the existing goods:

(a) different active ingredients; or
(b) different quantities of active ingredients; or
(c) different dosage form; or
(d) such other different characteristics as the regulations prescribe;

Currently, Regulation 11 of the Regulations prescribes that different characteristics are:

(a) a different name; or
(b) different indications; or
(c) a different excipient; or
(d) for medicines that contain any restricted ingredients:
  (i) a different quantity of a restricted ingredient that is an excipient; or
  (ii) if the restriction on a restricted ingredient relates to its concentration in a relevant medicine – a different concentration of the restricted ingredient; or
  (iii) if the restriction on a restricted ingredient relates to its quantity in the recommended single or daily dose in a relevant medicine – different directions for use setting out a different recommended single or daily dose.

For registered complementary medicines

Section 16(1) of the *Therapeutic Goods Act 1989* (the Act) outlines those criteria which make registered medicines separate and distinct from the existing goods:

(a) a different formulation, composition or design specification; or
(b) a different strength or size (disregarding pack size); or
(c) a different dosage form or model; or
(d) a different name; or

(e) different indications; or
(f) different directions for use; or
(g) a different type of container (disregarding container size).

The Therapeutic Goods (Groups) Order

Therapeutic Goods (Groups) Order No. 1 of 2001 (Groups Order) provides the circumstances in which a 'separate and distinct' medicine can be 'grouped' under the ARTG entry of the existing medicine and assigned the same AUST R or AUST L number.

A grouping is appropriate when the goods are intended to replace the currently supplied goods, enabling the transition of one product to another. However, individual products within the group remain separate and distinct products under sections 16(1) and (1A) of the Act.

Process for applying for a new listed medicine that may meet the criteria for a gazetted therapeutic goods group

All changes to existing listed medicines (other than those listed for export only) are made via the online listed medicine application and submission portal which is part of the TGA's Business Services framework. When a change to a product record is made that will result in a separate and distinct good, the application portal will, upon validation, recognise if the type of change meets the criteria for grouping.

Process for applying for a new registered medicine that may meet the criteria for a gazetted therapeutic goods group

If you consider that the proposed change to your registered complementary medicine would meet the criteria allowing grouping of different registrable therapeutic goods in the same group by using a Groups Order, you can submit a registered medicine application—grouped medicines (complementary medicines). If approved by the Delegate, the new medicine is 'grouped' in the ARTG under the same AUST R number. Should the application be refused, a rejection letter containing reasons for the decision and details of procedures for review of the decision will be provided to you.

Variations to complementary medicines permitted under section 9D of the Act

Section 9D (1), (2) and (3) of the Act provides the circumstances under which a sponsor may request an amendment to the ARTG entry for their listed or registered medicine. Briefly, the provisions under section 9D include:

- section 9D(1) provides for correction of an ARTG entry of a medicine that is incomplete or incorrect
- section 9D(2) provides for making certain safety-related variations to an ARTG entry of a medicine. A variation is safety-related if it reduces the patient population (such as by removing an indication), or has the effect of adding a warning or precaution (such as an adverse effect or interaction)
- section 9D(3) provides for other variations to an ARTG entry of a medicine to be made, provided that the Delegate of the Secretary is satisfied that the change does not reduce the quality, safety or efficacy of the medicine.

Applications to change listed medicines

Sponsors make changes to listed medicines via the online listed medicine application. Refer to the Listed medicines application and submission user guide for more information. For information on the changes that can be made to listed complementary medicines and whether they will incur a fee, refer to the document Guidance on product changes in ELF 3.

There is a provision in the application and submission portal to request the same change to be made across a number of currently listed medicines. Each medicine change will incur any applicable fees.

Applications for changes to registered complementary medicines

All applications for changes to registered complementary medicines attract a processing fee. For certain applications a separate evaluation fee is also payable. Information on current fees is available on our website. Regulation 45 provides for the waiver or reduction of evaluation fees under certain circumstances.

It is a standard condition of registration that sponsors are required to notify the TGA of any changes in the information previously provided in relation to their therapeutic good. However, in specific circumstances some minor changes are not required to be notified, for example: additional analytical tests or tightening of product specifications. Changes tables for registered complementary medicines provides the possible changes to registered complementary medicines, applicable fees and the type of assurances or data required to support the application.

Chart A1 provides an overview of avenues for changing information for registered complementary medicines. This diagram is provided as general guidance and is not comprehensive. You should contact us when specific guidance relating to possible changes to your medicine is required.

Chart A1: Changing information for registered complementary medicines

Is the proposed change to your medicine:

a. a different formulation, composition or design specification; or
b. a different strength or size (disregarding pack size); or
c. a different dosage form or model; or
d. a different name; or
e. different indications;* or
f. different directions for use; or
g. a different type of container (disregarding container size)?

*Note: If the proposed change to the medicine indication is only to reduce the patient population, a variation application under section 9D(2) of the Act may be possible. Contact the TGA.

No

Is the change of a type specified in section 9D of the Act? That is:

- 9D(1): A variation of the information in the ARTG entry that is incomplete or incorrect?
- 9D(2): A safety-related variation whereby it reduces the patient population or has the effect of adding a warning or precaution?
- 9D(3): another variation to an ARTG entry of a medicine that does not reduce the quality, safety or efficacy?

Yes

You can submit a 9D variation to the TGA for consideration.

No

Contact TGA for advice on requirements for the proposed change.

Yes

The medicine is considered a 'separate and distinct' good [as per Section 16(1) and of the Act].

You are required to submit an application for a NEW medicine.

The TGA will determine if the Groups Order is applicable.

That is, if the new medicine intended to replace the existing medicine in use (or registered in place of the existing medicine) and the proposed change involves:

- a change in the quantity of an ingredient that is not an active ingredient; or
- the removal or addition of an ingredient that is used only for the purpose of fragrance, flavouring, printing ink or colouring; or
- different indications for use and/or different directions for use; or
- a different name.

If yes

The new medicine will be grouped under the ARTG entry for the existing medicine and assigned the same AUST R number.

If no

New medicine with new AUST R number.

Process for applying for a variation to a registered complementary medicine under section 9D of the Act

Sponsors can apply for variation of a medicine using the Registered medicine variation form (complementary medicines). For most applications you will need to submit supporting documentation with the variation application form, for example: if you wish to change details of the label, you will need to send a copy of the present label and a proposed label. In some instances, certain assurances about the change will also need to be made before the application can proceed—refer to the Changes for registered complementary medicines.

Some changes affect other aspects of the medicine, which may require further clarification from the sponsor, for example: a manufacturing process change may also require change to finished product specifications. You can minimise the potential for delays by ensuring the medicine complies with all current legislative requirements.

If approved, the change to the ARTG entry is made by the TGA and the AUST R number is retained. Should the application be refused, a rejection letter containing reasons for the decision and details of procedures for review of the decision will be provided.

Where the same change is made across a number of products an individual application form is required for each product entry sought to be varied. Applicable fees are required to be paid for each product varied.

Changing information in the ARTG for 'grandfathered' products

'Grandfathered products' are those products that were available in Australia prior to the Act coming into effect in 1990. If a sponsor of a 'grandfathered' medicine wants to change information in the ARTG for their medicine, the same rules apply as for other medicines.

TGA post market regulatory activity of complementary medicines

We monitor the continuing safety, quality and efficacy of therapeutic goods in the market through therapeutic product vigilance activities. We adopt a risk management approach to regulating therapeutic goods. Information on our approach to managing compliance risk is available at: TGA regulatory framework.

The types of post market regulatory activities include the following.

Adverse events reporting for complementary medicines

We receive reports of adverse events from consumers, health professionals, the pharmaceutical industry, international medicines regulators or by medical and scientific experts on TGA advisory committees.

If you experience an adverse event to a complementary medicine, you should seek advice from a health professional and then report the adverse event to the TGA.

Section 29A of the Act requires sponsors of medicines registered or listed in ARTG to report adverse reactions about which they become aware. Guidance for sponsors is provided in Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines.

Inspection of manufacturers

Manufacturers of therapeutic goods supplied in Australia are subject to regular inspections for compliance with good manufacturing practice. Details of the requirements for the manufacture of medicines are specified in the PIC/S Guide for Good Manufacturing Practice for Medicinal Products. For more information regarding the GMP inspection of medicine manufacturers please refer to Manufacturer inspections - an overview.

Sampling of medicines in the marketplace for testing

We undertake a laboratory testing program which complements the desk-based compliance reviews of listed complementary medicines and evaluation of registered medicines, as well as other post market regulatory activities. The laboratory testing program prioritises therapeutic goods considered to carry a higher risk, while still allowing for responsive testing for issues arising in the marketplace, for example: adverse events and complaints about specific medicines. For more information on the laboratory testing program, refer to the Laboratories Branch activities.

Compliance reviews of listed complementary medicines

The regulatory process for listed complementary medicines allows for early market access for low-risk complementary medicines. In facilitating early market access, there is reliance on a comprehensive risk-based system of post market monitoring. We review a proportion of listed complementary medicines for compliance with the regulatory requirements. These reviews may be:

- random reviews: a proportion of newly listed medicines are randomly selected by computer; or
- targeted reviews of listed medicines identified with potential non-compliance issues.

For more information on the random and targeted compliance reviews, including possible regulatory actions and appeal rights, refer to Listed complementary medicine compliance reviews.

Cancellations from the ARTG following compliance review are routinely published on our website.

Further to the product compliance reviews described above, specific safety and efficacy reviews in response to issues arising in the market place may be carried out for:

- ingredients
- individual medicines
- medicine groups.

Product recalls of therapeutic goods

A product recall is the removal of therapeutic goods from supply on the Australian market for reasons relating to their quality, efficacy or safety. Recall of any distributed goods is required whenever public safety is at risk as a result of product noncompliance. A recall can occur because of problems such as: labelling or packaging errors; contamination issues; or an increase in unexpected side effects. Further information on recalls of therapeutic goods is provided on our website: About recall actions.

Literature-based submissions for complementary medicines

Literature-based submissions

If you do not have your own supportive data, but have published scientific literature you consider to be supportive of an application, you may opt for a literature-based submission (LBS).

Examples where this may be appropriate include the following types of applications:

- changes to indications or label claims
- changes to directions for use
- changes to clinical or non-clinical aspects of the Product Information
- new medicine applications (less common)

Mixed applications (part LBS, part complete study reports) may also be appropriate.

Requirements for literature-based submissions

Our complementary medicine requirements for literature based submissions are essentially the same as for prescription medicines except that:

- You do not need to consult or gain approval of LBS search strategies prior to submitting your application.
- We do not have a formal pre-submission phase for applications.

You will need to conduct a systematic literature search for most literature based submissions, including those in support of new indications or label claims.

For further guidance on when an LBS may be suitable and what type of LBS to prepare, refer to the Pre-submission guidance for literature based submissions.

Conducting the literature search

There is no single search strategy that can be applied in all cases. Whatever methodology you use, ensure that you:

- clearly explain and justify that methodology in the application
- include full details of the search methodology used to obtain the data supporting the application

There may be instances (i.e. literature on traditional preparations) where literature based on a non-systematic review of the literature as outlined in Literature based submissions not based on a systematic search of the literature are appropriate. However, justification for providing this type of review rather than a systematic review of the literature is required.

Scope of the literature search

Chemical identification and constituents

- Identify as many descriptors as possible for the substance and use them when you retrieve relevant literature for both traditional use and scientific evidence. Ensure you include generic names (where relevant) and trade names, traditional names, botanical terminology and Chemical Abstracts Service (CAS) registry numbers
- For botanicals, or substances where there may be multiple constituents, search the terms for the constituents (e.g. in the case of *Zingiber officinale*, search terms such as zingiber, ginger, zingerols, and zingiberenes)
- Where several different terms are used (either for substances or constituents), there should be clear evidence of where terms refer to the same entity (e.g. *shosaikoto* (Japanese) is *xiao chai hu tang* (Chinese Pin Yin), and both are called '*Minor bupleurum decoction*' in the Chinese literature). Similarly, there should be evidence of chemical identity (e.g. CAS registry numbers should be consistent across different records)
- Include details of where and how you established the terminology (this search is non-systematic)

Literature on traditional use

Where possible provide evidence from both databases and print sources. This type of search is usually a non-systematic search as it is does not need to be based on an extensive search of all the literature. Sources for such literature include:

- pharmacopoeias (which may be national or international)
- current and/or classical references in the specific field under review (e.g. herbal or homoeopathic pharmacopoeias or Materia medica)
- standard works on the ethnobotany, or use of medicinal plants in a geographic area
- databases of biological literature (such as BIOSIS or CAB Abstracts)

Include details of where and how you sourced the evidence. Ensure you include a summary of the references retrieved, ideally in a table format with full bibliographic citations. Provide full copies of the references.

Further considerations for using traditional evidence

Traditional evidence may be used to support an application for a registered complementary medicine when there is a clear history of use as a medicinal or food substance. Usually a traditional substance with a well-established[2] history of use will have information published in official pharmacopoeias and other published literature. It is essential that this literature demonstrates:

- traditional indications are based on evidence of a history of medicinal use that meets or exceeds three generations (75 years) of use
- that the proposed medicine is consistent with the traditional preparation and the traditional use (including dose, route of administration and duration of use)
- the population and culture in which this tradition occurred must be identified

[2] Well established use means that a sufficient number of people were treated or exposed to the medicine or food over a period sufficient to support the safety or efficacy for its intended purpose.

- in some cases, evidence of traditional use, for examples: aboriginal bush remedies, would require robust anthropological research data due to limited published/documented data

It can be difficult to establish the safety and/or efficacy of a RCM based solely on traditional and anecdotal evidence However, it may be used in combination with study reports or additional literature. If your application is to rely on traditional use to support safety or efficacy please arrange a pre-submission meeting to discuss the suitability of the evidence.

NOTE: Modern extraction methods or other processes may produce, in some cases, substances that have a considerably different compositional profile from those produced using traditional methodology. For examples: modern highly concentrated *Acetea racemosa* (black cohosh) herbal extracts have been linked with serious adverse reactions that have not been reported from traditional extracts. In some instances, the extraction of a substance from its natural matrix may make it more prone to oxidation to a toxic product or to inactivation, for example: carotenoids or resveratrol.

Mechanism for review of decisions made under the Act

Section 60 reviews

Initial decisions made under a provision of the Act by the Secretary of the Department of Health, or a delegate of the Secretary, can be reviewed under section 60 of the Act. This means that if a person's interests are affected by the decision, they may seek reconsideration by the Minister. If a decision can be reviewed by the Minister, details of the appeal rights will usually accompany the decision. Appeals must be lodged within 90 days of decisions.

Examples of appealable decisions include:

- a refusal to register or list goods on the ARTG
- the variation or addition of conditions applying to a registration or listing
- suspension or cancellation of a registration or a listing
- revocation or suspension of a manufacturing licence.

An appeal letter should be clearly marked 'Request for reconsideration under section 60 of the *Therapeutic Goods Act 1989*' and sent to:

The Minister for Health
Parliament House
CANBERRA ACT 2600

The request should include supportive information for the Minister to consider. Under subsection 60(3A) of the Act, the Minister is not able to consider any information provided after the request is submitted. This is unless the additional information is provided in response to a request from the Minister or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable. Information provided in support of your request should include:

- a copy of the decision to be reconsidered
- a specific description and reasons why parts of the decision are believed to be incorrect or in relation to which you object
- describe how your interests are affected by the decision.

The Assistant Minister may either personally deal with the request or send it to be dealt with by one of the Minister's delegates within the Department.

The Administrative Appeals Tribunal (AAT)

If not satisfied with the outcome of a section 60 appeal, an application may be made to the Administrative Appeals Tribunal (AAT) for review. Applications to the AAT must be made within 28 calendar days of the Minister's decision regarding a section 60 appeal.

Federal Court

Whereas the AAT provides a merit review process, affected parties may appeal at any time to the Federal Court on the grounds of the legality of a decision.

ARGCM Part B: Listed complementary medicines

Overview of listed complementary medicines

Listed medicines are considered 'low risk' medicines. Most, but not all, complementary medicines are listed, rather than registered, on the Australian Register of Therapeutic Goods (ARTG) (however, note that not all listed medicines are complementary medicines, for example: sunscreens and 'export only' medicines are also listed medicines).

Regulation 10 of the Therapeutic Goods Regulations 1990 (the Regulations) provides the therapeutic goods that should be either listed or registered on the ARTG. In order for a complementary medicine to be eligible for listing on the ARTG, it needs to be of a kind mentioned in Schedule 4 to the Regulations.

On 1 January 2016 the TGA commenced a new legislative instrument under section 26BB of the Act which contains a list of ingredients permitted for use in listed medicines, the Permissible Ingredients Determination.

Medicines listed on the ARTG are assigned a unique AUST L number, which must be displayed on the medicine label.

Unlike registered medicines, we do not evaluate listed medicines prior to inclusion on the ARTG. The listing process allows for rapid market access for listed complementary medicines. Upon submission of a listing application, a sponsor legally certifies (under section 26A of the Act) that their medicine meets all applicable legislative requirements in relation to safety, quality and efficacy.

As listed medicines are not evaluated, we use a variety of mechanisms to assure the safety and quality of the ingredients used, as well as the resultant listed medicines. One of these mechanisms is that after listing on the ARTG, a proportion of listed medicines are reviewed for compliance with regulatory requirements.

In order for a complementary medicine to be listed on the ARTG it:

- may only contain low risk (active, excipient and homoeopathic preparation ingredients) ingredients permitted for use in listed medicines
- may only carry indications permitted for use in listed medicines
- must not be a prohibited import for the purposes of the *Customs Act 1901*
- must not be required to be sterile
- must comply with all legislative requirements in relation to quality, safety and efficacy.

Ingredients permitted for use in listed medicines

Listed complementary medicines may only contain low risk ingredients permitted for use in listed medicines as included in the Permissible Ingredients Determination. To be consistent with their low risk status, regulatory limits/requirements may be placed on the use of certain ingredients in listed medicines. These are specified in the Permissible Ingredient Determination.

The majority of ingredients that can be included in listed medicines are those that were included in therapeutic goods supplied in Australia before the Act came into operation in 1991. Since then, all new active and excipient ingredients have undergone a safety assessment by the TGA. If a person wishes to include an active or excipient ingredient that is not currently approved for

use in listed medicines, the substance must be evaluated by the TGA before such use is permitted.

Ingredients derived from animal materials may present a safety risk to consumers, as they may contain certain viruses and/or agents capable of carrying Transmissible Spongiform Encephalopathies (TSEs). Information on the TGA's approach to minimising the risks associated with ingredients of human or animal origin is available in Guidance 10: Adventitious agent safety of medicines. Pre-clearance of animal derived ingredients should be sought from TGA before making a medicine application—refer to Pre-clearance application for animal-derived ingredients).

The current regulatory system provides for listed medicines to contain a wide range of herbal substances provided that it can be adequately demonstrated that the herbal substance is safe. Addition guidance on herbal materials and herbal materials and extracts is provided on our website:

- Identification of herbal materials and extracts
- Equivalence of herbal extracts in complementary medicines
- Guidance on the use of modified unprocessed herbal materials in complementary medicines

TGA Business Services ingredient database

A searchable database of ingredients is accessible via the TGA Business Services website. Instructions on searching this database are provided below.

Searching for ingredients via the TGA Business Services website

Select 'Public TGA Information' from the left hand menu.

- From the dropdown menu select 'Ingredients'.
- Enter the ingredient name or synonym you are looking for in the 'search field' and ensure that in 'all fields' is selected. Click 'Go'.
- When looking at the search results, the right hand column will indicate if the ingredient is 'listable' (that is, if the ingredient is able to be included in listed medicines). The ingredient summary must be checked to determine in what context the ingredient is listable (Step 5).
- To the left of each ingredient is a down arrow icon. Click on this icon to reveal the 'Ingredient summary'. The 'Ingredient summary' provides the approved role of the ingredient (active or excipient).

Information on 'Product warnings', amongst other things, can be accessed via 'Code tables' under 'Public TGA Information' on the left hand menu.

This database will only provide the approved name or synonym for the ingredient. Sponsors must be aware of any ingredient restrictions, such as those in the Poisons Standard or in the Permissible Ingredients Determination. It is the sponsor's responsibility to ensure that all ingredient restrictions are met. For example; vitamin B6 above a certain dose is scheduled and therefore no longer listable.

Note that substances marked as components (C) are Herbal Component Names which are not approved as substances in their own right and only can be used in conjunction with an approved source. For example, iodine is not approved as a substance in its own right, but is permitted

when expressed as a component of *Fucus vesiculosus* (kelp), which is known to naturally contain iodine.

Some substances refer to edible substances fit for human consumption as a food and are permitted as excipients only (Approved Food Names), for example: apple, pear. Only certain preparations are permitted for most food excipients, such as: fresh dry or powdered plant material and fresh, dried or concentrated juices. Juice preparations may only be named where the fresh plant part has a high water content.

Indications permitted for use in listed complementary medicines

In relation to therapeutic goods, the definition of 'indications' is provided in section 3 of the *Therapeutic Goods Act 1989* (the Act) as: 'the specific therapeutic use/s of the goods'. 'Therapeutic use' is also defined in section 3 of the Act.

Indications must be included in the ARTG entry for a medicine. Statements or claims which do not convey a specific therapeutic use do not need to be included in the ARTG, for example: references to the properties of the product or the packaging, such as '25% more' or 'new formula'.

At the time of listing, applicants must certify that they hold evidence to support any indications as well as any other claims made for the medicine—refer to Requirements of section 26A of the Act).

When listing a complementary medicine on the ARTG via the electronic application portal (refer to Listed medicines application and submission user guide), sponsors are able to enter indications for their listed medicine by either selecting from a list of 'standard indications' or by entering their own specific indication using a 'free text' field. The standard indications are provided to sponsors as a convenience. Selecting an indication from the standard indications list does not absolve a sponsor from any obligations under the Act or related regulations.

As part of the Government's complementary medicine reforms, TGA is developing a list of permitted indications will be made as a legislative instrument and will be registered on the Federal Register of Legislation. The instrument will contain a comprehensive list of permitted indications that have been assessed as being compliant with the regulatory requirements. When the list of permitted indications is implemented in early 2018, sponsors will only be able to select indications for their medicine from the prescribed list. Sponsors will no longer be able to enter indications in a 'free text' field. Refer to Draft list of permitted indications for more information.

Schedule 4 to the Therapeutic Goods Regulations 1990 (the Regulations) states that for a medicine to be eligible for listing, the sponsor of the medicine cannot propose an indication that refers to the treatment of any of the diseases, conditions, ailments or defects specified in Appendix 6 Parts 1 or 2 of the Therapeutic Goods Advertising Code. Medicines with these indications must be registered, rather than listed, on the Australian Register of Therapeutic Goods.

It is a separate requirement that any advertising for complementary medicines (including advertising by way of inclusion of an indication on the label or packaging of a medicine) comply with the advertising requirements set out in Part 5-1 of the Act and the Therapeutic Goods Advertising Code—refer to Advertising requirements for complementary medicines.

Under these advertising requirements it is both an offence under the Act (see paragraph 42DL(1)(c)) and a breach of the Therapeutic Goods Advertising Code (see clause 5(2)) for a sponsor to refer to a 'serious form' of any disease, condition, ailment or defect listed in Part 2 of

Appendix 6 of the Therapeutic Goods Advertising Code without prior TGA approval. Such a reference is known as a restricted representation—refer to Prohibited and restricted representations in advertising for complementary medicines. An approval can be given either in response to an application by a sponsor or advertiser under section 42DF of the Act or generally under section 42DK of the Act.

For the removal of any doubt, these regulatory requirements apply notwithstanding that the advertising relates to an indication selected by the sponsor from the list of standard indications.

TGA is developing a comprehensive list of permitted indications for sponsors to be able select when entering their medicine on the ARTG.

Indications relating to vitamin and mineral supplementation

Vitamin or mineral supplementation indications are only permitted where the recommended daily dose of the product provides at least 25% of the Australian Recommended Dietary Intake (RDI) for that vitamin or mineral. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Indications should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level. The dose must be consistent with the evidence to support the indication being made.

Listed medicines legislative requirements

This guidance is provided for applicants and sponsors of listed medicines.

Requirements of section 26A of the Act

A medicine is listed on the ARTG on the basis of information provided by the applicant and a certification by the applicant that the goods (that are the subject of the application) meet the requirements of section 26A(2) (a)–(k) inclusive, and if applicable, subsection 26A(3) of the Act. The Act allows for cancellation of a product from the ARTG if the goods are ineligible for listing and a sponsor's certification is incorrect.

Clarification on the requirements of section 26A of the Act is provided below.

The medicine is eligible for listing

Schedule 4 provides conditions that must be met for medicines to be eligible for listing for example:

- the medicine only contains ingredients and complies with the requirements specified in the Permissible Ingredients Determination
- the proposed indications are not for the treatment of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 to the Therapeutic Goods Advertising Code; and
- ingredients must not be subject to a Schedule of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) also known as the Poisons Standard.

The medicine is safe for the purposes for which it is to be used

Certain regulatory restrictions and/or controls may be imposed to ensure that the use of a listed medicine is consistent with low risk, for example: label advisory statements, restrictions on dosage and restrictions on route of administration.

You must ensure that you are fully aware of every condition or restriction affecting the use of ingredients in your products so that the product fully complies with all legislative requirements applicable in Australia.

The medicine presentation is acceptable

All aspects of the product are considered to comprise the 'presentation' including:

- the name
- indications
- directions for use
- warning and cautionary statements
- packaging
- dosage form
- logos
- symbols and pictures on a medicine label.

Section 3(5) of the Act and 3(A) of the Regulations state when the presentation of a good is considered unacceptable:

Section 3(5) of the Act

For the purposes of this Act, the presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use or identification of the goods and, without limiting the previous words in this subsection, the presentation of therapeutic goods is unacceptable:

(a) if it states or suggests that the goods have ingredients, components or characteristics that they do not have; or

(b) if a name applied to the goods is the same as the name applied to other therapeutic goods that are supplied in Australia where those other goods contain additional or different therapeutically active ingredients; or

(c) if the label of the goods does not declare the presence of a therapeutically active ingredient; or (ca) if the therapeutic goods are medicine included in a class of medicine prescribed by the regulations for the purposes of this paragraph—if the medicine's label does not contain the advisory statements specified under subsection (5A) in relation to the medicine; or

(d) if a form of presentation of the goods may lead to unsafe use of the goods or suggests a purpose that is not in accordance with conditions applicable to the supply of the goods in Australia; or

(e) in prescribed cases.

Regulation 3A of the Regulations: Unacceptable presentations

(1) For paragraph 3 (5) (e) of the Act, any labelling, packaging or presentation of therapeutic goods (including novelty dosage forms in the shape of animals, robots, cartoon characters or other similar objects) that is likely to result in those goods being mistaken for or confused with confectionery or toys is an unacceptable presentation of the goods.

(2) For paragraph 3 (5) (e) of the Act, the presentation of therapeutic goods is unacceptable if the name applied to the goods is not sufficiently distinctive to allow for the identification of the goods for the purposes of recovery.

The presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use or identification of the goods. Examples of *unacceptable* presentations include, but are not limited to:

- Therapeutically active ingredients are present in the formulation but not declared as such on the label (and/or misleadingly declared as 'excipients' in the application).
- Statements are made attributing a therapeutic role to ingredients that have not been declared as active ingredients, that is: excipient ingredients.
- Statements or pictures suggest that the product has uses or actions different from, or in addition to, the indications for use included on the ARTG.
- Presentation of a product is in a form likely to result in its being confused with food, for example: in confectionery-like novelty shapes and packaging.
- Product names are used that are likely to be misleading as to the composition of the medicine.
- The appropriate dosage for all age-groups in the likely target population is not stated, for example: 'adults', 'children 6-12 years' etc., as appropriate.
- The dosage form or directions are inappropriate for the target population, for example: a capsule dosage form is not appropriate for infants.
- Warning or cautionary statements needed for proper usage of the product are omitted.

- A reformulated product that does not have labelling adequately informing the consumer that it has different active ingredients from the product previously supplied under that name.
- Claims are made that a formulation is 'hypo-allergenic' or 'non-irritant', unless the sponsor holds supportive evidence from clinical tests that can be produced on request.
- Claims are made that a product is free from certain substances, for example: 'free from artificial colours' if not true.

The medicine conforms to every standard applicable

Therapeutic goods must comply with applicable standards before they can be entered on the ARTG. Criminal or civil penalties can be imposed on persons who import, export, manufacture or supply goods that do not comply with applicable standards (unless you have consent to supply such a good under section 14 of the Act—refer to Consent to supply goods not compliant with prescribed standards.

The medicine complies with manufacturing requirements

Australia has codes of good manufacturing practice (GMP) and quality system requirements for the manufacture of therapeutic goods, including complementary medicines. For more information—refer to Manufacturing principles for medicinal products.

In Australia the Act requires, with certain exceptions, that manufacturers of therapeutic goods hold a licence. Where a product is imported, or if any steps in the manufacture of a listed medicine take place outside Australia, the international manufacturer must hold a TGA GMP license, or a license accepted by the TGA—refer to Manufacturing standards for overseas manufacturers.

You must ensure that all the manufacturers of your medicine are included in your product ARTG entry. Use of a manufacturer who is not nominated on the product ARTG entry constitutes an incorrect certification against paragraph 26A(2)(h) of the Act.

The medicine conforms to every requirement relating to advertising

You must ensure that all advertising for the medicine complies with any applicable requirements of Part 5-1 of the Act and the Therapeutics Goods Advertising Code.

The medicine label may not include any claim that is inconsistent with the information included in the ARTG for the medicine and must comply with applicable standards and advertising requirements—refer to Complementary medicine labels.

The medicine complies with all applicable prescribed quality or safety criteria

You, the sponsor, are responsible for the quality of your listed complementary medicine—refer to Quality of listed medicines. You must hold information or evidence to demonstrate that your medicine:

- complies with all legislative requirements
- meets all specifications for the shelf life of the medicine, the recommended storage conditions and the expiry date stated on the medicine label.

You are required to certify under paragraph 26A(2)(fc) of the Act at the time of listing that you hold this information. A Delegate of the Secretary can request information or documents about the quality of a listed medicine under paragraph 31(2) (ca) of the Act; and can cancel your listing if they determine that the quality of the medicine is unacceptable.

The sponsor holds evidence to support indications made for the medicine

At the time of listing, the applicant of a listed medicine legally certifies under paragraph 26A(2)(j) of the Act that you hold evidence to support any indication or claim that you make about your medicine. Subsection 28(6) of the Act provides, as a condition of listing, that you must provide this evidence to the TGA if requested to do so. After listing, your medicine may be subject to a compliance review of evidence held by you as part of the TGA's random and targeted post-market monitoring activities or in response to either product safety concerns, or as a result of a complaint about a product.

Evidence guidelines: Guidelines on the evidence required to support indications for listed complementary medicines assist you to determine the appropriate evidence to support therapeutic indications made in relation to your listed medicine.

The information included in the application is correct

You must ensure that the information contained in your application is correct. An incorrect certification against paragraph 26A(2)(k) of the Act could result in the product being cancelled from the ARTG under the provisions of paragraph 30(2)(ba) of the Act.

Conditions of listing

Statutory conditions of listing

Section 28 of the Act provides a number of statutory conditions of listing that automatically apply when your medicine is listed on the ARTG. Failure to comply with a condition of listing may result in the cancellation of the medicine from the ARTG.

General additional conditions of listing

Section 28 of the Act provides legislative powers for the Secretary to impose, vary or remove additional conditions on listed therapeutic goods at the time the medicine is listed, or any time thereafter. There are a number of general 'Additional Conditions of Listing' imposed by the delegate of the Secretary at the time a medicines is listed on the ARTG, which are notified to the sponsor in writing, including the following:

- The sponsor shall keep records relating to this listed medicine as are necessary to: (a) Expedite recall if necessary of any batch of the listed medicine, (b) Identify the manufacturer(s) of each batch of the listed medicine. Where any part of or step in manufacture in Australia of the listed medicine is sub-contracted to a third party who is not the sponsor, copies of relevant Good Manufacturing Practice agreements relation to such manufacture shall be kept.
- The sponsor shall retain records of the distribution of the listed medicine for a period of five years and shall provide the records or copies of the records to the TGA, upon request.
- The sponsor of the listed medicine must not, by any means, intentionally or recklessly advertise the medicine for an indication other than those accepted in relation to the inclusion of the medicine in the ARTG.
- All reports of serious adverse reactions or similar experiences associated with the use or administration of the listed medicine shall be notified to the TGA, as soon as practicable after the sponsor of the goods becomes aware of those reports. Sponsors of listed medicines must

retain records of such reports for a period of not less than 18 months from the day the TGA is notified of the report or reports[3].

- The sponsor shall not supply the listed medicine after the expiry date of the goods.
- Where a listed medicine is distributed overseas as well as in Australia, product recall or any other regulatory action taken in relation to the medicine outside Australia which has or may have relevance to the quality, safety or efficacy of the goods distributed in Australia, must be notified to the National Manager, TGA, immediately the action or information is known to the sponsor.
- Colouring agents used in listed medicine for ingestion, other than those listed for export only under section 25 of the Act, shall be only those included in the list of 'Colourings used in medicines for topical and oral use' as amended from time to time.

Substance specific conditions of listing

Specific conditions of listing may be imposed on a medicine in relation to specific ingredients included in the medicine. These conditions are imposed when the product is listed on the ARTG and are notified to the sponsor in writing. For example, the following condition of listing is imposed on listed complementary medicines that contain preparations of the herbal material, *Ginkgo biloba* leaf extract:

> 'The *Ginkgo biloba* leaf extract used in the manufacture of this medicine must comply with the requirement of Identification Test B of the monograph Powdered Ginkgo Extract in the United States Pharmacopeia 32—National Formulary 27 (USP32-NF27). This condition does not apply to powdered or dried leaf'.

Imposition and changes to conditions of listing and sponsor's rights to appeal

Under subsections 28(2B) and 28(3) of the Act, while a medicine is listed on the ARTG, new conditions of listing may be imposed and/or existing conditions may be varied or removed, as determined by a Delegate of the Secretary. A sponsor may also request that a condition of listing be imposed or varied (an application fee may apply)—the Delegate of the Secretary will review the request and sponsors will be advised in writing of the decision.

The imposition or variation of a condition will take effect:

- on the day on which the notice is given, if the notice states that the action is necessary to prevent imminent risk of death, serious illness or serious injury; or
- in any other case, on the day specified in the notice, which will be a day not earlier than 28 days after the notice is given.

Sponsors are advised in writing of any conditions of listing and may appeal against a decision to impose, vary or remove a condition of listing. Rights of appeal will be advised in the letter from the TGA imposing the conditions—refer to Appeal mechanisms.

[3] The timing of and the type of adverse reactions to be reported are outlined in Pharmacovigilance responsibilities of medicine sponsors - Australian recommendations and requirements.

Quality of listed complementary medicines

It is a requirement under paragraph 26A (2) (e) of the Act that each step in the manufacture of a listed medicine in Australia is carried out by a licensed manufacturer (unless the therapeutic good is exempt from this requirement)—refer to Manufacturing therapeutic goods. It is an offence, carrying heavy penalties, to manufacture therapeutic goods for human use without a licence unless the manufacturer or goods are exempt. The manufacturer's licence carries details of the types of manufacture permitted under the licence.

Where a product is imported, each nominated international manufacturer must demonstrate an acceptable standard of good manufacturing practice (GMP) as would be required of an Australian manufacturer. Pre-clearance of international manufacturers is mandatory for listed complementary medicines—refer to Manufacturing standards for overseas manufacturers.

Australia has adopted manufacturing principles for medicinal products for the manufacture of therapeutic goods, including complementary medicines. Each code/quality system sets out requirements relating to quality management, personnel, premises and equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall and self-inspection. The observance of these requirements is necessary through all stages of manufacture to consistently provide a high level of assurance of the quality, safety, and efficacy of therapeutic goods. Compliance with GMP and the quality system requirements in Australia is determined by carrying out regular on-site inspections.

Some complementary medicines comprise relatively simple ingredients (for example: amino acids, mineral salts, vitamins) and the quality parameters applying to such products are essentially the same as for other medicines. Special considerations are required for those complementary medicines that contain complex ingredients, that are difficult to characterise, and/or certain combinations of multiple active ingredients.

Guidance on quality for complementary medicines

There are a number of scientific guidelines of particular relevance to listed medicines:

- Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, rev 1).
- Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products (CPMP/QWP/2819/00 Rev. 2) provides guidance to achieve consistent quality for products of herbal origin. Note herbal ingredients included in listed medicine must meet the definition of a herbal substance.
- Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev. 2) provides general principles for setting and justification of a uniform set of specifications for products of herbal origin.

Sponsors and potential applicants should also be aware of the following documents that provide specific guidance for complementary medicines:

- Annex 7 of the Guide to good manufacturing practice for medicinal products provides specific guidance on the manufacture of herbal medicinal products.
- Supplier qualification provides the steps by which supplier qualification may be achieved.
- Identification of herbal materials and extracts provides common questions and answers relating to identification of herbal materials.
- Sampling and testing of complementary medicines covers the sampling and testing requirements for raw materials used in the manufacture of intermediate, bulk or finished

complementary medicine products. It also describes a plan for reduced sampling and testing once an approved supplier has been qualified.

- The guideline Starting material analytical procedure validation for complementary medicines describes the minimum approach acceptable to achieve validation of the test procedures used for starting materials for use in complementary medicines.
- Finished Product Specifications and certificate of analysis.
- The document Equivalence of herbal extracts in complementary medicines assists sponsors of medicines containing herbal extracts to determine how and when a herbal extract may be considered 'equivalent' to an ingredient currently included in a therapeutic good and when it may be used as a substitute without causing the product to be considered a different therapeutic good.
- Use of modified unprocessed herbal materials in complementary medicines assists sponsors in identifying situations where the composition of an unprocessed herbal material has been modified to the extent that it is significantly different from the original material approved for use in listed or registered medicines.
- On-going stability testing for listed complementary medicines provides guidance on the development of a stability protocol for complementary medicines. The approach taken by TGA in relation to stability testing of herbal and certain other listed complementary medicines, recognises the differences between these types of therapeutic products and pharmaceutical products that usually contain a single, chemically defined, active.
- Stability testing of listed complementary medicines provides common questions and answers on stability testing.
- Product quality review for listed complementary medicines provides guidance on product quality reviews, which are part of GMP requirements.
- The Process validation for listed complementary medicines document provides guidance to ensure that the validation process used is effective in producing a quality medicinal product.
- Consistent with the TGA's risk-based approach to the regulation of medicines, it may be possible to justify certain situations where it is not necessary to assay an ingredient in every batch of finished product. In such situations, the content of an ingredient, or a component within the ingredient, may be estimated from the amount dispensed during the manufacture of the product. This practice is termed 'quantified by input' (QBI). However, based on risk to consumers, it is not appropriate to apply this practice to all ingredients—refer to Guidance on the use of the term 'quantified by input' for listed complementary medicines for more information.
- Sponsors and potential applicants should also be aware of information included in ARGCM Part D 'Table D6: Allowed changes to the nominal amounts of certain excipients', which is also relevant for listed complementary medicines.

Finished product specifications, certificate of analysis

Finished product specifications

The finished product specification is the set of tests and limits applicable to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should include all critical parameters in which variations would be likely to affect the safety or efficacy of the product, for example: assay.

The specifications against which a finished product is tested before release for sale are referred to as the 'batch release specifications'. The specifications against which a finished product is tested to ensure satisfactory quality throughout its shelf life are referred to as the 'expiry specifications' or 'end of shelf life specifications'. The product, if tested at any time within its shelf life, must comply with the requirements in the expiry specifications.

Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev. 2 provides general principles for setting and justification of a uniform set of specifications for finished products containing ingredient(s) of herbal origin.

Specifications should also take into account Australian legislative requirements for finished products.

The standards recognised under the *Therapeutic Goods Act 1989* (the Act) are those made by the Minister under Section 10 of the Act (Therapeutic Goods Orders) and the default standards, which currently are relevant statements in monographs in any of the following: British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.) or the United States Pharmacopeia - National Formulary(USP). It should be noted that any matter specified in an order under section 10 of the Act has precedence over requirements of the default standards.

The general monographs of the BP, Ph. Eur. and USP are also relevant, for example: the BP monographs 'Herbal Drugs', 'Herbal Drug Preparations' and 'Extracts'.

The most recent edition of the cited pharmacopoeia should be used.

Where a finished product does not comply with Australian legislative requirements, for example: Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules (TGO 78), a consent to supply the product is required—refer to ARGCM Part A 'Consent to supply goods that are not compliant with certain legislative requirements'.

Information required for a finished product specification

Product details

- name of product
- product code
- date of specification
- revision or version number
- a table listing the tests performed, the expiry requirements or acceptance criteria for the tests (and where different, the release requirements) and reference to the test method (for example: BP HPLC method, 'in-house' TLC method).The tests performed should include the following:
  - appearance of the product [note that the requirements should include: a description of the type of dosage form and any special characteristics (for example: modified release)]
  - physical tests including: average weight, uniformity of weight/ content, disintegration/dissolution (where relevant)

  - chemical tests, including: identification, assay, related substances (where relevant)
  - the microbiological tests
  - any other tests

- a statement of whether all the tests are performed on each batch of finished product; and if not, what tests are performed on rotation and the frequency.

Certificate of analysis for finished products

A certificate of analysis (used for 'release for supply' purposes) is a document certified as a truthful statement of the tests and test results for an individual, manufactured batch of a particular finished product.

Information required for a certificate of analysis

- the manufacturer
- the product name
- the batch number of the product
- the date of manufacture of the batch, the date of the testing and the date of the certificate
- the tests, the tests results, acceptance criteria and a reference to each test method
- the signature of the appropriate company official.

Use of the term 'quantified by input' for listed complementary medicines

If a manufacturer of a listed complementary medicine meets certain criteria, they may not be required to assay an ingredient in a finished product. The guidance also provides wording that a manufacturer could use on a certificate where an ingredient has been 'Quantified by input' (QBI). Please note that the guidance provided in this document does not override or replace the need to comply with all relevant statutory requirements, nor affect the legal obligations of the medicine's sponsor who is ultimately responsible.

It is intended that this guidance be used by manufacturers, in consultation with the relevant sponsor, as part of product development. It is most relevant where a quantitative claim (see note 1) is made for a particular active ingredient in a listed complementary medicine. However, in certain circumstances, these principles may also be applied to other ingredients or components, including those that are considered to be 'restricted ingredients' (see note 2).

Background

Under good manufacturing practice (GMP), it is a requirement that all active ingredients in medicines be tested to confirm that the content complies with prescribed standards. However, it is recognised that in some circumstances this may not be possible or practical to achieve. Where it is established that such medicines are manufactured in accordance with the principles of the Australian adopted Manufacturing principles for medicinal products and other criteria are met, quantitative testing of the active ingredient in the finished product may be omitted and the ingredient in the product can be 'QBI'. However, based on risk to consumers, it is not appropriate to apply this practice to all ingredients.

If certain specific testing of a listed complementary medicine is not going to be performed, it is important that all other aspects of its manufacture are performed under appropriate GMP. That is, if the finished product is not fully tested, testing of the raw materials becomes more critical. In addition, if there are quantity-based restrictions that affect the medicine's eligibility for listing

on the Australian Register of Therapeutic Goods (ARTG), careful consideration needs to be given as to whether reduced testing of the finished product is appropriate.

Where a manufacturer does not intend to assay an active ingredient, or a restricted ingredient or component, in a batch of a complementary medicine, this decision must be supported by written justification. The justification may be reviewed at a Therapeutic Goods Administration (TGA) GMP inspection of the manufacturer or by the TGA during a listing compliance review.

Assessing the suitability of QBI for a listed complementary medicine

When determining whether the content of an active ingredient or restricted ingredient/component in a listed complementary medicine could be QBI, the following points need to be addressed:

- any quantitative claims made for the ingredient in the finished product
- any restrictions applicable to the ingredient or any component in the ingredient: these can relate to scheduling entries in the Poisons Standard (see note 3), or be identified in the Permissible Ingredients Determination
- critical testing of the active raw material, in accordance with GMP principles
- the availability of a validated assay method for the ingredient/component in the finished product
- whether QBI would be applied to all batches or only certain batches (testing would be done on a rotational basis).

Complex active ingredients

Many ingredients of biological origin used in complementary medicines are not single component ingredients, for example: shark cartilage, non-standardised herbal extracts. In these situations, where the ingredient/component is not subject to any restrictions and no associated quantitative claims are made in the finished product, the ingredient may be quantified by input. The words 'Not assayed, quantified by input', or words to that effect, may be used on the certificate of analysis of the finished product.

Simple ingredients and components of ingredients

In cases where the active ingredient consists of a single component, or where a quantitative claim is made for any component within an ingredient, it is usually expected that the ingredient/component would be assayed in the finished product. This is particularly important when, to ensure the safety of the medicine, an ingredient/ component is subject to restrictions in any relevant legislative instrument.

However, in certain situations it may be justifiable to QBI such ingredient/components, including those that are restricted, and not assay the finished product. This could occur as part of a rotational testing program (see note 4), where, for certain batches of medicine, the assay of a specified ingredient/component would not be performed. In these cases, a statement such as: 'Quantified by input. This ingredient is part of a rotational testing program and was not assayed in this batch' may be used on the certificate of analysis of the finished product. In some instances, a validated limit test for simple ingredients or components (see note 5) may be able to be used as part of a QBI justification. The use of such a test may provide an acceptable level of assurance that the ingredient/component is below the level which would affect the eligibility of the medicine for listing.

QBI justifications

Difficulties with testing methodologies may be the justification for using QBI for an active ingredient. For example, the formulation of the medicine may be of such complexity that a validated assay method for the ingredient in the finished product is unavailable or is difficult to

achieve. To be able to apply the principles of QBI to the manufacture of these medicines, the potency of the ingredient/component must have been established according to the Manufacturing principles for medicinal products prior to inclusion in the formulation. Once this has been done, the words 'Not assayed. Quantified by input' may be used for the ingredient/component on the certificate of analysis of the finished product.

For multi-active medicines (for example: multivitamin/mineral complexes) it may be justifiable to use QBI for ingredients for which a validated assay method for testing the finished product is available. If the quality and safety of the medicine is assured through other testing, the assay of certain ingredients may be put on a rotational testing program. Again, this can only be applied if the potency of the ingredient/component has been established according to the Manufacturing principles for medicinal products prior to inclusion in the formulation. Once this has been done, the words 'Not assayed, quantified by input' or 'Quantified by input. This ingredient is part of a rotational testing program and was not assayed in this batch' may be used for the ingredient/component on the certificate of analysis of the finished product.

Implementation

Consistent with the principles and guidance in this document, some testing must be performed on each batch of the finished product where a quantitative claim is made on the label. That is, there must be sufficient testing to provide assurance that the product is of intended quality.

Notes

Note 1: A 'quantitative claim' is a claim made for a medicine which states that a particular quantity of an ingredient, or component in an ingredient, is present in the medicine.

Note 2: An ingredient, or component within an ingredient, is considered to be 'restricted' where there is a quantity or concentration based restriction referred to in a legislative instrument, such as: the Permissible Ingredients Determination (see definition of 'restricted ingredient' below).

> 11(2) A substance is a restricted ingredient if:
>
> (a) it is an ingredient in a relevant medicine; and
>
> (b) for that medicine to be, or to remain, eligible for listing, the permissible quantity or concentration of the substance in the medicine is restricted by operation of any of the following:
>
> (i) Schedule 4;
>
> (ii) the Poisons Standard;
>
> (iii) a condition imposed under section 28 of the Act;
>
> (iv) a standard under section 10 of the Act;
>
> (v) the Required Advisory Statements for Medicine Labels document;
>
> (vi) any other provision in these Regulations or in the Act that deals with eligibility of medicines for listing.
>
> 11(3) In this regulation:
>
> relevant medicine means a medicine that is listable goods or listed goods and that is not an export only medicine.

Where a quantity based restriction may apply to an ingredient or component it is generally not appropriate for that ingredient to be QBI because of the on-going need to confirm that the medicine meets the quantity based restriction and remains safe. This means that any ingredient referred to or mentioned in any of the legislative instruments may generally not be QBI. However, there may be circumstances where, for example, the restriction applies to a component within an ingredient and it can be demonstrated that the concentration is appropriately controlled in the raw material. In these instances, it is possible to apply the principles of QBI and not assay the restricted component in the finished product. Further, if the

concentration is significantly below the restricted level, an appropriate limit test could be used on the raw material.

Note 3: A substance may be 'referred' to or mentioned in the Poisons Standard, but it may not be 'included' in a Schedule. That is, it may not be subject to the requirement of the Poisons Standard entry because the quantity/concentration of the ingredient is below that specified in the entry. It should be noted that, by definition, a listed medicine cannot contain any substance that is included in a Schedule. For example: vitamin D preparations are referred to in the Poisons Standard for internal human therapeutic use, although preparations containing 25 micrograms or less of vitamin D per recommended daily dose are not subject to restrictions in the Poisons Standard. Therefore:

- medicines which contain vitamin D at levels that provide a daily dose of more than 25 micrograms are included in Schedule 4 and cannot be used in listed medicines
- for listed medicines which provide 25 micrograms or less of vitamin D, a vitamin D assay of the finished product must be performed.

In instances where reference to an ingredient in a legislative instrument only relates to a requirement for a warning statement (for example: *Hypericum perforatum* in the Permissible Ingredients Determination) that ingredient may, subject to the principles of this document, be eligible for quantification by input. Please note that this would not be the case if the warning statements are quantity dependent.

Note 4: Rotational testing is the performance of specified tests on pre-selected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not fully tested must still meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should be supported by written justification. This justification may be reviewed at a TGA GMP inspection of the manufacturer or by COMB.

Note 5: A 'limit test' is a semi-quantitative assay for a component in a product. It generally provides a pass/fail result for the component. It should be developed with suitable specificity, precision and accuracy, but it is not expected to provide an exact value.

The use of a validated limit test may provide an acceptable level of assurance that a particular ingredient or component is present in a product at levels consistent with low risk and, subject to the principles of this document, be eligible for QBI. In instances where restrictions in the Poisons Standard or in the Permissible Ingredients Determination apply to an amount of an ingredient/ component in a recommended daily dose, the application of a limit test will require knowledge of the recommended dose. In instances where this is not known, manufacturers should liaise with the product's sponsor to ascertain this information.

Listing a complementary medicine on the ARTG

Listed medicines included on the Australian Register of Therapeutic Goods (ARTG) via a streamlined online listed medicine application and submission portal which is part of the TGA Business Services framework.

All necessary tools required to lodge, change and maintain an application for a listed medicine are accessible via TGA Business Services. The Listed medicines application and submission user guide fully describes the listed medicine application and submission process.

Step 1: Obtain access to TGA Business Services and the online application portal

To access the application portal you will require a user name and password. You must first submit an Organisation details form to obtain a client identification number. Having obtained a client identification number, you can submit a TGA Business Services Access Request Form to become the 'Business Administrator' for your company and then can apply for user accounts for yourself and other personnel in your company.

For further information about obtaining a client identification number or gaining access to TGA Business Services, contact the TGA by phone 1800 010 624 or email ebs@health.gov.au.

Step 2: Medicine details entered in the TGA Business Services application portal

The Listed medicines application and submission user guide provides a step-by-step description on how to enter your medicine details.

Step 3: Application passes validation in TGA Business Services application portal

During validation, the application and all related sub-documents are checked against the listed medicine business rules. The application must pass validation before it can be submitted to the TGA.

Successful validation of an application does not mean that the product has been approved by the TGA, nor that the product meets all the requirements for listing. The TGA Business Services application portal is a tool designed to allow electronic submission of an application for a listed medicine. The onus of responsibility is with the sponsor of the medicine to certify, upon submission, that the goods that are the subject of the application meet all the requirements of listing.

If you have problems with your application, you can contact the TGA by email: listed.medicines@health.gov.au or by phone: 1800 119 312.

Step 4: Submission

When the application has passed validation, the applicant (who will become the sponsor of the medicine) must electronically sign a statutory declaration certifying (as per Part 26 A of the Act) that the application meets all conditions of listing and that the information provided in the application is correct.

The application can then be submitted.

Step 5: Application fees paid

Fees for a listing application are non-refundable and non-transferable and must be paid within 14 days of the application being submitted to the TGA. If payment is not made within 14 days, you will receive an email notifying you that the application has been rejected. Should you wish to continue, you will need to draft a new application.

Step 6: TGA processing of the application

Once payment is finalised:

- the application is recorded on the ARTG
- the medicine is assigned an AUST L number
- a 'Certificate of medicine listing' is generated for the medicine.

Step 7: Finalisation

The sponsor of the medicine:

- is notified by email of application completion and provided with the AUST L number
- downloads the 'Certificate of medicine listing' from TGA Business Services
- receives the 'Conditions of listing' letter from the TGA
- can market the product.

If your listed medicine is selected for a random compliance review, you will receive a notice requiring you to provide specified information to the TGA (under section 31 of the Act). Usually, you will be given 20 working days to respond. Failure to provide the information within 20 working days after the date specified in the notice is grounds for cancelling the medicine from the ARTG and it is an offence to fail to respond to the notice or to provide information in response that is false or misleading in a material particular. For more information refer to Listed complementary medicine compliance reviews.

The product details will usually be viewable on the TGA Business Services website the day after the information has been recorded on the ARTG.

ARGCM Part C: Evaluation of a substance for use in listed complementary medicines

This guidance is for applicants requesting evaluation of a substance for use in listed complementary medicines.

Overview of evaluation of a substance for use in listed complementary medicines

Applications to vary the Permissible ingredients determination

Listed complementary medicines may only contain ingredients included in the Therapeutic Goods (Permissible Ingredients) Determination (the Permissible Ingredients Determination). The Permissible Ingredients Determination is a legislative instrument made by the Minister for Health under section 26BB of the *Therapeutic Goods Act 1989* (the Act).

For a substance to be included in the Permissible Ingredients Determination, an applicant must make an application to the Secretary under section 26BE of the Act for a recommendation that the Minister vary the Permissible Ingredients Determination. Applicants must use the application form: Application for evaluation of a substance for use in listed complementary medicines. An application can be submitted for:

- A new complementary medicine substance not currently included in the Permissible Ingredients Determination.
- A proposed new role or a change to a the existing requirements for use of a current permitted ingredient, for example:
  - for an ingredient permitted for use as an excipient to be used as an active ingredient
  - to change the permitted level of use
  - to change the permitted route(s) of administration

The Secretary will evaluate the substance taking into account whether it is of appropriate quality and safety to be permitted for use in listed complementary medicines. A TGA delegate of the Secretary must either, make a recommendation (successful applications) or refuse the application (rejected applications).

If the substance is determined to be safe, it will be recommended for inclusion in the Permissible Ingredients Determination and the Minister may vary the instrument. In some cases, 'requirements' (for example, restrictions on the concentration of an ingredient in a product or restrictions on the maximum daily dose of the product) may be attached to the use of the ingredient in a listed complementary medicine so that safety and quality can be maintained.

Once an ingredient is included in the Permissible Ingredients Determination, it may be used in any listed complementary medicine provided any requirements for use are complied with.

Route of evaluation for complementary medicines

Schedule 10 of the Therapeutic Goods Regulations 1990 (the Regulations) prescribes which area within the TGA conducts the evaluation of specific therapeutic goods.

Part 2 of Schedule 10 states that complementary medicines (including substances) that do not meet the criteria for inclusion in Schedule 4, 8 and 9 of the Poisons Standard are evaluated by the Complementary and OTC Medicines Branch.

If you are of the view that your application has been incorrectly referred to a particular TGA area for evaluation, you may make a submission in support of which route of evaluation you consider more appropriate. In making such a submission, you should provide all relevant information that would enable the assessment of the therapeutic good against Schedule 10 of the Regulations.

Substances eligible for evaluation for use in listed complementary medicines

Schedule 14 to the Regulations provides a list of designated active ingredients for complementary medicines. If a substance is of the type listed in Schedule 14 to the Regulations, it may be eligible for evaluation for use in listed complementary medicines providing:

- The substance is not a prohibited import.
- For a substance of herbal origin, the substance or its constituent(s) is/are not subject to the conditions of a Schedule (or applicable Appendix) to the Poisons Standard.

Some substances are subject to the conditions of a Schedule (or applicable Appendix) to the Poisons Standard only if present in a certain quantity in a finished product. Accordingly, appropriate restrictions (for example, dose or route of administration) must be placed on the use of such an ingredient in listed complementary medicines.

If the proposed new substance is not currently in a Schedule to the Poisons Standard but the substance, or its constituent, has a potential safety concern that may meet the criteria for inclusion in a Schedule, you should seek advice from the TGA prior to submitting an application. Should it be identified during the course of the evaluation that the substance meets the criteria for inclusion in a Schedule, the matter will be referred to the relevant scheduling advisory committee. It may be determined that the substance is not suitable for use in listed medicines on the basis of the scheduling decision.

If you consider the scheduling of a substance should be reconsidered, you can submit an Application to amend the Poisons Standard.

Application categories for evaluation of substances

Applications for evaluation of a substance to be used in listed complementary medicines are categorised into four application levels (IN1, IN2, IN3 and IN4). Each application category has defined submission requirements. Less supporting information is required and shorter evaluation times apply to lower level applications. IN1, IN2 and IN3 application categories require submission of pre-evaluated information from an acceptable comparable overseas regulator (COR).

Table C1 provides the application categories and the key application requirements for evaluation.

Table C1: Application categories for evaluation of substances

Category	Description	Evaluation and application requirements
IN1	Evaluation of safety and quality based on evaluation reports from a COR.	• Supporting information to demonstrate that report(s) from a COR meets all information required to demonstrate the quality of a substance for use in listed complementary medicines
IN2	• Evaluation of safety based on evaluation reports from a COR. • Independent evaluation of quality by the TGA.	• Supporting information to demonstrate that report(s) from a COR meets all information required to demonstrate safety of a substance for use in listed complementary medicines. • All information required to demonstrate quality of a substance for use in listed complementary medicines to be submitted for evaluation by the TGA.
IN3	• Evaluation of quality based on evaluation reports from a COR; or a monograph contained in a default standard. • Independent evaluation of safety by the TGA.	• Supporting information to demonstrate that report(s) from a COR or a monograph contained in a default standard meet all information required to demonstrate quality of a substance for use in listed complementary medicines. • All information required to demonstrate safety of a substance for use in listed complementary medicines to be submitted for evaluation by the TGA.
IN4	Full independent evaluation of safety and quality by the TGA.	• All information required for an application for evaluation of a substance for use in listed complementary medicines (safety and quality data) to be submitted for evaluation by the TGA.

Where possible, the TGA makes use of COR evaluation reports for evaluation of a substance for use in listed complementary medicines. As part of the Government's reforms arising from the Medicines and Medical Devices Review (MMDR) the TGA is developing:

- A list of countries and jurisdictions from whom TGA will accept reports for use in the COR report-based process.
- Transparent criteria for identifying CORs.
- A process for using overseas reports.

Please note, COR evaluation reports that are provided for IN1, IN2 and IN3 applications must be from a list of CORs that is determined by the TGA under Regulation 16GJ.

Guidance on the use of COR reports will be available on the TGA website in 2018.

Timeframes and fees for evaluation of substances

Regulation 16GI of the regulations provides for legislated timeframes for evaluation of a substance for use in listed complementary medicines. There are different evaluation timeframes for each of the four application categories (refer to Table C1). While the TGA is required to complete the assessment within the specified timeframes, applicants should not presuppose the outcome of an application.

The timeframes for evaluation of a substance for use in listed complementary medicines are provided in Table C2.

Table C2: Timeframes for the evaluation of a substance for use in listed complementary medicines

Application level	Screening time	Evaluation time
IN1	40	70
IN2	40	120
IN3	40	150
IN4	40	180

Within 40 working days of receiving an application, the TGA delegate of the Secretary will notify the applicant in writing, whether the application has or has not been accepted for evaluation.

The timeframes for the evaluation of a substance for use in listed complementary medicines:

- only commence once an application is accepted for evaluation and the evaluation fee has been paid
- apply to working days only and exclude public holidays and weekends

- exclude the time when the evaluation clock has stopped (for example: the time taken by the applicant to provide responses to formal requests for information; or when the applicant and TGA agree to a mutual stop clock)

If the Secretary does not make a recommendation within the evaluation timeframe, the TGA must refund 25% of the prescribed application fee.

Exclusive use of new ingredients

Following an evaluation of a substance, subsection 26BB(2A) of the Act allows the Minister to permit the successful applicant to have exclusive use of that ingredient (the protected ingredient). Exclusivity periods will be specified in the Permissible Ingredients Determination as a 'requirement' relating to the use of the ingredient in listed medicines (under paragraph 26BB(1)(b) of the Act).

During the specified exclusivity period the use of a protected ingredient in a listed medicine will be restricted to:

- the applicant who requested evaluation of the substance (who may or may not be a medicine sponsor)
- other persons nominated by the applicant

The exclusivity period will start from the date the protected ingredient is included in the Permissible Ingredients Determination and end two calendar years later (for example, an exclusivity period starting 1 July 2018 will end 1 July 2020).

At the end of the exclusivity period, any sponsor can include the ingredient in a medicine and list that medicine in the ARTG.

An ingredient that is the subject of an exclusivity period cannot be used by other applicants to list a medicine in the ARTG unless they have been nominated by the ingredient applicant during the exclusivity period. Use of a protected ingredient within the exclusivity period without an approval from the ingredient applicant would contravene the requirement relating to the use of the ingredient and is grounds to cancel the medicine from the ARTG under section 30 of the Act.

Eligibility for exclusivity

Exclusivity will only be permitted for a new complementary medicine ingredient (active or excipient) that is not currently included in the Permissible Ingredients Determination (that is, the ingredient is a new item in Table 1 in Part 2 of Schedule 1 to the Permissible Ingredients Determination, provided that:

- it has not previously been evaluated by the TGA for use in listed or registered medicines
- it is not used in, or available for use in registered medicines

Exclusivity will **not** apply to applications submitted for a new role or a change to any existing requirements for use of a permitted ingredient, for example:

- for an ingredient permitted for use as an excipient to be used as an active ingredient
- to change the permitted level of use (for example, from 0.5% to 1%)

- to change the permitted route(s) of administration (for example, from topical use to oral use)
- to change the permitted use of a herbal ingredient (for example, to add a different plant part or preparation method)
- to change the requirements to allow use of another strain of a species which is a permitted ingredient (for example, addition of the LA-5 strain to *Lactobacillus acidophilus*)

How to apply for evaluation of a substance for use in listed complementary medicines

Application phases for evaluation of a substance for use in listed complementary medicines

An application for evaluation of a substance for use in listed complementary medicines passes through the following phases:

- Phase 1: Pre-submission meeting (recommended)
- Phase 2: Lodgement of application and payment of application fee
- Phase 3: Screening of application
- Phase 4: Evaluation
- Phase 5: Recommendation
- Phase 6: Finalisation

Phase 1: Pre-submission meeting

We recommend you arrange a meeting with the TGA prior to submitting an application for evaluation of a substance for use in listed complementary medicines. See Pre-submission meetings with the TGA for details on arranging a meeting. There is no fee associated with a pre-submission meeting.

The purpose of the meeting is to ensure that you are aware of the legislative requirements for ingredients used in listed complementary medicines and the data required for a submission to be accepted for evaluation. If it is determined at the meeting that the proposed data dossier is likely to be critically deficient, you have the opportunity to address these deficiencies prior to submitting the application.

Phase 2: Lodgement of application

You are required to submit:

- a completed Application for evaluation of a substance for use in listed complementary medicines
- the dossier containing all required Information required for evaluation of a substance for use in listed complementary medicines for the selected application category
- the application fee (refer to Summary of fees and charges for applicable fees)

All data should be submitted at the time you lodge your application. Omitting relevant data from your application may jeopardise the acceptance of your application or cause unnecessary delays in the evaluation.

The TGA will acknowledge receipt of your application and provide you with an invoice and an application number that you should reference in all communication on the application.

Phase 3: Screening of application

In general, screening aims to identify applications that, for whatever reason, are unacceptable, for example: the data dossier is insufficient. Only critical deficiencies in the dossier will be identified at this stage.

The screening of the application consists of two parts:

- an administrative screen
- a technical screen

The administrative screen confirms that the correct application level has been selected, all fields on the application form have been completed and the correct application fee has been paid. If these basic requirements are not met, we will not accept the application for evaluation.

The technical screen determines whether the data requirements for the selected application level have been met.

Application accepted for evaluation

Applications that are accepted in the screening phase progress to the evaluation phase. You will be notified in writing that the application has been accepted for evaluation and an invoice will be issued for the evaluation fee. The evaluation process will not commence until the evaluation fee has been paid in full. The evaluation fee will not be refunded if the application is withdrawn during the evaluation phase.

Application not accepted for evaluation

If your application is not accepted for evaluation, you will receive a letter explaining the reasons why. Any other administrative matters in relation to the application will be discussed with you directly. The application fee will not be refunded if your application is not accepted for evaluation.

An application will not proceed to evaluation if:

- The substance is not eligible for use in listed complementary medicines (see Substances eligible for evaluation for use in listed complementary medicines).
- Any portion of the application fee remains outstanding.
- The application is presented in an unacceptable format (refer to Application format), for example:
  - no table of contents
  - unsearchable electronic data
  - no overview
  - no sequential page numbering

  - no certified English translation of foreign language documents

- There is gross deficiency or insufficiency of information.
- No appropriate justification is provided to address data gaps, for example: if substance specific toxicological data are not available, you should provide toxicological data from similar substances or evidence of history of use in other jurisdictions. Please note that the adequacy of the justification will not be evaluated at this stage.

Phase 4: Evaluation

Data will be reviewed to determine if the substance is of sufficiently low risk to be used in listed medicines. The same evaluation process applies for substances proposed for use as active or excipient ingredients.

The main parameters considered when evaluating a substance for suitability for use as an ingredient in listed medicines are quality and safety:

- The quality aspects (such as: chemical identity, manufacturing process, process controls and stability) are evaluated for the purpose of characterising the substance (identifying the physical and chemical properties). Where there is a default standard for the substance, the quality of the substance is assessed against that standard. Where there is no specific default standard applicable to the substance, a TGA compositional guideline is required.
- The safety evaluation determines whether the toxicological profile of the substance meets the requirements for the purpose for which it is to be used and is, therefore, considered safe to be used as an ingredient in listed medicines.

Although efficacy of a substance is not assessed, the evaluation process includes consideration of the proposed therapeutic indication(s) for medicines (containing the proposed ingredient) in order to determine if the proposed ingredient is safe at the dose, route of administration and duration of exposure required for therapeutic effect. For example, when evaluating a substance that is proposed to be used as an ingredient indicated for long-term use, we will consider whether submitted safety studies are of sufficient duration. In addition, clinical and other efficacy data, while not evaluated from an efficacy perspective, often include information on adverse events that is useful in the safety evaluation.

When a permitted ingredient is included in a new, the sponsor of the medicine is required to certify (under section 26A of the Act) that they hold evidence to support the indications and claims made for their medicine. It is a condition of listing that the sponsor of the medicine must provide this evidence to the TGA, if requested to do so. The medicine may be cancelled from the ARTG if any of the sponsor's certification under specified provisions of section 26A of the Act is found to be incorrect.

Requests for information (RFI)

The TGA may make a request under subsection 26BE(2A) of the Act for additional information to clarify or address issues identified during the evaluation. The time between the RFI being issued and receipt by the TGA of the applicant's response will not be counted as part of the evaluation timeframe (the 'evaluation clock' will stop).

Evaluators may also seek clarification of minor issues on an informal basis and in these circumstances, the evaluation clock will not stop.

The applicant should provide an electronic copy of the requested information. No additional unsolicited data will be accepted. Applicants will be notified of the timeframe for the response. It is important that applicants respond to an RFI within the timeframe provided. If the response is not received within the timeframe specified, or if the issues identified in the RFI remain unaddressed, the application will proceed to the decision phase without the additional information. This may result in a refusal to recommend the inclusion of the substance in the Permissible Ingredients Determination. Although the TGA may grant extensions to the RFI due date, this will only be done at the discretion of the delegate if the request is received well before the due date, and if the applicant provides a reasonable justification as to why the extension is necessary

Consideration by a TGA advisory committee

In some circumstances the Minister or Secretary of the Department of Health may seek advice, in relation to the application, from a TGA advisory committee, for example:

- the Advisory Committee on Complementary Medicines
- the Advisory Committee on Medicines Scheduling
- the Advisory Committee on Medicines

You will be informed that a committee's advice is being sought and given opportunity to provide comment for the committee's consideration. Subsequently you will be informed of any relevant advice given by the committee.

Phase 5: Recommendation

After considering the quality and safety of the substance, any response to a RFI from the applicant and any advice from advisory committee(s), the Secretary may:

- make a recommendation that the Minister include the substance in the Permissible Ingredients Determination (successful applications), or
- refuse to make a recommendation (rejected application)

If the application is refused, you will be advised in writing as soon as practicable and provided the reasons why it was not successful.

Applicants requesting an evaluation of a substance for use in listed complementary medicines can appeal the Secretary's decision about that application under section 60 of the Act.

Phase 6: Finalisation

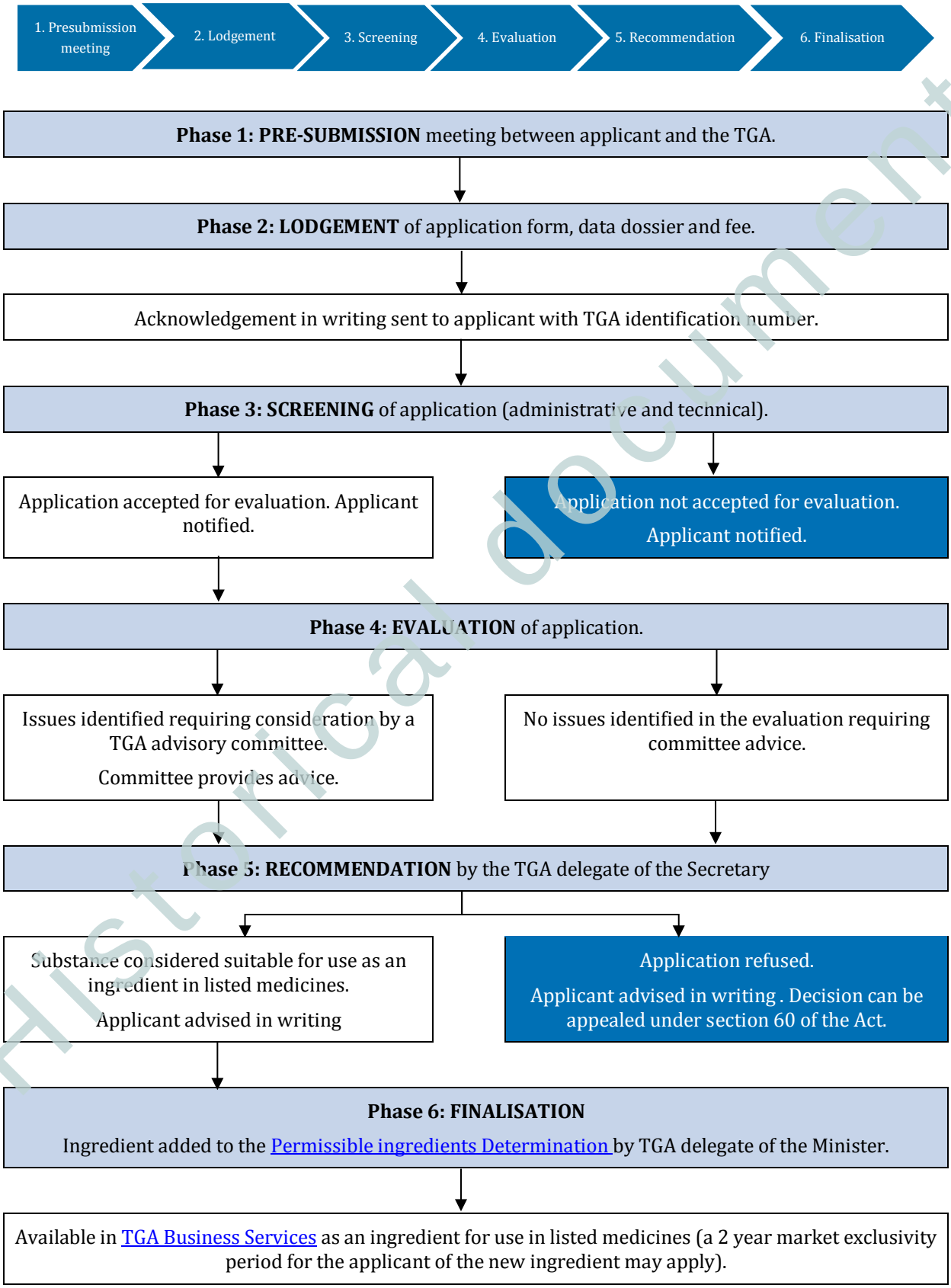
If the Secretary makes a recommendation, a TGA delegate of the Minister will then make a final decision to vary the Permissible Ingredients Determination to include a new ingredient or refuse to do so.

If an ingredient (active or excipient) is determined to be suitable for use in listed medicines, the approved ingredient is added to the Permissible Ingredients Determination for use in listed medicines. All permissible ingredients are also made available in TGA Business Services.

If an exclusivity period for use of the ingredient is applicable, this will be included as a requirement for the ingredient in the Permissible Ingredients Determination.

Chart C1 illustrates the application stages and evaluation process for the evaluation of a substance for use in listed complementary medicines.

Chart C1: Applications phases and evaluation of a substance for use in listed complementary medicines



Information required for an application for evaluation of a substance for use in listed complementary medicines

Table C3 outlines the type information required in an application for evaluation of a substance for use in listed complementary medicines. Specific data requirements are described in more detail below.

Table C3: Required information for evaluation of a substance for use in listed complementary medicines

Required information	
Administrative information	
Completed application form	
Covering letter/overview of the application	
Table of contents	
Outcome of any pre-submission meeting	
Request for confidentiality	
Proposal for a new ingredient name -**where required**	
General substance information	
Name/nomenclature	Australian approved name (or proposed name) and any synonyms
Role of substance	Active and/or excipient
Route of administration	Of therapeutic goods proposed to contain the substance
Dosage	Dose form, range, frequency, duration of use (of therapeutic goods proposed to contain the substance)
Any restrictions	For example: dosage, target population, route of administration
Type of substance	Simple (type 1 or 2) or complex (type 1 or 2) complementary medicine substance
Information required to demonstrate the quality of a substance for use in listed complementary medicines	
Definition	Description of the substance State if the substance is derived from or contains genetically modified substances.

Required information	
Chemical identity/structure	Molecular formula and mass, molecular structure and Chemical Abstracts Service (CAS) registry number for the substance and/or known components
General properties	Physiochemical properties, for example: appearance, melting point, solubility
Manufacturing details	Manufacturer's details
	Description of manufacturing process and process controls
	Control of raw materials
	Control of critical steps and intermediates
	Manufacturing process development
	Process validation and/or evaluation
Characterisation	Elucidation of structures and other characteristics
	Impurities and incidental constituents
	Residual solvents
	Incidental metals and non-metals
	Pesticide residues and environmental contaminants
	Other organic or inorganic impurities or toxins
	Microbiological standard
Control of substance	Default standard or compositional guideline with justification of tests and limits
	Specification with justification
	Analytical procedures with validation data
	Batch analysis
Reference standard	Authentication of reference materials
	Profile chromatogram for herbal materials

Required information	
Container closure system	Storage conditions, for example: 'protect from light'
Stability	Stability data throughout storage period (with trend analysis)
Information required to demonstrate safety of a substance for use in listed complementary medicines	
Literature search	Search strategy and results with justification for inclusion/exclusion of data
History and pattern of human use	Use in therapeutic goods
	International use
	Use as a food
	Traditional use
	Overall human exposure
Biological activity	Pharmacodynamic and pharmacokinetic studies
Toxicological data	Single dose toxicity studies
	Repeat dose toxicity studies
	Genotoxicity studies
	Carcinogenicity studies
	Reproductive and development toxicity studies
	Local tolerance studies
	Other studies, for example: metabolite studies, phototoxicity studies
	Toxicity studies for substances to be used for topical administration
Clinical trials	Any safety issues arising in clinical trials should be addressed
Adverse reactions	Nature, severity and frequency of adverse reactions, case reports of human poisoning
Substances of human or animal origin	Information on clearance of risk for transmissible spongiform encephalopathy (TSE)

Application format

You are required to provide a comprehensive package of relevant safety and quality data. It is preferred that the dossier be presented in an electronic format that is able to be electronically copied and searched. Hard copy dossiers may be submitted, however in this case, two complete sets must be provided. All pages in the dossier should be sequentially numbered (either as the whole dossier or within each section) and a table of contents provided. Electronic submissions should have hyperlinks from the table of contents to each section/subsection of data.

All documents, including references, must be in English and legible. If original documentation is in another language, it should be translated to English by a certified translator and both the English version and the original document should be provided. Non-English documents without certified translations and non-certified translations will not be considered as valid data.

The European Medicines Agency (EMA) Common technical document (CTD) is an internationally agreed set of specifications for a submission dossier format for a new medicine. Where applicable, applications for substances are encouraged to use the CTD format, for example: ICH M4Q CTD for the Registration of Pharmaceuticals for human use - Quality. However, in recognition that not all parts of the CTD are relevant for a substance application, the following guidance describes the information required in an application for evaluation of a new complementary medicine substance.

Administrative information

Completed application form

Provide a completed Application for evaluation of a substance for use in listed complementary medicines.

Covering letter/overview of the application

Provide a covering letter/overview which provides a critical scientific summary explaining how the safety and quality of the substance has been established.

Table of contents

The table of contents can be provided for the complete dossier or for each individual part/module. For electronic dossiers, provide hyperlinks to each section of data.

Outcome of any pre-submission meeting

Provide meeting outcomes of any pre-submission meeting with the TGA.

Request for confidentiality

You may request that data contained in your application remain commercially confidential—see Treatment of information provided to the TGA.

Where required, you should identify data that is not in the public domain and may be commercially confidential.

Proposal for a new ingredient name

All ingredients, claimed components and units of measurement in the application must be named using approved terminology—refer to Approved terminology for medicines. If the proposed substance, components or units do not have approved names, you are required to submit a proposal for a new name with your application and the TGA will determine the appropriate name(s). The various forms for this purpose are available on the TGA's website.

General substance information

Name/nomenclature

Provide the approved name for the substance, known synonyms, common names or trade names. For traditional Chinese medicine substances, include the Chinese name in Pin Yin and Chinese characters.

Role of substance

State whether the substance is intended for use as an active or excipient ingredient. For an active role, provide the proposed therapeutic use. For an excipient role, provide the proposed purpose in a medicine, for example: filler.

Route of administration

Provide the intended route of administration for medicines containing the substance.

Dosage

Provide the intended dose forms, dose range, frequency and duration of medicines containing the substance.

Any restrictions

Provide any proposed restrictions for medicines containing the substance, for example: target population age group restrictions.

Type of substance

State if the substance is a Type 1 or Type 2 simple or complex complementary substance. A Type 1 substance application requires less quality information than a Type 2 substance application.

Simple and complex complementary medicine substances

A simple complementary medicine substance is a single chemical entity that can be readily characterised, for example: ubiquinol-10 or calcium carbonate.

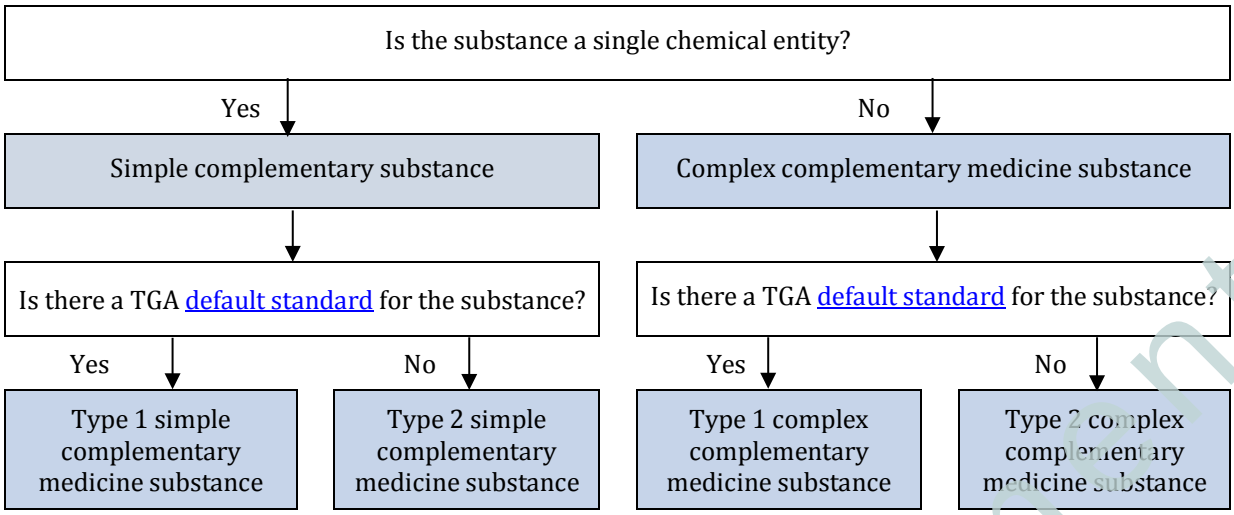
Substances other than single chemical entities are considered to be complex complementary medicine substances. Herbal ingredients are an example of a complex complementary medicine substance. Herbal raw materials are mainly whole, unfragmented or cut plants or plant parts in an unprocessed dry or fresh state. Herbal preparations are obtained by subjecting herbal raw materials to certain treatments (for example, extraction or distillation) and are diverse in character, ranging from simple, comminuted or powdered plant materials to extracts, tinctures, essential oils, fatty oils and exudates. Other examples of complex complementary medicine substances include marine oils and microorganisms.

Simple and complex complementary medicine substances are classified according to whether the substance is subject to the requirements of a TGA default standard (Type 1) or not (Type 2). Chart 3 shows the classifications of complementary medicine substances.

Where there is a default standard, you must provide this in the application. Please note that stated compliance with a specific default standard may be sufficient to address some of the quality data requirements in an application.

Where there is no applicable standard, you must provide and justify a draft compositional guideline for the substance.

Chart C2: Classification of complementary medicine substances



Information required to demonstrate the quality of a substance for use in listed complementary medicines

Information on quality is required to characterise (identify the physical and chemical properties of) a complementary medicine substance. Where a substance is the subject of a default standard (Type 1 substance) the substance must comply with all requirements of that standard.

For herbal ingredients where there is no default standard (Type 2 substance), characterisation (including a detailed evaluation of the botanical and phytochemical aspects of the plant and the manufacture of a preparation) is essential to develop a compositional guideline that is comprehensive and relevant to safety and quality. The quality of a herbal ingredient is determined by the quality of the herbal raw material, in-process controls, good manufacturing practice controls, process validation and compositional requirements applied to them throughout development and manufacture.

The quality of herbal raw materials is determined by such things as:

- botanical characteristics of the plant part
- phytochemical characteristics of the plant part—known therapeutic or marker constituents, toxic constituents (identity, assay, limit tests)
- biological/geographical variation
- cultivation/harvesting/drying conditions (microbial levels, aflatoxins, toxic elements)
- pre/post-harvest chemical treatments (pesticides, fumigants)
- profile and stability of the constituents

In addition to the above, the quality of a herbal preparation is determined by:

- method of preparation, including any diluents and extraction solvents
- profile chromatogram and stability of the constituents
- microbial stability

For herbal complementary medicine substances, the following scientific guidelines provide guidance on general quality aspects:

- Quality of herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2819/00 Rev. 2
- Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2

The general monographs of the BP, Ph. Eur. and the USP are also relevant, for example: the BP monographs 'Herbal Drugs', 'Herbal Drug Preparations' and 'Extracts'.

TGA encourages data on quality in an application to be presented in a manner consistent with the document: ICH M4Q CTD for the Registration of Pharmaceuticals for human use - Quality (CPMP/ICH/2887/99 Rev 1).

The following TGA guidance on information required to demonstrate quality uses headings largely consistent with those provided in 'ICH M4Q'. The amount of information required will vary depending upon whether the substance is classified as a Type 1 or Type 2 substance.

Definition

Provide a description of the substance.

State if the substance is derived from or contains genetically modified substances.

Chemical identity

For simple substances, provide the molecular formula, molecular weight, Chemical Abstracts Service (CAS) Registry Number and any nominated characterised constituents or similar information that will demonstrate identity.

For complex substances, where applicable, a description of the constituents with known therapeutic activity or markers and other constituents should be provided.

General properties

Provide information about the physico-chemical properties relevant to the characterisation of the substance or that may be important for the manufacture, performance or stability of its intended final dosage form, for example: solubility, particle size. Provide qualitative and quantitative particulars of the substance, including information on all physical properties such as appearance, colour, texture and smell.

Manufacturing details of a substance for use in listed complementary medicines

Manufacturer(s) details

Provide the manufacturer's name, address and addresses of all sites involved in the manufacture/testing of the substance. This information will assist in the evaluation process should it be necessary to obtain confidential information directly from the manufacturer—see text box below.

Where a manufacturer is unwilling to supply manufacturing details to the applicant, the information can be supplied directly to the TGA with written authorisation from the applicant. In this case, any matters arising from the review of data will be pursued with the manufacturer. The applicant will be notified that matters have been raised with the manufacturer, the details of which will only be provided to the applicant if authorised by the manufacturer.

Description of manufacturing process and process controls

Provide a flow chart of the process which identifies the starting materials, reagents and solvents used, yield ranges and operating conditions for all manufacturing steps.

Provide a sequential, procedural narrative of the manufacturing process, including a detailed description covering the quantities of raw materials, solvents, catalysts and reagents that reflect a representative batch scale for commercial manufacture; critical steps and process controls; equipment; and operating conditions, for example: temperature, pressure and pH.

Identify any reprocessing steps and provide evidence that they have no significant effect on the final quality of the substance.

For herbal substances, information to adequately describe the plant production and collection, including geographical source cultivation, harvesting, drying and storage conditions and batch size, should be provided. Any changes in the manufacturing process, and degradation products produced during storage, may result in a herbal substance that differs from that used to establish safety. The significance of these changes should be considered. Linking compositional guidelines/specifications to a manufacturing process is important, as it aids in identifying any potential process-related constituents and process-related impurities.

Control of materials

Materials used in the manufacture of the substance (such as: raw materials, starting materials, solvents, reagents and catalysts) should be listed identifying where each material is used in the process. Provide the measures used for quality and control of these materials. These are usually given in the form of specifications or a reference to an acceptable standard, for example: 'ethanol BP'.

Controls of critical steps and intermediates

Provide details of critical steps of the manufacturing process and details of how it is ensured that the process is controlled. This should include tests performed, acceptance criteria and experimental data.

Provide information on the quality and control of any intermediates isolated during the process.

Manufacturing process development

Provide a description of the development of the manufacturing process. Describe any significant changes made to the manufacturing process of the substance used in producing scale-up, pilot and production-scale batches that may affect the composition of the substance.

Process validation and/or evaluation

Process validation and/or evaluation studies should be provided, if available.

Characterisation of substance for use in listed complementary medicines

Elucidation of structures and other characteristics

Provide the graphic chemical structure of the substance and any characterised constituents in the substance, including potential isomerism. Specifically, provide information on any known constituents with a toxicological risk profile. Also provide information on the basis for confirming the structure, for example: spectral analysis.

Literature reports may be used to support this component of a submission.

Impurities and incidental constituents of complementary medicine substances

Incidental constituents and impurities are those constituents that may be present in a substance—as contaminants, as by-products of production, or arise during processing or storage of a substance, for example:

- residual solvents
- process related impurities arising from the manufacturing process
- incidental metals and non-metals, for example: lead, arsenic, selenium
- agricultural and veterinary chemicals, for example: pesticides, fumigants
- general contaminants, for example: dioxins, polychlorinated biphenyls
- manufacturing by-products, for example: reagents, catalysts, co-extractives
- degradation products
- radionuclides—particularly where substances might be sourced from contaminated areas
- radiolytic residues
- microbial contamination
- mycotoxins, for example: aflatoxins, ochratoxin A

Their presence should be minimised consistent with legal and appropriate production, processing and storage practices, for example: principles of Hazard Analogy Critical Control Point or Good Manufacturing Practice. Reliance upon finished product testing alone is not a comprehensive means of managing their presence.

Pharmacopoeial monographs do not include a comprehensive list of all impurities and incidental constituents. Where there is a default standard for the substance, provide information concerning impurities that are not dealt with in the monograph. While this information is not mandatory, you should be aware that the manufacturing process for the substance may differ from the process for the substance upon which the monograph is based and, consequently, different impurities may be present.

The potential for the manufacturing process to concentrate residues should be addressed. A summary should be provided of any degradation studies carried out to identify impurities arising from exposure to stress conditions, for example: heat, light, pH or moisture.

Where there is no default standard for the substance, the draft compositional guideline must include requirements for all known or likely impurities and incidental constituents.

Specifications and descriptions of analytical procedures must be submitted. As a starting point, the tests or methods used in pharmacopoeial references should be used. Other useful references

include the methods used by the US Environmental Protection Agency (US EPA) and the US Food and Drug Administration (FDA).

Where non-compendial methods are used, appropriate validation, rationale and justification should be provided.

Analytical procedures should be validated in accordance with the scientific guideline Note for guidance on validation of analytical procedures: Text and Methodology (CPMP/ICH/381/95) Rev 1.

Residual solvents

Any solvent(s) that may be used in the production, preparation, manufacturing or formulation should be controlled as per the requirements of the BP supplementary chapter for 'Residual Solvents'.

Incidental metals and non-metals

The material should comply with default standard limit tests for heavy metals, for example: lead, cadmium, mercury and arsenic.

The Poisons Standard may stipulate a particular limit for a metal or non-metal constituent in a substance, for example: a substance containing more than 10 mg/kg lead would be subject to the conditions of the Poisons Standard. If a substance is subject to the conditions of a Schedule (or applicable Appendix) to the Poisons Standard, then it is not acceptable as a permitted ingredient.

If the Poisons Standard requirements are not applicable, limits for metal or non-metal constituents can be determined using a similar approach similar to that used in the default standards for pesticide residues. This is based on the amount of a residue from a daily dose of a therapeutic good being less than 1 per cent of the acceptable daily intake (ADI) of that residue. The equation for calculating the upper limit is:

$$\text{Limit} = \frac{\text{ADI xM}}{\text{MDD x100}}$$

where: ADI = the acceptable daily intake in mg/kg bodyweight per day for the metal or non-metal, as specified by a source such as the Food and Agriculture Organization – World Health Organization, US EPA, US FDA or Food Standards Australia New Zealand

M = body weight in kilograms (for example. 60 kg)

MDD = daily dose of the formulation/substance in kilograms

Example: calculation of the limit for lead

ADI of lead = 0.0036 mg/kg bodyweight.

M= 60 kg

MDD= 200 mg tablet three times a day, expressed in kg=0.0006 kg

$$\text{Limit} = \frac{\text{ADI xM}}{\text{MDD x100}} = \frac{\text{0.0036mg/kg X 60kg}}{\text{0.0006 kg X 100}} = 3.6 \text{ mg/kg}$$

If a raw material is intended for the preparation of extracts, tinctures or other pharmaceutical forms the preparation method of which modifies the content of metals and non-metals in the finished product, the limits are calculated using the following equation:

$$\text{Limit} = \frac{\text{ADI xMxE}}{\text{MDD x100}}$$

where: E = the extraction factor of the method of preparation, determined experimentally.

If typical levels are above the acceptable limits calculated from the expressions above, the reason for this should be determined. There are materials that contain elevated levels of incidental metals and non-metals, for example, seaweed contains high levels of iodine. You should justify that the levels of the incidental metal or non-metal are typical and are not associated with contamination of the substance or indicative of poor quality. Proposed limits must be indicative of typical levels in the substance and take into account any expected or typical variation. Limits that would result in exposure greater than the ADI for a metal or non-metal are not acceptable.

Having established limits for relevant incidental metals or non-metals, appropriate means of determining compliance with these limits should be provided. Limit tests in the default standards are a useful starting point, provided they are suitable for the substance being analysed. 'In house' methods should be validated. Applicants should consider adopting tests where the limit of reporting is at least 10 per cent of the limit proposed for the incidental metal or non-metal in the substance or therapeutic good. This may not always be possible where a very low limit is proposed. However, results that are well below the proposed limits provide greater confidence that the limits proposed will not be exceeded.

Pesticide residues and environmental contaminants: (including agricultural and veterinary substances)

Pesticide residues may be found in a raw material as a result of intentional treatment or from inadvertent environmental contamination, of particular relevance are:

- organochlorins (for example: dichlorodiphenyltrichloroethane and endosulfan)
- organophosphates (for example: chlorpyrifos and parathion)
- carbamates (for example: carbaryl and methomyl)

The effects of processing and storage may affect these residues and result in a concentration or reduction of residues in finished goods.

The method, acceptance criteria, methodology and limits stipulated for pesticide residues in the default standards, for example: BP Appendix XI L – 'Pesticide Residues', should be followed as well as any additional residue limits that may be relevant. If a complementary medicine substance contains a pesticide residue that is not specifically restricted in the BP, then the risk associated with that pesticide should be assessed based on the generic approach described in the BP. Applicants should identify the likely pesticide residue risks; determine the likelihood and consequences of these risks; and develop, implement and review approaches for managing these risks.

Information from the US Environmental Protection Agency or the Codex Committee on Pesticide Residues can often provide good information about the effects of processing for specific chemicals. Other sources of information include pesticide manufacturers.

Other organic or inorganic impurities or toxins

Other organic or inorganic impurities or toxins may include:

- foreign matter
- total ash
- sulfated ash/residue on ignition
- ash insoluble in hydrochloric acid
- related substances, for example: synthetic impurities, degradation products

- other manufacturing by-products, for example: reagents, catalyst residues or process impurities
- radionuclides: where substances are sourced from contaminated areas
- radiolytic residues: for substances sterilised using ionising radiation
- residues of decontamination treatments
- any other organic or inorganic impurities or toxins (for example: dioxins, polychlorinated biphenyls and microbial toxins such as aflatoxins, ochratoxins)

The likely presence of manufacturing by-products (for example: catalyst residues, synthesis or process impurities and degradation products) should be determined and typical levels in regular production batches documented, particularly where they are of significance to safety or quality. Attention should also be given to the presence of isomers, metabolites and co-extractives.

Substances may be sterilised using ionising radiation. You should consider what radiolytic products may be formed in the substance and what constituents of the substance may be affected by such treatment, for example: vitamin A. You should have documentation about substances that have been irradiated, monitor levels of radiolytic products or constituents and, if necessary, establish and document limits.

If a decontaminating treatment has been used, it must be demonstrated that the quality of the substance has not been adversely affected and that no harmful residues remain.

In relation to other pharmaceutical raw materials and finished products, it is recommended that ethylene oxide be used only when essential and where alternative processes and/or decontamination agents cannot be used. Refer to the scientific guideline: Note for Guidance on Limitations to the use of ethylene oxide in the manufacture of medicinal products CPMP/QWP/159/01. In relation to herbal materials, the BP dictates that 'the use of ethylene oxide for the decontamination of herbal products is prohibited'.

Depending upon the substance, specific contaminants (for example: dioxins and polychlorinated biphenyls) may be present and the range of their concentrations should be given.

Microbial contamination

While substance manufacturers are encouraged to include limits for objectionable microorganisms, it is the product into which those substances are formulated that is subject to a legally binding set of criteria. The Therapeutic Goods Order No. 77 Microbiological Standards for Medicines mandates that any finished product that contains the ingredient, alone or in combination with other ingredients, must comply with the microbial acceptance criteria set by the Order.

While the TGA applies limits for certain micro-organisms in finished products, it is advisable to implement appropriate controls at the raw-material stage. There may be a need to specify the total count of aerobic micro-organisms, the total count of yeasts and moulds and the absence of specific objectionable bacteria. Microbial counts should be determined using pharmacopoeial procedures or other validated procedures. The source of material should be taken into account when considering the inclusion of possible pathogens, for example: Campylobacter and Listeria species.

Control of a substance for use in listed complementary medicines

You must include information on the controls used to ensure the quality of the complementary medicine substance. Relevant guidance can be found in:

- Compositional guidelines for complementary medicine substances

- Guideline on Specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2
- Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances CPMP/ICH/367/96

The following major points must be addressed.

Default standard/compositional guideline

For Type 1 substances, provide the TGA default standard. For Type 2 substances, provide the draft compositional guideline with justification of tests and limits.

Specification with justification

The specification of the substance must be provided.

Provide justification of the specification of the substance.

Analytical procedures with validation data

Provide analytical tests and methods used to demonstrate quality.

Provide validation data for analytical test methods. This is not applicable where the procedures described in the monograph or standard are employed.

Validation should be conducted based on the scientific guideline: Note for guidance on validation of analytical procedures: Text and Methodology (CPMP/ICH/381/95).

Batch analysis

Provide certificates of analysis for at least two recent, commercial-scale production batches to demonstrate routine compliance with the monograph or proposed compositional guideline. If data on commercial-scale batches are not available, provide certificates of analysis for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

The date of manufacture, batch size and number, place of manufacture, analytical methods used, should be provided. Tests results should be expressed numerically, for example, impurity levels. Results which merely state that the material 'complies' with the test are insufficient.

If available, provide certificates of analysis for any batches of material used in toxicity tests and clinical trials reported in support of the application. This will help the TGA to determine if the substance intended for supply is the same as that on which safety data have been provided.

Reference standard

Authentication of reference materials

Provide information about the reference standards used in tests, for example: identification, assay and impurities testing. Information should also be provided about how these reference substances were established, and where applicable, how their potencies were assigned. Where 'in-house' reference materials are used, provide information on how the reference material has been characterised.

For more information on the requirements of herbal reference standards, applicants should refer to the scientific guidelines referred to above and Identification of herbal materials and extracts on the TGA website.

Profile chromatograms

A profile chromatogram or 'fingerprint' chromatogram is a chromatographic profile of a botanical raw material or other substance that can be compared with that of an authenticated reference sample or standard.

Provide chromatograms in the application accompanied by complete details of the extraction steps and procedures (including detectors or detection systems) involved in their production. The information should be of sufficient detail to allow an independent authority to generate the same profile chromatogram.

A profile chromatogram is useful for both qualitative and semi-quantitative assessments. Even in situations where some or all of the constituents are unknown, profiling can identify variations due to differences in quality of raw materials including contamination issues, batch-to-batch consistency concerns and stability issues. If profiling is used semi-quantitatively as part of quality control for a substance, for example it is included in the compositional guideline, consideration would need to be given to the amount of variability that is acceptable.

On its own, a profile chromatogram is not suitable where a constituent of toxicological or therapeutic activity has been identified in a substance. In this case, specific methods to determine the amount of the toxicologically or therapeutically active constituent are required.

Importantly, a profile chromatogram may not be indicative of all components within a substance. For example, a profile chromatogram may be generated for the flavonoids in a substance and yet the majority of the substance comprises other components, such as starches or sugars. If known and where practicable, a profile chromatogram should be accompanied by information about the other constituents in the substance that are not profiled. Justification for not profiling these other constituents should be provided in the application.

Container closure system

Provide a description of the general characteristics of the container closure system where this might influence the stability of the substance, for example: protection from moisture and light.

Stability

Stability testing should be conducted in accordance with the TGA-adopted scientific guidelines for stability testing of drug substances.

The application should include a summary of the studies undertaken (conditions, batches, analytical procedures). The summary should also include results, for example, from forced degradation studies and stress conditions (light stress, higher temperature) as well as a brief discussion of the results, conclusions, the proposed storage conditions; retest date or shelf life where relevant.

A tabulated summary of the stability results, with graphical representation where appropriate should be provided.

Information required to demonstrate safety of a substance for use in listed complementary medicines

The safety of a substance for use in listed complementary medicines may be supported by history of use, published literature and/or original study data. The safety of a substance can be demonstrated using a combination of data from human exposure information and in vivo and in vitro preclinical studies. Clinical and other efficacy data, while not evaluated from an efficacy perspective, often include information on adverse events that is useful in the safety evaluation.

The safety profile of a substance for use in listed complementary medicines must be consistent with the low risk status of these goods. Conditions may be placed on the use of an ingredient to

ensure appropriate level of risk. For example, label advisory statements or restrictions to daily dosages commensurate with exposure data may be required.

Key requirements for the safety dossier include:

- A complete dossier of relevant data, selected on a comprehensive literature search including both positive and negative reports.
- Data must be of sufficient standard to enable full scientific assessment, for example: provide individual animal data, if available.
- Published material such as papers, expert reports and reviews must be provided. Copies of unpublished study reports must also be provided, if available. Abstracts are not acceptable as evaluable material.
- Evaluation reports from other regulatory agencies should also be provided.
- All information must be in English. Where published material is not in English, a certified English translation must be supplied with the original language version.
- Ideally, all studies should be conducted in accordance with an acceptable code of good laboratory practice (GLP) and, in the case of clinical studies, good clinical practice (GCP). The report should include certification of compliance in the conduct of each study.

If the balance and range of evidence has been documented in an authoritative/expert review, this may be sufficient to establish the safety of the substance and allow for submission of an abridged application. However, additional recent literature may be required to support the review. For example, a recent comprehensive review of a substance performed by FSANZ, in the context of recognition as a novel food could form the basis of an application.

Literature search

The dossier must include a well-constructed (systematic) literature search strategy—refer to Literature-based submissions for complementary medicines. The data submitted should be relevant to the particular substance and reflect the totality (balance and range) of the available evidence. Consistent evidence from different studies increases the strength of the evidence. All evidence, both favourable and unfavourable, should be documented. Where there is a large search output, it may not be appropriate to include all of the papers in the submission and in this case, justification for the inclusion/exclusion of papers should be provided, for example: on the basis of the quality of the study or provision of a recent review of high quality.

History and pattern of previous human use

To establish safety, sufficient numbers of people must have been treated or otherwise exposed to the substance or to products containing the substance (or to a substance justified as essentially identical to the substance in question).

When there is sufficient clinical and/or historical human evidence to support safety of a substance, conventional studies involving animal and in vitro studies are not necessary. However, where human evidence is lacking or there are clear reasons to suspect that clinical data are deficient or incomplete, the safety assessment will need to be supported by other studies, for example: single and repeat-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity and local tolerance studies.

Use in other therapeutic goods

Where a substance has been an ingredient of a registered good, such history of use will be considered, but it is essential to demonstrate that the proposed substance is the same as that used in those goods.

Post-marketing experience with other products containing the same or a similar substance should be supplied in the application.

International use

Availability of the substance in other countries, the length of time it has been available, and the regulatory conditions controlling its availability must be provided.

Reports from international regulatory authorities or agencies must be provided and discussed, for example:

- the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives
- the US Food and Drug Administration
- European Food Safety Authority (EFSA)

It is important to highlight the purpose of the particular agency's evaluation, which may have been for a more restricted purpose than that proposed, for example: an evaluation of safety for cosmetic use (topical) is unlikely to have considered safety for oral use. Similarly, an evaluation of a food additive is unlikely to have considered dermal toxicity. These reports may also have recommended particular restrictions on the substance; if so, these should be discussed. The outcome of such applications must be provided. Applicants must not omit any scientific or regulatory report that could influence assessment of safety of the substance.

Where the evaluation done by these agencies is directly relevant to the use proposed in Australia, the overall data requirements for the application may be reduced.

Some substances are available in countries that have regulatory controls that are different to Australia's regulation of complementary medicines, for example: complementary medicine products are regulated as foods or dietary supplements in many countries. Generally, food regulation does not include pre-market evaluation, rigorous post-market vigilance or a system for adverse reaction reporting. The use of substances regulated under less stringent controls may not provide a high degree of assurance of their safety in use, particularly if there is limited control on composition and adverse reaction reporting. However, information about such use may still be helpful in supporting safety.

Use as food

Information from well-established medicinal or food use of the substance can be used to support or establish safety. 'Well-established use' means that a sufficient number of people were treated or exposed to the substance over a period sufficient to support the safety of the substance for its intended purpose. Usually a substance that has a long history of use will have information published in official pharmacopoeias and other published literature. However, in some cases, particularly when tradition of use cannot be demonstrated based on written records, for example: indigenous medicine, you should submit information gathered from traditional users. If an application is to rely on traditional use, you are encouraged to meet with the TGA prior to submission—refer to Phase 1: Pre-submission meeting.

Where results from epidemiological studies of food or dietary supplements are of sufficient power or other adequate post-market safety studies are available, these data may be sufficient to support safety.

If the use of a substance is permitted in food in Australia, any applicable reference in the Australia New Zealand Food Standards Code should be given.

A substance used in therapeutic goods may present a different risk profile to that resulting from its use in food. Other components in the food matrix, such as fibre, may affect the rate of

absorption or otherwise interact with the substance when it is present in food. There may be no such effect when the substance is delivered in a therapeutic formulation. These matrix effects may be significant in terms of safety for some substances and may require limits on the proposed unit or daily dosage.

Traditional use

If you are relying, in part or in total, on evidence of traditional use to demonstrate safety, you must clearly indicate whether the substance under review is the same as that used traditionally, that is: the same plant part, preparation, dosage and dosage form, route of administration and typical schedule of administration.

The population and culture in which this tradition occurred must be identified. In some cases, evidence of traditional use, for example: aboriginal bush remedies, would require robust anthropological research data.

Modern extraction methods or other processes may produce, in some cases, substances that have a considerably different compositional profile from those produced using traditional methodology. It is insufficient to rely entirely on evidence of traditional use to support the safety-in-use of these substances. For example: modern highly concentrated *Actea racemosa* (black cohosh) herbal extracts have been linked with serious adverse reactions that have not been reported for traditional extracts. In some instances, the extraction of a substance from its natural matrix may make it more prone to oxidation to a toxic product or to inactivation, for example: carotenoids or resveratrol.

Overall human exposure

To assess the safety of a substance for use as an ingredient in complementary medicines, it is necessary to estimate the overall human exposure to the substance, particularly if the substance is present in typical diet. The exposure evaluation determines the amount of the substance that populations may be exposed to from all sources.

In determining possible total exposure to a substance, consideration must be given to the net and total amount of exposure from other sources and from use in complementary medicines. The duration and route of exposure must be considered.

Where possible, information on population exposure data should be included in the application. Where data are not available on the particular substance, data derived from related substances (such as the precursor, metabolite or a close analogue) may be useful as supporting evidence. For some nutrients and food types, the National Nutrition Survey will contain useful estimates of consumption.

Biological activity

Pharmacodynamic and pharmacokinetic studies

Appropriate studies, including human exposure and animal in vivo and in vitro studies using appropriate experimental models and routes of administration, should provide information on absorption, tissue distribution and storage, metabolism and the mode and extent of excretion or elimination of the parent substance and its degradation products.

For detailed information regarding safety pharmacology studies, applicants should consult the scientific guideline: Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals CPMP/ICH/539/00.

Toxicological data

Toxicological data for new complementary medicine substances must be included in the application.

It is acknowledged that conventional toxicity data normally available for pharmaceutical ingredients are rarely, if ever, available for complementary medicine substances. However the absence of these data does not imply that the substance is safe. Justification to demonstrate why an acceptable level of safety can be assured, even though some studies are lacking, must be provided. A substance is likely to be considered unsuitable for use as an ingredient in listed medicines, not just because of direct evidence of risk, but also because of insufficient evidence to provide assurance of safety.

Study details should include the:

- route of administration
- dose levels
- number of animals or subjects per dose level
- animals' or subjects' origin, gender, weight range and age
- frequency at which observations were made
- duration of each study
- the relationship between the time of administration and the onset of the effects observed
- all measurements made

All studies should be conducted using internationally recognised methodology as described in relevant Organisation for Economic Co-operation and Development (OECD)/ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

Applicants must specify the purity and batch number of the material used in each test. It may be appropriate to cross-reference with data in the substance profile. Pivotal studies, from which a no observable adverse effect level (NOAEL) is established, should be undertaken with the substance proposed for use or a substance of comparable composition (subject to justification) to that proposed for use.

A table providing a summary that concisely describes every aspect of toxicity studied should be provided in the application. The summary should not extend beyond a few pages and should identify all substance-related biochemical and physical changes observed in the study, with appropriate cross-referencing to the detailed data. Studies reported in the summary should be cross-referenced with reports in the main submission.

Toxicological data should be presented under the sub-headings provided below (which follow the EMA CTD format - Module 4 – (nonclinical study reports). Where data are not available for each of the headings, this should be clearly stated. This provides evidence that information has been sought in these areas and that they have not been overlooked.

Single dose toxicity in animals

Reports of acute oral toxicity studies on at least one mammalian species should be provided, if available. The inclusion of the results of LD50 testing for each species and route of administration is not mandatory.

The availability of acute toxicity studies for a novel ingredient may be limited due to international agreement to limit such studies, particularly when data for a similar substance or a class of chemicals are available. If so, this should be noted in the application.

Studies of acute toxicity provide insights into bioavailability, potency comparisons with other known toxic agents and an indication of which organs might be affected. They may also offer insight into likely acute poisoning effects.

Provide data in order by species and route.

Repeat-dose toxicity in animals

Repeat-dose studies (short-term, sub-chronic and chronic toxicity) allow proper, long-term assessment of the substance or its metabolites, which may accumulate in the body. The length of the repeat-dose study should be related to the duration of the proposed therapeutic use of the substance.

Generally, short-term use (up to a week) would need to be supported by a short-term, 28-day toxicity study; longer therapeutic use would require a sub-chronic (90 days) study; and prolonged use must be supported by long-term, chronic-exposure studies.

Include detailed results from individual animals in all toxicity studies and supplementary tables or diagrams, for example: growth curves and tumour incidence tables should be provided. It should be possible to organise tables so that the most appropriate comparisons, for example: control and treated groups, appear on the same page and results of histopathological observations can be readily evaluated in relation to dose, sex and duration of treatment.

The interpretation of chronic-toxicity studies may be greatly influenced by toxicokinetic considerations, particularly when species differences are apparent. Wherever possible, plasma levels of the test substance (and/or its metabolites) should be measured at steady state.

For further information, refer to the following scientific guidelines:

- S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
- S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
- OECD Guidelines for the Testing of Chemicals

Provide data in order by species, by route, and by duration from 2-week to chronic.

Genotoxicity studies

Mutagenicity studies are conducted to determine the potential for a substance to contribute to genetic damage in humans. A basic dossier of genotoxicity studies will generally comprise:

- An investigation of the potential to induce point mutations (base-pair substitution and frame shift) using Ames assays, with and without appropriate metabolic activation system
- An investigation of the potential to induce chromosome damage using mammalian cells in vitro, such as the chromosomal aberration assay, with and without appropriate metabolic activation systems.
- If a positive result is returned in either of these two assays, results of the following two in vivo or in vitro tests should be provided:
  - an investigation of the potential to induce cytogenetic damage, such as the micronucleus test in the bone marrow or other proliferative cells of intact animals
  - an investigation of the potential to induce genotoxic damage involving other than cytogenetic damage (for example: unscheduled DNA synthesis (UDS) or P32 post-labelling adduct formation) and preferably using a tissue known or suspected to be a toxicity target for the substance.

Supplementary tests (for example, sister chromatid exchange) can also be used to provide clarification of unexpected or equivocal results in the basic test package, or to provide additional evidence. In vivo germ cell tests using laboratory animals (for example, mouse specific locus tests, heritable translocation assay) could also be considered for the evaluation of a suspected mammalian mutagen.

For further information, refer to the following documents:

- S2A: Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals
- S2B: Genotoxicity: A Standard Battery for Genotoxicity Testing for Pharmaceuticals provide details of a standard battery of tests
- OECD Guidelines for the Testing of Chemicals

If reports of many studies are submitted, they should be presented under appropriate subheadings: 'In vitro' and 'In vivo', both with further subheadings such as 'Gene mutations', 'Chromosomal effects', 'Unscheduled DNA synthesis'.

Carcinogenicity studies

The toxicity profile of a substance and the indication and duration of the intended use may influence the need for carcinogenicity studies (see: Guideline on Repeated Dose Toxicity CPMP/SWP/1042/99 Rev 1).

We will not generally consider an application ineffective simply because a carcinogenicity study for the substance was not provided. While in vitro mutagenicity studies have, individually, a low predictive value in terms of human carcinogenicity, any unusual results arising from a number of different mutagenicity studies could indicate the need for further investigation. In addition, chronic toxicity studies may identify issues of concern in relation to carcinogenicity. For most complementary medicines, there is a history of human exposure through the diet or traditional medicine use that can provide some information on carcinogenic potential.

Further information about carcinogenicity studies is provided in the following scientific guidelines:

- Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals CPMP/ICH/299/95
- Note for Guidance on Carcinogenic Potential CPMP/SWP/2877/00
- Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals EMEA/CHMP/ICH/383/1995

Reproductive and developmental toxicity studies

A single, well-designed, multi-generation, prolonged exposure reproduction and developmental study should provide sufficient information on the effects of a substance on all aspects of reproduction, including sexual behaviour, gonadal function, spermatogenic and oestrus cycles, fertility, fecundity, parturition, lactation, pre- and post-natal growth, development and maturation of the offspring. The study may also provide adequate data on teratogenesis. However, particularly if some findings in the initial multi-generation study are equivocal, separate developmental studies are intended to provide information on embryotoxicity, teratogenicity, altered growth and the induction of functional deficits (post-natal behaviour).

For detailed information about the conduct and regulatory requirements of reproductive toxicology, applicants should refer to the relevant scientific guideline: S5(R2) Detection of

Toxicity to Reproduction for Medicinal Products including Toxicity to Male Fertility and OECD guidelines.

Presenting the data under subheadings will aid in their assessment. Typical subheadings would be, if there is information available:

- pharmacokinetics in pregnancy and lactation
- fertility and general reproductive performance
- teratology studies
- perinatal and postnatal studies

Local tolerance studies

Local tolerance testing should be focused at the proposed sites of administration for human use or other sites of likely local toxicity, for example: stomach. The dose, frequency and duration of exposure for the tests should closely resemble the proposed therapeutic use of the substance. The inclusion of site(s) which may come into contact with the substance through accidental exposure is also recommended. It is likely that if a substance will be used in a product applied dermally to the face, it may require assessment for eye or mucosal irritation. Phototoxicity and photosensitization testing should be considered for all substances suspected of presenting such risk.

Other toxicity studies

In some instances, incidental exposures may occur via routes other than intended (for example, inhalation after dermal application); also, unusual findings in main toxicity studies may warrant further investigation. In such circumstances additional targeted toxicity studies should be considered.

Toxicity studies are normally performed for the proposed substance. However, as impurities, degradation products and metabolites may be relevant to safety assessment; specific toxicological information on these compounds may be useful.

Toxicity studies for substances to be used for topical administration

With respect to new substance applications for ingredients to be included in sunscreens listed on the ARTG, refer to the Australian regulatory guidelines for sunscreens (ARGS).

For complementary medicine substances that are to be included as excipients in listed topical complementary medicines the following additional studies may be requested in individual cases where concerns become evident at the time of evaluation:

- irritation study – skin; animal or alternative method
- sensitisation study – skin; animal or alternative method
- eye irritation study
- in vitro mutagenicity (Ames) test
- in vitro percutaneous absorption test

Clinical trials

Data from clinical trials addressing safety issues should be submitted. Clinical trial data submitted in support of the safety of complementary medicine substances will not be evaluated for efficacy, but subject to future approval for such use, such data may be required to demonstrate efficacy of a product with a substance as an active ingredient.

A summary table (see Table C4) is very useful in reviewing clinical studies, and when available, these should be tabulated, in descending order of duration of exposure, within the trial type, for example: a 6-month trial before a 10-day trial.

Table C4: Example format – Summary of safety aspects of clinical trials

Type of study (reference)	Subject details	Treatment details (dose, duration, route)	Adverse reactions and safety indicators	Endpoints	Key outcomes
Randomised, placebo controlled double blind (Cunningham et al. 2001)	56 patients, mean age 60 years: 7 male; 49 female. Hypercholesterolaemic	5 mg per day PO for 8 weeks after 6 weeks of dietary stabilisation.	No differences between test and placebo for heart rate, systolic & diastolic bp, ALT, glucose, creatinine. Adverse reaction reports: cephalea (1/27), insomnia (1/27), muscle cramps (1/27).	At least two plasma lipid (overnight fast), blood biochemistry measurements & clinical examination at 15-day intervals.	Total cholesterol and LDL cholesterol decreased significantly ($p<0.001$) in the (substance) treatment group by 15 per cent 8 weeks after the start of treatment. Difference between groups also significant ($p<0.001$). There were no significant changes in HDL cholesterol, plasma triglycerides, or VLDL cholesterol levels compared with the placebo values.

Adverse reactions

All reports, published and unpublished and individual case reports relevant to the safety of the proposed substance should be submitted. Include information on the nature, severity and frequency of adverse reactions and information on potential interactions of the substance with food or medicines. Reports of poisonings (for example: accidental poisoning or suicide attempts) must be provided with details of doses consumed, the specific form of the substance (for example: sodium selenate and selenomethionine) and the circumstances of the poisoning, for example: inadequate closures on bottles or chronic toxicity via the diet.

When searching for reports of adverse reactions, use known synonyms for the substance and, if relevant, for closely related substances or components of the substance, for example: for kava, the search should include, among other things, *Piper methysticum*, kava, *Piper inebrians*, kavain, dihydrokavain and methysticin.

The TGA has a searchable Database of Adverse Event Notifications. Similarly, Health Canada also has a database which can be useful for information on drugs and health products.

Adverse reaction reports obtained from national medicine safety surveillance authorities should include a description of all available clinical information and the outcome of the reaction. If there are several such reports, the narratives should be included as an attachment. An example of the format for the presentation of data is given in Table C5.

A summary and conclusion about the safety of the substance, based on the reports of adverse reactions, should be provided. The number of reported adverse reactions and degree of their seriousness should be commented on against the overall usage of the substance as an ingredient in therapeutic products. It is important to highlight any particular characteristics of the user group of certain medicines. For example, herbal medicines based on Ginkgo biloba may be used predominantly by elderly people who are likely to already be using other medications and who may have pre-existing medical conditions. This may be the group most strongly represented in adverse reactions.

Table C5: Example format – Summary of adverse events

Report reference and date reported							
Adverse Drug Reactions Systems (Aust) Report No. 24369 30-6-98	Male, 34 years	Brand name Ingredients: (active ingredient details)	480 mg tablets PO 3 times daily for 10 weeks	Aspirin off and on; cod liver oil 275 mg PO twice daily	Psychosis, (psychotic ideation); manic reaction (hypomania)	Recovery after (Brand name) stopped	Probable
BfArM 9204235 (Germany) 16-6-92	Female, 59 years	Brand name Ingredients: (active ingredient details)	200 mg capsules twice daily PO	Headache; impaired alertness; amnesia, nausea	Serepax 45 mg daily PO	Recovery after all medication stopped	Possible

PO: (per os) oral administration ALT: alanine aminotransferase LDL: low-density lipoprotein HDL: high-density lipoprotein LDL: very-low-density lipoprotein

Ingredients of human or animal origin

Ingredients of animal and human origin with potential viral and Transmissible Spongiform Encephalopathy (TSE) risks must be approved before their inclusion in listed medicines.

Refer to the TGA's website for the Transmissible Spongiform Encephalopathies (TSE): TGA approach to minimising the risk of exposure.

Compositional guidelines for complementary medicine substances

Overview of compositional guidelines

What compositional guidelines are

A Therapeutic Goods Administration (TGA) compositional guideline is a summary of descriptions, tests and appropriate acceptance criteria (which are numerical limits, ranges or other criteria) that define the characteristics and specify the composition of an ingredient permitted for use in listed medicines. For the current list of compositional guidelines—refer to List of compositional guidelines.

How compositional guidelines are used

Compositional guidelines are used for an approved excipient or active ingredient where there is no default standard recognised in the *Therapeutic Goods Act 1989* (the British Pharmacopoeia, United States Pharmacopoeia - National Formulary and the European Pharmacopoeia).

If an applicable new default standard is published for an ingredient where a compositional guideline exists, the compositional guideline is withdrawn and the ingredient must comply with the requirements of the new default standard.

Compositional guidelines assist sponsors to:

- understand the specific nature of the ingredient that has been approved for use
- determine whether their material conforms to the requirements for that ingredient
- minimise any risk associated with the ingredient by complying with the parameters of the specification

While compliance with the compositional guideline is not a legal requirement, using an ingredient that does not meet the specifications of a compositional guideline may result in the TGA having concerns about the safety of that ingredient and any medicines containing it.

Where a sponsor wishes to include an ingredient in listed medicines that does not meet the compositional guideline, a request may be made to justify the safety of that specific material and/or the safety of any listed medicines containing that material. Where an ingredient is found to be unjustifiably different from the relevant compositional guideline, a sponsor may be requested to no longer use that material.

When compositional guidelines are generated

Compositional guidelines are usually generated when a new complementary medicine substance is approved for use as an ingredient in listed medicines. If the new ingredient is not subject to a specific default standard, a draft compositional guideline for the substance must be submitted in the application. The information the applicant includes in the proposed compositional guideline is based on the quality data submitted in the application.

On occasion a compositional guideline may be generated for some ingredients currently permitted for use in listed medicines, for example: 'grandfathered' ingredients that were available in Australia prior to the commencement of the *Therapeutic Goods Act 1989* and are not subject to a default standard or have a compositional guideline. The TGA will work with relevant stakeholders, including industry stakeholders, to develop these compositional guidelines when required.

Publication of compositional guidelines on the TGA website

When a new ingredient is permitted for use in listed medicines, the compositional guideline for the ingredient is published on our website under current compositional guidelines.

Procedure for amending compositional guidelines

A stakeholder can request the TGA to consider amending a compositional guideline. The request must be accompanied by appropriate justification that the safety profile of the ingredient will not be compromised (which would make it unsuitable for use as an ingredient in listed medicines).

Consideration will be given to whether the compositional guideline should be amended or a separate ingredient recognised (which would require an application for evaluation of a new substance). If the amendment is considered warranted, we will seek initial comment from the original applicant prior to determining if a revised draft should be published.

How to develop compositional guidelines

The following information assists prospective sponsors and substance manufacturers in drafting a compositional guideline for a new complementary medicine ingredient.

A compositional guideline template is available on our website that provides broad guidance to the type of information/data that should be included. However, if certain parameters included in the template are not relevant, these can be omitted provided that justification is given, for example: 'The production of this substance does not require the use of solvents and therefore the compositional guideline requirement for solvent residues has been omitted'.

Sources of data for development of compositional guidelines

Data from a variety of sources, including published literature, can be used in the development of compositional guidelines. The information on the compositional guideline should be justified (verified) from analysis of production batches of the material. The following documents may contain relevant information:

- The general monographs of the *British Pharmacopoeia*, for example: Herbal Drugs, Processed Herbal Drugs, Herbal Drug Preparations, and Extracts
- European Medicines Agency guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products CPMP/QWP/2820/00 Rev. 2

Linking compositional guidelines to a manufacturing process is important in order to identify any potential process-related constituents and impurities.

General information required in a compositional guideline

In general, the information included in a compositional guideline should:

- provide the physical and chemical properties of the substance
- identify and quantify major components and any significant (that may affect the safety or quality of the substance) minor components
- distinguish the substance from similar substances, adulterants or substitutes
- be specific for components of safety and/or therapeutic significance
- provide the limits of possible contaminants and impurities
- describe the biological, botanical, chemical and physical variations that may reasonably occur between batches of the substance
- be capable of providing for objective validation of the substance's composition using described analytical methodology.

Information on methods and procedures in a compositional guideline

The method of analysis used to establish compliance with the limits must be included in the compositional guideline, for example: high-performance liquid chromatography (HPLC). Methods in pharmacopoeias for similar substances should be used wherever possible, for example: pH measurements. If the method and limits are based on a pharmacopoeia or published reference, these references must be provided.

If proprietary or company analytical non-compendial methods are employed, a brief description in the draft compositional guideline is acceptable, for example: 'Acetone extraction and analysis by HPLC with ultraviolet (UV) detection'. However, complete details of the analytical methods and their validation must be provided as part of the application for evaluation for a new complementary medicine substance.

Information on biological, chemical and physical variations in a compositional guideline

Complex complementary medicine substances, particularly those of herbal origin, may be subject to variation due to such factors as: genetic variation; geographic variation; growing conditions; maturity and time of harvesting; post-harvest treatment; storage conditions; and/or processing treatments. Limits taking into account this variation must be included in the compositional guideline and justification for the limits provided, for example: 'the constituents in certain plants may vary seasonally and batches may contain, at certain times of the year, less of a certain constituent'.

Information on objective validation in a compositional guideline

Any methods or procedures identified in the compositional guideline should be able to be reproduced by an independent authority. Methods should be fully validated. Guidance on validating analytical test methods can be found in Starting material analytical procedure validation for complementary medicines.

ARGCM Part D: Registered complementary medicines

This guidance is provided for an 'applicant' - the person who submits an application for a new registered complementary medicine. You (the applicant) may or may not become the sponsor of the new registered medicine if it is approved.

This guidance applies to proposed registered medicines that are eligible for evaluation by the TGA's Complementary Medicines Branch (CMB) - refer to Route of evaluation for complementary medicines.

Where a medicine is/would be subject to Schedules 4, 8 and 9 of the Poisons Standard (SUSMP) it will be evaluated as a prescription medicine - refer to Australian Regulatory Guidelines for Prescription Medicines.

Overview of registered complementary medicines

Registered medicines are considered to be of higher risk than listed medicines based on their ingredients and/or therapeutic indications they carry. Medicines must be registered on the Australian Register of Therapeutic Goods (ARTG), where they:

- do not solely comprise ingredients permitted for use in listed medicines; or
- contain an ingredient or ingredient component that is subject to the conditions of a Schedule or relevant appendix to the Poisons Standard; or
- are required to be sterile; or
- have indications that are not indications permitted for use in listed medicines.

Prior to being approved for entry on the ARTG, registered medicines are subject to critical assessment by the TGA to determine whether the proposed medicine meets the requirements for quality, safety and efficacy.

Scheduling of registered complementary medicines

Registered complementary medicines may be subject to the conditions of a schedule (not Schedules 4, 8 and 9) or an appendix of the Poisons Standard, for example:

- Schedule 2 – 'Pharmacy Medicine'; or
- Schedule 3 – 'Pharmacist Medicine'.

It is important that you consider possible scheduling requirements before submitting an application for registration - refer to the Principles of Scheduling in the Poisons Standard and the AHMAC - Scheduling policy framework for medicines and chemicals. The decision to include a medicine in a schedule takes into consideration toxicity, the purpose of use, potential for abuse, safety in use and the need for the substance.

Products with similar substances and indications are likely to be subject to similar schedules. If a medicine contains a substance that requires scheduling control and it is not already scheduled, the TGA may classify the substance in one of the Poisons Standard's schedules when making the registration decision. If you are unsure of potential scheduling of your proposed medicine you should seek advice from the TGA.

Registration process for complementary medicines

This guidance is to assist applicants to register a complementary medicine on the ARTG.

This guidance:

- identifies the regulatory process you need to follow
- navigates you through the process step-by-step
- links to relevant guidance and forms.

Steps to register a complementary medicine

- Step 1—Verifying your complementary medicine and access to Business services

You can skip Step 1 if you have already determined that you have:

- a complementary medicine that you wish to register on the ARTG
- access to TGA Business services.

- Step 2—Checking ingredients and scheduling
- Step 3—Ensuring valid GMP evidence
- Step 4—Determining your application category
- Step 5—Checking guidelines and requirements
- Step 6—Requesting exemptions as part of your application
- Step 7—Compiling data for your application
- Step 8—Arranging a pre-submission meeting
- Step 9—Completing and submitting your application
- Step 10—Paying your fees
- Step 11—Screening your application
- Step 12—Evaluating your application and requesting information
- Step 13—The decision
- Step 14—Finalising your registration

Step 1—Verifying your complementary medicine and access to TGA Business Services

If you have already determined your product is a complementary medicine that you wish to register, and you have a client ID number and password to access TGA Business services, go to Step 2.

Verifying you have a complementary medicine

To verify you have a complementary medicine for registration on the ARTG, go to What are complementary medicines?

Related information and guidance

- Pathway to evaluating your medicine

Client identification and access to TGA Business services

Applications are created and lodged through TGA Business services.

You will need both of the following to make an application:

- a Client ID number
- password access to our Business services.

If you do not have a Client ID number or access to our business services:

- go to our Business services: getting started with TGA
- complete and submit the online organisation details form.

Next step

Go to Step 2—Checking ingredients and scheduling

Step 2—Checking ingredients and scheduling

Before you prepare your application to register a complementary medicine you need to make sure its active ingredients are designated active ingredients only.

If the formulation contains at least one non-complementary medicine active ingredient:

- your medicine will be evaluated via an alternate pathway (either an OTC or prescription medicine)
- you will need to follow the appropriate registration process (OTC medicines or prescription medicines).

Checking for ingredient names in our tables

Check whether the ingredients in the medicine are included in our Tables under Public TGA Information on the business services homepage:

- Ingredients Table
- Proprietary Ingredients Table

These code tables only provide the approved name or synonym for the ingredient.

It does not mean we have approved the ingredient for use in therapeutic goods.

New proprietary ingredients

You will need the proprietary ingredient ID number to complete your application and to register the medicine in Step 9.

If the proprietary ingredients are new (i.e. not in the Code tables), submit the completed Notification of a Proprietary Ingredient form to obtain a proprietary ingredient ID number.

We will issue you a proprietary ingredient ID number.

Proposing a name for new substances

If your registered complementary medicine contains a substance that is new, you will also need to propose a name for it. To do this:

- Follow the guidance on how to propose a new substance name.
- Select the relevant application form for proposing names:
  - Australian Approved Name (chemical substances)
  - Botanical name for a herb (an Approved Herbal Name)
  - Herbal component name
- Submit the relevant form via email to TGA Names.
- Make sure that you state that you have submitted the form in the cover letter of your complementary medicine application.

Scheduling ingredients

You also need to check if your complementary medicine is subject to the conditions of a schedule (excluding Schedules 4, 8 and 9) or an appendix of the Poisons Standard.

Medicines may be subject to the conditions of a schedule or an appendix of the Poisons Standard, for example:

- Schedule 2 – 'Pharmacy Medicine'
- Schedule 3 – 'Pharmacist Medicine'.

Consider possible scheduling requirements before submitting an application.

Medicines with similar substances and indications are likely to be subject to similar schedules.

If a medicine contains a substance that requires scheduling control, and it is not already scheduled, we may classify the substance when making the registration decision.

If you are unsure of potential scheduling of your medicine, you can contact Complementary medicines.

Next step

Go to Step 3—Ensuring valid GMP evidence

Step 3—Ensuring valid GMP evidence

You will need valid evidence that the manufacturer(s) of your complementary medicine have applied Good Manufacturing Practice (GMP) for each step of manufacture. To ensure this you will need:

- For Australian manufacturers**:** a copy of a GMP licence issued by the TGA
- For overseas manufacturers**:** a GMP clearance issued by the TGA.

Duration of GMP for overseas manufacturers

We cannot finalise your application without current and valid GMP clearance (issued by the TGA) for each overseas manufacturer.

You need to ensure that the GMP clearance will not expire during the evaluation timeframe.

As part of the Government's complementary medicine reforms, TGA will be consulting on target assessment timeframes for registered complementary medicines in late 2017.

GMP clearance that is due to expire

If the GMP clearance is due to expire within the minimum timeframe or is likely to expire before the application is finalised:

- Before you submit the application, you need to either:
  - apply to renew the GMP clearance
  - seek an extension to the GMP clearance expiry.

We recommend renewing the GMP clearance for applications with a target evaluation time exceeding 6 months rather than seeking extension of the GMP clearance because extension to the expiry may not cover the full period, to completion, of the application.

If you have requested an extension, or applied to renew the GMP clearance, state this in the application cover letter.

Guidance to complete this process

- Guidance on manufacturing medicines
- Chapter 2 of the GMP clearance for overseas manufacturers.

Next step

Go to Step 4—Determining your application category

Step 4—Determining your application category

There are 5 categories for applications to register complementary medicines based on risk, with category 1 being the lowest and category 5 being the highest risk.

The data requirements and target evaluation times increase with the level of assessment and risk mitigation required, so it is important that you determine the application category correctly.

To help determine the correct application category, see Application categories for registered complementary medicines.

If your application does not include the data required for its application category, we may not accept it for evaluation under section 23(2)(b) of the *Therapeutic Goods Act 1989*.

As part of the Government's complementary medicine reforms, TGA will be consulting on application category types for registered complementary medicines in late 2017.

Next step

Go to Step 5—Checking relevant guidelines and requirements

Step 5—Checking guidelines and requirements

When planning your application to register a complementary medicine, you will need to identify and understand the relevant technical and regulatory requirements and guidelines.

Guidance for effective applications

Use the following guidance to prepare your dossier of supporting information in Step 7. It will assist you to compile a complete application to pass the screening in Step 11 and progress to evaluation in Step 12.

- CTD Module 1—For complementary medicines (for all applications)
- General dossier requirements (for all applications)
- Cover letter (for all applications)
- Common Technical Document (relevant to the application category).

Technical document modules

For guidance on information needed for the evaluation of quality safety and efficacy, see:

- Module 2 - Summaries for quality, safety and efficacy
- Module 3 Quality data for RCM3, RCM 4 and RCM 5
- Module 4 Safety (non-clinical) for RCM 4 (if safety not previously demonstrated) and RCM 5
- Module 5 Efficacy (clinical) for RCM 4 (if efficacy not previously demonstrated) and RCM 5
- Presentation of non-prescription medicines
- Data requirements matrix
  - New registration
  - Change to existing ARTG entry.

Relevant guidelines

Ensure you check:

- all of the relevant European Union and ICH guidelines adopted in Australia for any specific requirements that apply to your application
- Therapeutic Goods Orders 69, 77, 78, 80 and 92.

Need assistance

If you have read the guidance and need our assistance, contact Complementary medicines.

Next step

Go to Step 6—Requesting exemptions as part of your application

Step 6—Requesting exemptions as part of your application

Exemption to use a restricted representation on the label

You will need an exemption if you are using a restricted representation on your medicine label.

You can include your request for an exemption in your application to register your medicine.

To do this:

- Complete the Application for approval to use a restricted representation in advertising.

Include this application in Module 1.2.5 Form for approval to use a restricted representation.

Restricted representations

Please note that approval for the use of a restricted representation can only be considered once the complementary medicine is registered on the ARTG.

Next step

Go to Step 7—Compiling data for your application

Step 7—Compiling data for your application

General requirements for your dossiers

Compile your electronic dossiers (includes Module 1 and the technical modules) according to the general dossier requirements and the data requirements matrix.

Dossier format

Compile the technical information consistent with the data requirements matrix, noting some parts may not be relevant for your application.

The dossier is divided into five modules:

- Module 1 for complementary medicines
- Module 2 summaries of quality, safety and efficacy
- Module 3 Quality
- Module 4 Safety (non-clinical study reports)
- Module 5 Efficacy (clinical study reports).

Further information on CTD modules can be found on the TGA website.

The minimum requirements for registered complementary medicine dossiers are:

- Single PDF document for each module
- PDF documents must be text searchable and either bookmarked or hyperlinked
- CTD heading and numbering must be used in each module.

Full or modified CTD dossiers may also be submitted.

The dossier format can be discussed with us at the pre-submission meeting (Step 8).

Data requirements

As part of the Government's complementary medicine reforms, TGA will be consulting on data requirements for registered complementary medicines in late 2017.

Follow the data requirements matrix to identify the data you will need for your application category.

The following guidance will help you to compile the data needed for each CTD Module:

- Data for CTD Module 1
- Summaries on quality, safety and efficacy for Module 2
- Quality data for Module 3
- Safety and efficacy of complementary medicines for Modules 4 and 5.

Make sure you submit all relevant data in the modules you need for your application category. Provide justifications as to why any data is omitted and discuss with us at the pre-submission meeting in Step 8.

Guidance for applications to be effective

Check to ensure your dossier:

- is complete
- is in the required format
- includes the information required for an evaluation of quality, safety and efficacy
- includes your application cover letter.

We will check whether the application can be accepted for evaluation during screening in Step 11.

If your application is incomplete or deficient, we will not accept it and it will not progress to evaluation.

Next step

Go to Step 8—Arranging a pre submission meeting

Step 8—Arranging pre-submission meeting

We recommend you arrange a pre-submission meeting with us prior to submitting your application for a new registered complementary medicine.

This will assist you to submit a high quality and complete dossier.

Discussion will focus on the structure of your proposed application, the identification of critical issues and the suitability of your proposed approach.

We do not:

- ✘ assess or evaluate as part of a pre-submission meeting.
- ✘ charge a fee for a pre-submission meeting.

To arrange a meeting, follow the guidance on pre-submission meeting with TGA.

Include the meeting record in Module 1.7 Compliance with meetings and pre-submission processes.

Next step

Go to Step 9—Completing and submitting your application

Step 9—Completing and submitting your application

In this step, you will be completing the application form and submitting your application to register a complementary medicine.

How to complete the application form

To complete and submit your registered complementary medicine application, follow the instructions within:

- Getting started online
- Using the online RCM application form
- Completing the online application form for RCMs

Submission ID number

You will be automatically issued a submission number, which uniquely identifies the application.

Use this submission number in all future communications about the application.

Monitoring the application progress

You can monitor the workflow status of your applications through Business Services.

Use the sponsor portal and the menu option 'View lodged submissions', under the column 'Workflow Status'.

The application start date is the date that the fees are processed.

Withdrawing an application

You can withdraw an application at any time up until the decision is made.

You can use Business Services to withdraw an application. Follow the instructions in Using the online RCM application form. Alternatively, you can advise us in writing of your intention to withdraw the application.

If the application is withdrawn due to safety issues, we may ask you to provide any adverse safety data.

When an application is withdrawn, we may retain the application and any material submitted in connection with the application.

Refund when an application is withdrawn

We will:

- ✓ refund the evaluation fee if the application is withdrawn *before* it enters the *evaluation step* in the process
- ✘ not refund the application fee.

Next step

Go to Step 10—Paying your fees

Step 10—Paying your fees

When you apply to register a complementary medicine, we will invoice you for both the application fee and the evaluation fee together.

For details of the current fees, go to Schedule of fees and charges.

Invoicing the fees

You will automatically receive an invoice when you submit the application.

It is important to pay the application and evaluation fees when you receive the invoice as we do not start screening the application until the fees are processed.

We may need to adjust the evaluation fee from that invoiced at the time of submission if:

- the application contains clinical or toxicological data for evaluation—that is, a higher evaluation fee applies, based on page count
- we grant your request to waive or reduce the evaluation fee.

We will assess the evaluation fee during screening (see Step 11) and, if necessary, we will issue:

- an invoice, for any additional fees that apply
- a refund, if we waive or reduce the evaluation fee.

Waive or reduce evaluation fees

- In some circumstances, we may be able to waive or reduce the evaluation fee (not the application fee) under Regulation 45 of the *Therapeutic Goods Regulations 1990*.
- Check these regulations to see if you are eligible for a waiver or reduction in evaluation fees.
- Once you have checked, if you then think you may be eligible include a request and justification in the application cover letter.
- We will make a decision prior to accepting the application for evaluation.

Paying the fees

For information on fees and the available payment methods see:

- Fees & payments
- Payment options

Making payments by cheque

If you are paying the application fees by cheque:

- indicate in the covering letter that payment has been forwarded to TGA Finance.
- forward payment, together with a copy of the relevant invoice, by *separate post* to:

  TGA Finance
  PO Box 100
  WODEN ACT 2606
  Australia

Do not:

- ✘ include cheque or credit card details with the submission.

Paying additional evaluation fees

You will need to pay any additional evaluation fees in full within 2 months of the date of the invoice or the following will occur:

- the application will lapse (section 24(2)(a) of the *Therapeutic Goods Act 1989*) and will not be evaluated
- you will forfeit the application fee.

Next step

Go to Step 11—Screening your application

Step 11—Screening your application

We will screen your application to verify it meets both the administrative and technical requirements.

What makes an effective application

Your application is effective if it meets the requirements under section 23(2) of the Act. This means:

- The prescribed application fee has been paid.
- The application includes all **information required**, for the correct application category, to enable us to make a decision.
- Applications for restricted medicines[4] include a form for providing product information that is approved under section 7D of the *Therapeutic Goods Act 1989* (section 23(2)(ba) of the Act).
- Samples of the medicine have been delivered to the TGA (only if requested).

We rely on information in your application cover letter to confirm the application category and corresponding data requirements.

Screening checks

The screening checks aim to identify at the outset whether your application is effective.

Ensure you:

- complete all required fields on your application form
- have paid the applicable fee
- provide sufficient information in your dossier
- choose the appropriate pathway for evaluating your medicine.

Effective applications

If your application is effective, we will notify you in writing regarding both:

- the acceptance of your application for evaluation
- the applicable evaluation fee, if it differs from what you have paid on application.

The evaluation process will not commence until you have paid the evaluation fee in full.

Opportunity for minor corrections

You will have an opportunity to make minor corrections, detected during the screening process, if the issue can be rectified promptly. For example, if we cannot locate an attachment mentioned in the application we will give you an opportunity to provide the attachment.

[4] Defined in the *Restricted Medicine Specification 2011* and include prescription medicines (see Schedules 4 and 8 of the current Poisons Standard) and medicines that are only available from a pharmacist (Schedule 3 of the current Poisons Standard).

Ineffective applications

If your application is ineffective, we will:

- not accept it for evaluation
- remove your application from Business services
- write to you and explain why the application is ineffective
- refund the evaluation fee.

You will forfeit the application fee.

If you reapply to register the medicine, ensure your application meets the requirements for an effective application.

You cannot lawfully import, supply or export the medicine until you have an ARTG registration.

Lapsing applications

Your application will lapse if evaluation fees are not paid within two months of becoming payable.

We will notify you that your application has lapsed.

You will need a new application if you wish to register the medicine.

Next step

Go to Step 12—Evaluating your application and requesting information

Step 12—Evaluating your application and requesting information

During this step in the process, to register a complementary medicine, we will undertake the evaluation and may request information under Section 31 of the Act.

During evaluation of your application, we will:

- evaluate the data and information on the quality, safety and efficacy and presentation of the medicine
- review your responses to our requests for information
- document our findings.

Evaluation target timeframes

We are implementing target timeframes for evaluating registrable complementary medicines.

As part of the Government's complementary medicine reforms, TGA will be consulting on target assessment timeframes for registered complementary medicines in late 2017.

Quality data

We evaluate the quality of the medicine, including the identity, impurities and stability of all ingredients and take into account information about:

- The manufacturing processes and the compliance with GMP.
- Quality-controls to determine if the quality of the medicine will be consistent.
- Stability data to confirm the medicine is of appropriate quality over its proposed shelf–life.

Safety data

Our assessment of safety data includes:

- history of use
- pharmacology and pharmacokinetics
- drug interactions
- toxicology
- clinical trials
- reports of adverse reactions.

Efficacy data

We assess efficacy data to determine whether it supports the indication(s)/claim(s) including:

- a detailed evaluation of the proposed indication(s)
- any claims that you intend to make for the medicine.

Presentation of the medicine

We assess all aspects of the medicine presentation, including, for compliance with the various legislative requirements (including advertising requirements) and to ensure clarity for consumers in relation to the medicine and its proposed use. This includes:

- proposed labelling
- Product Information and Consumer Medicine Information (when provided).

Requesting information

We may request you to provide information to clarify or address issues that we identify.

We make these requests for information under section 31 of the Act and include a timeframe for you to respond.

Responding to requests for information

It is important that you respond to our requests for information within the given timeframes and provide complete and accurate information.

Preparing your response

If the request for information relates to the content of a module of the submission dossier:

Provide an electronic copy of the response in the format described in step 7.

✘ Do not provide additional data (Unsolicited information) unless we request it.

Due date for responding to requests for information

✘ Do not wait until the response is due to request an extension of time.

✘ We will not extend the due date unless you can demonstrate that the time allowed is not reasonable.

If we do not receive your response within the timeframe or you only send a partial response, we will proceed with the evaluation based on the information we have available.

If you do not provide all of the information requested and the outstanding issues are significant, the decision maker may decide **not to** register the medicine (in Step 13) based on available information.

Unsolicited information

We do not evaluate unsolicited information or data, unless it is:

- New safety data that might negatively influence the benefit-risk assessment of the medicine. You are obligated to inform us about this as soon as it becomes available.
- Updated TGA manufacturing licences or clearances for the sites listed in the application.

Expert advisory committee advice

We may decide to seek advice from an expert advisory committee, such as the Advisory committee for complementary medicines (ACCM).

We will inform you about:

- the committee meeting and give you an opportunity to provide comment for the committee's consideration
- any relevant advice from the committee.

The advisory committee process will typically extend the evaluation timeframe.

Related information

- Statutory expert committees

Next step

Go to Step 13—The decision

Step 13—The decision

Before the delegate makes a decision on whether to register a complementary medicine, you may need to verify the details of the application, including any changes during the evaluation.

Matters considered before making a decision

When making the decision under section 25 of the *Therapeutic Goods Act 1989* on whether to register the medicine on the ARTG, the decision maker (the delegate of the Secretary of the Department of Health) will:

- review all documentation associated with the application, including:
  - the application and submission dossier
  - the evaluation reports
  - responses to requests for information
  - advice from expert advisory committees
  - other relevant advice or information.
- consider the matters detailed under section 25 of the Act, including whether the quality, safety and efficacy of the medicine have been established.

We will send you a written notification of the decision.

Next step

Go to Step 14—Finalising your registration

Step 14—Finalising your registration

This step involves finalising the registration once a decision has been made on whether to register the medicine.

Decision to register the medicine

If the decision is to register the medicine, we will send you the decision letter.

This letter will include standard and specific conditions on the registration of your medicine under Section 28 of the Act.

It is important that you read, understand and comply with these conditions.

If you do not comply with any one of these conditions of registration, your medicine may be cancelled from the ARTG under section 30(1)(da) of the Act.

The decision letter will also request you to provide assurance that all details of the medicine are correct before we create the ARTG entry.

Related information and guidance

- Appendix 4 of DR4—Conditions-standard and specific

Patent certification under the Australia/USA free trade agreement

You need to provide a patent certificate under subsection 26B(1) of the Act, or notification that this is not required before the medicine can be registered on the ARTG.

If you have not already provided the patent certificate or notification form with your application, complete either the:

- approved form for notification that 26B(1) certificate is not required
- relevant approved subsection 26B(1)(a) or (b) certificate.

Send the completed and signed notification form or certificate by email to complementary.medicines@health.gov.au quoting the application submission number.

Registering the medicine and your ARTG certificate

Once we receive the completed and signed notification form or patent certificate:

- We will register the medicine on the ARTG.
- You can download your certificate of registration from Business Services. To do this, follow the guidance on printing your ARTG certificate.

Date of effect of the registration

The registration of your medicine will commence on the day specified in the certificate of registration.

The medicine cannot be lawfully imported, exported or supplied by the applicant prior to this date.

Annual charges

Annual charges will apply once the medicine starts generating turnover.

Related information and guidance

- Annual Charge Exemption Scheme

Decision not to register the medicine

If the decision is not to register the medicine, the decision letter will include both:

- a statement of the reasons for the decision
- information on your rights to seek a review of the decision.

Related information and guidance

- TGA internal review guideline

Getting started online

Getting a user ID

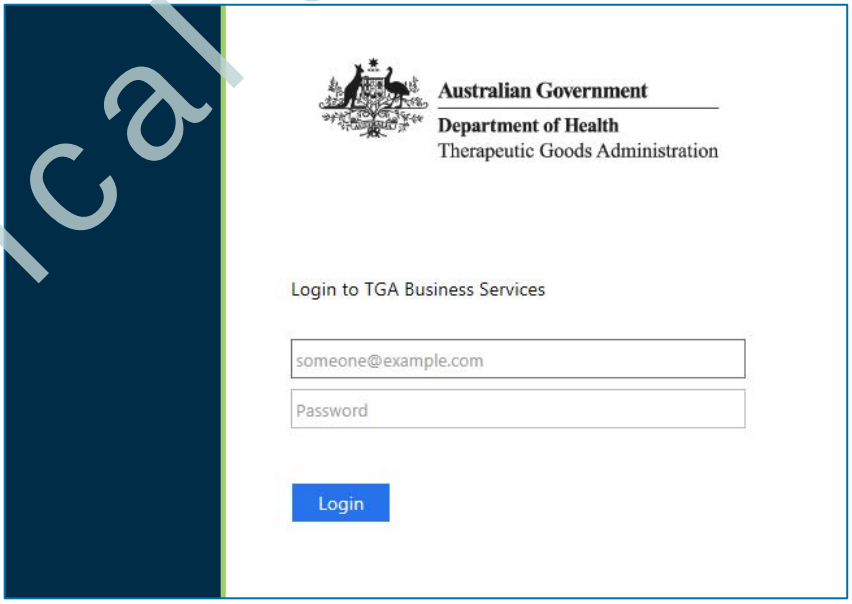
To submit an application for a registered complementary medicine you will need both a client identification number (Client ID) and access to our secure online TGA Business Services (TBS) website. This site is separate to our main website, www.tga.gov.au.

If you already have access and a Client ID, skip to Logging in. If you don't have these, follow the steps below:

- Go to TGA Business services: getting started with the TGA.
- Follow the instructions provided for completing the Organisational details form.
- Page 2 of the organisational details form asks you to nominate one representative from your organisation to have Administrator access. This person will be able to add and remove access for other representatives from your organisation. More information about the various 'roles' within TBS can be found at TGA Business services - how to use the site.
- You will be notified by email when you receive Administrator access, and the email will contain a guide to setting up your password.
- Once you are ready, go to Logging in.

Logging in

Go to our secure online TGA Business Services site and you will then be prompted to enter your login details on the right hand side of the screen:

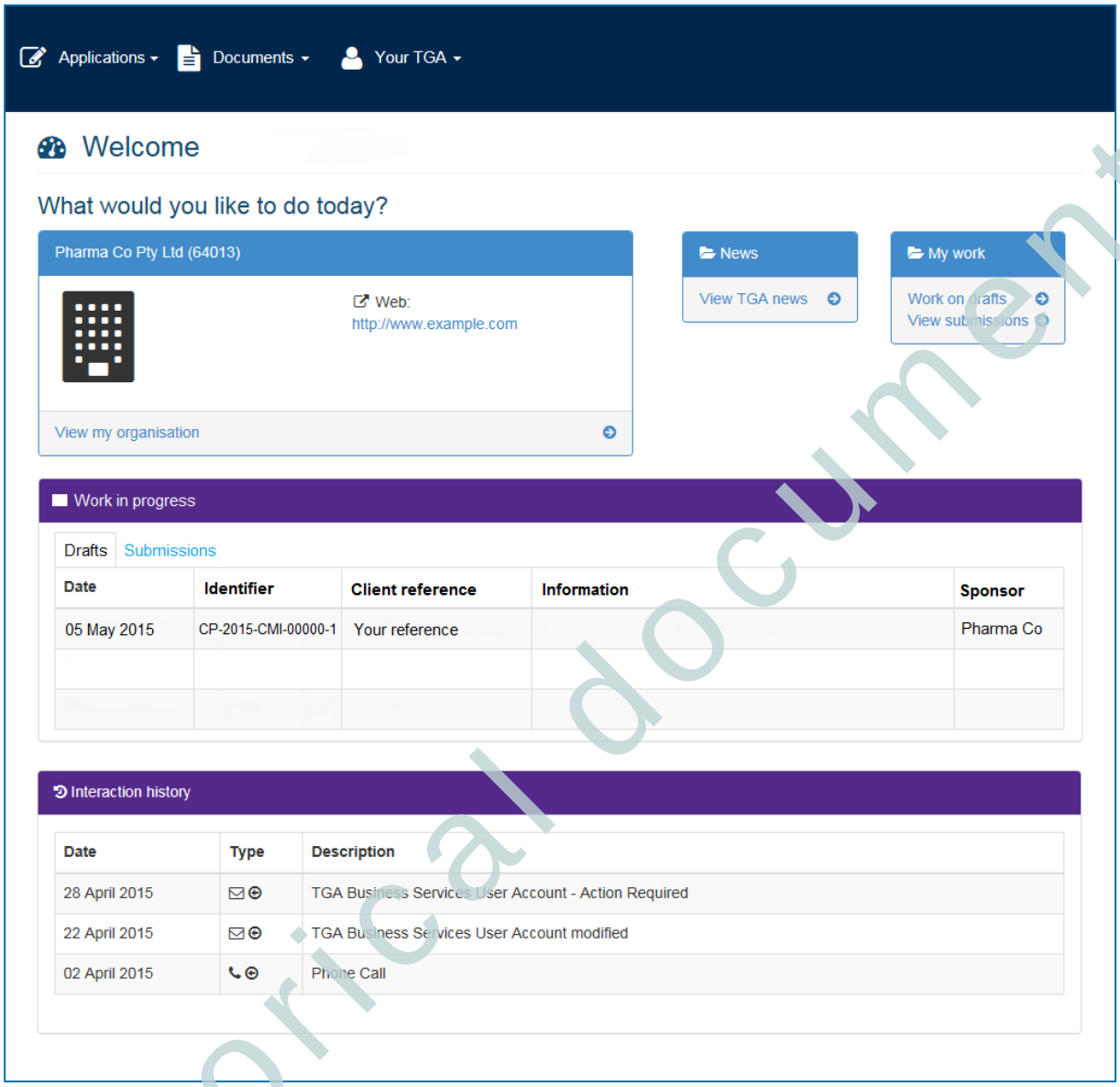


Once logged in, you will see a personalised work page or 'Dashboard'. What you can see and do on the Dashboard will depend on what role you have been given. Further information on what each role can see or do can be found at TGA Business services - how to use the site.

The dashboard

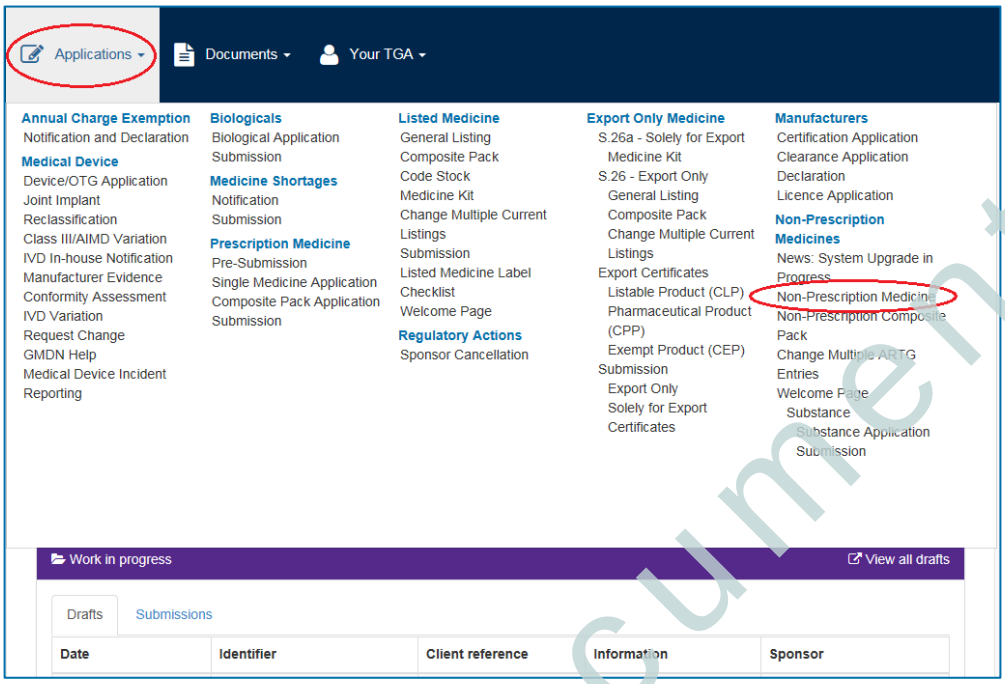
Across the top of the dashboard there are three main menus: ***Applications***; ***Documents***; and ***Your TGA***. If you also have Financial access, you will see an additional ***Financials*** menu displayed.

- To begin completing a new application form, select the ***Applications*** menu.
- If you want to open an existing draft you have saved, select ***Work on drafts*** from the ***My work*** menu.



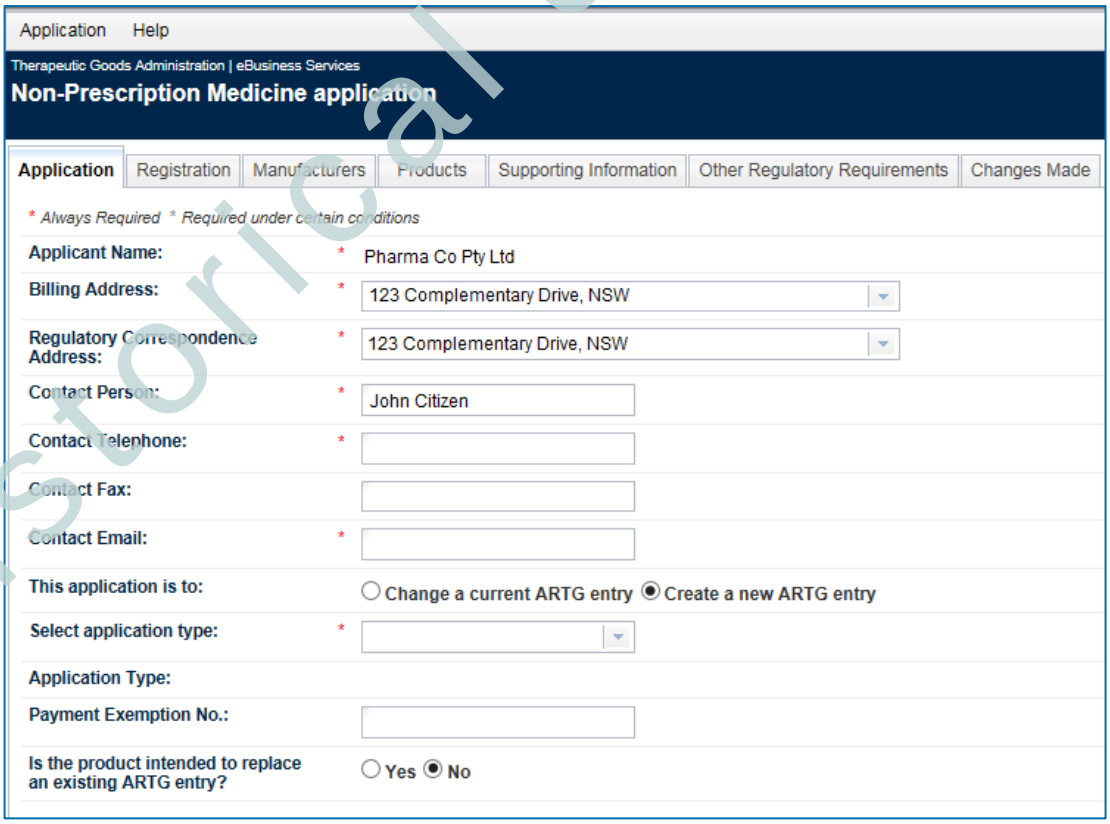
Starting a new application form

Select ***Applications*** from the top menu. This will open a list of various application types.



Select ***Non-Prescription Medicine***, which will take you to the first page of the application form, starting with the ***Application*** tab.

Some of the fields will already be pre-filled; however, you should confirm these are correct.



Using the online RCM application form

Data entry and field types

If you haven't used one of our online forms before, this guide will introduce you to the different field types that are used, and how to save, edit and validate application forms.

Fields that have a red asterisk* against them are mandatory, and fields that have a grey asterisk* against them are 'required under certain conditions'.

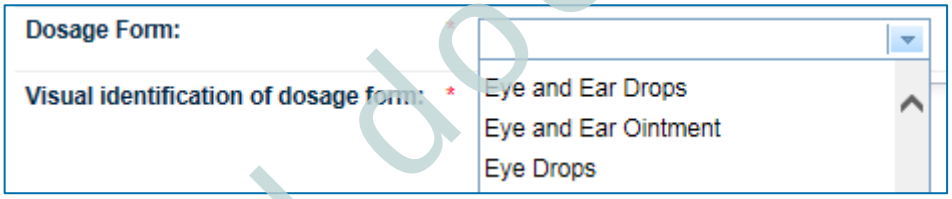
You can leave some fields blank while drafting a new application, and save the draft to finish later. However, be aware that the form will not validate (and therefore, it cannot be submitted) until all mandatory fields have been completed.

Radio buttons

Radio Buttons are used when only one option may be selected, for example:

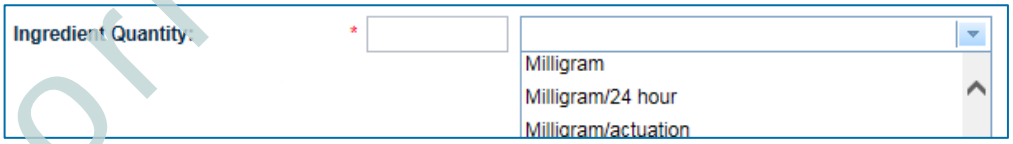
Drop-down lists

A drop-down list allows the user to select one choice from a list.



Numeric fields

Only enter numbers in this field, and do not enter negative numbers. Decimal points are acceptable if required. In many cases, there will also be a drop down menu next to the quantity field to select the relevant unit of measurement.



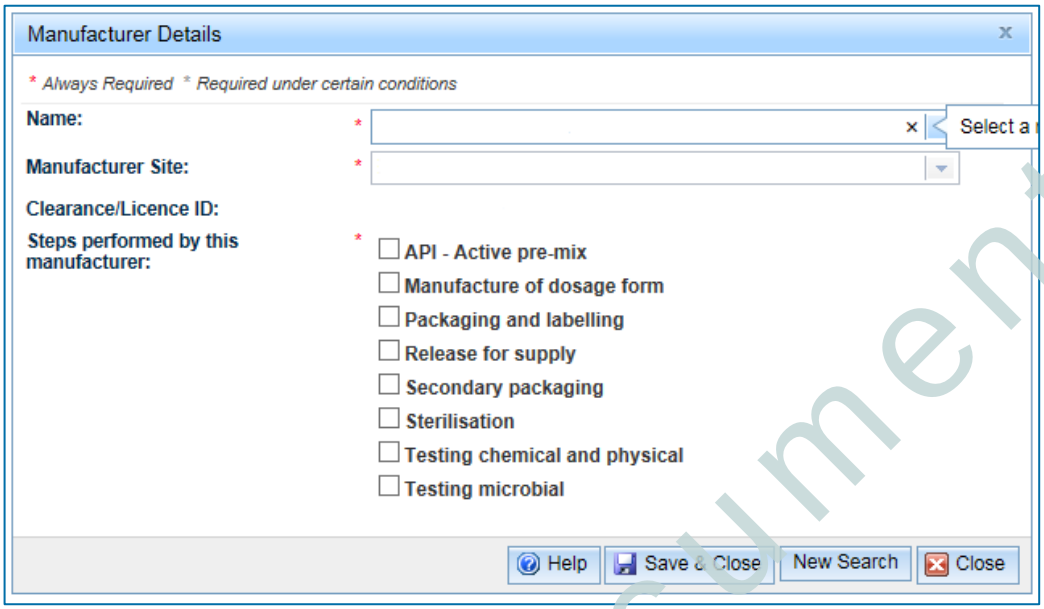
'Free text' entry fields

You can type (or paste) text in these fields:

If the text exceeds the amount displayable in the text box, a vertical scroll bar will appear so you can move the text up and down to view, however if text reaches the field limit no further input will be possible.

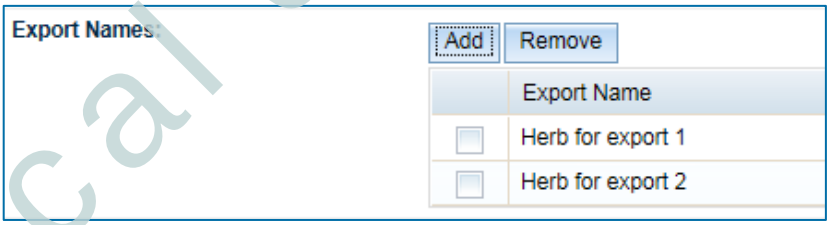
Check boxes

Check boxes are used when more than one option may be selected from a list. Clicking a check box may open up additional fields or sub-forms you will need to complete. For example:



Add/remove buttons

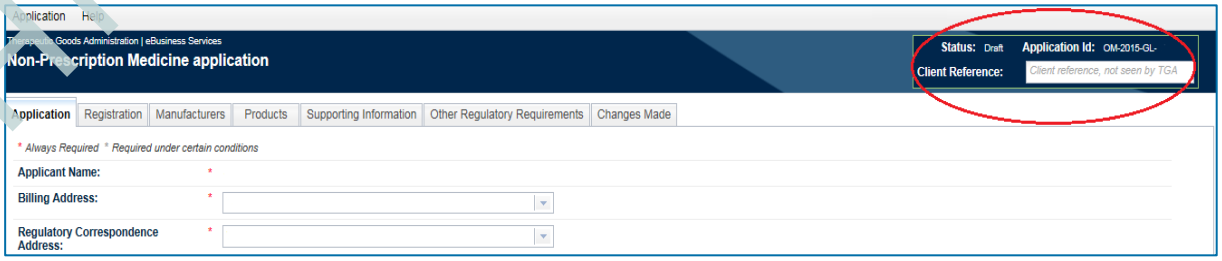
The application form has various fields to enter additional details by selecting the ***Add*** button where available, and entries within the form can be removed by selecting the check box next to that entry and then selecting the ***Remove*** button.



Form layout

The top right of the application form displays:

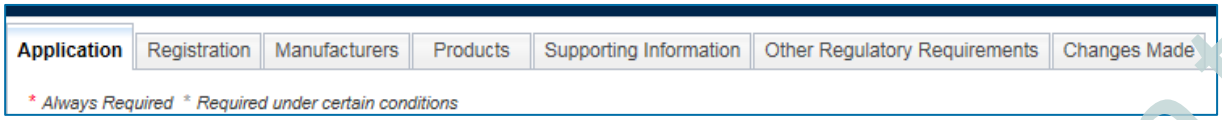
- the Application ID (generated when the form is first saved)
- status of the form (e.g. Draft)
- a client reference 'free text' field (for the sponsors' use, and not visible to TGA).



Form tabs

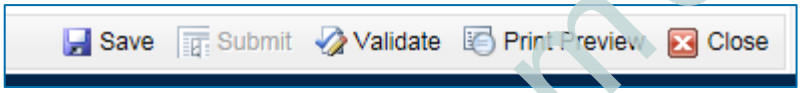
There are seven (7) tabs that make up the application form: ***Application***, ***Registration***, ***Manufacturers***, ***Products, Supporting Information, Other Regulatory Requirements***, and ***Changes Made***.

These are located from the top left of the form, and you can navigate through the form by clicking on the individual tabs.



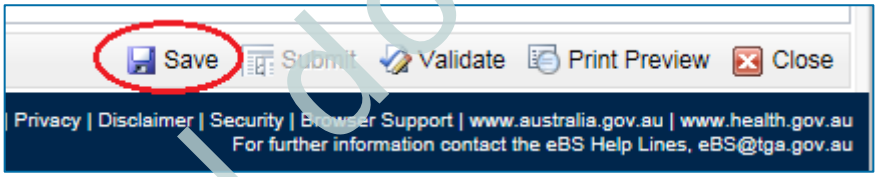
Action toolbar

The action toolbar is located at the bottom right of the form, and is described later in this guide.

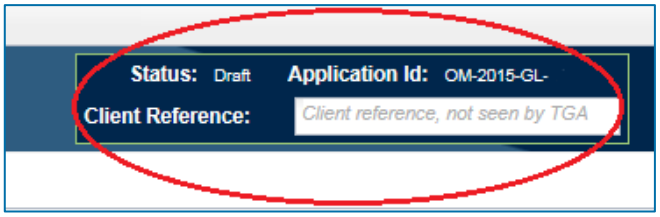


Saving a draft

You can save a draft notification at any time by selecting ***Save*** at the bottom right of the application form screen. We recommend you save the application at regular intervals, to ensure no ongoing work is lost.



When the application form is first saved, an Application ID is generated and will be displayed at the top right of the application form.

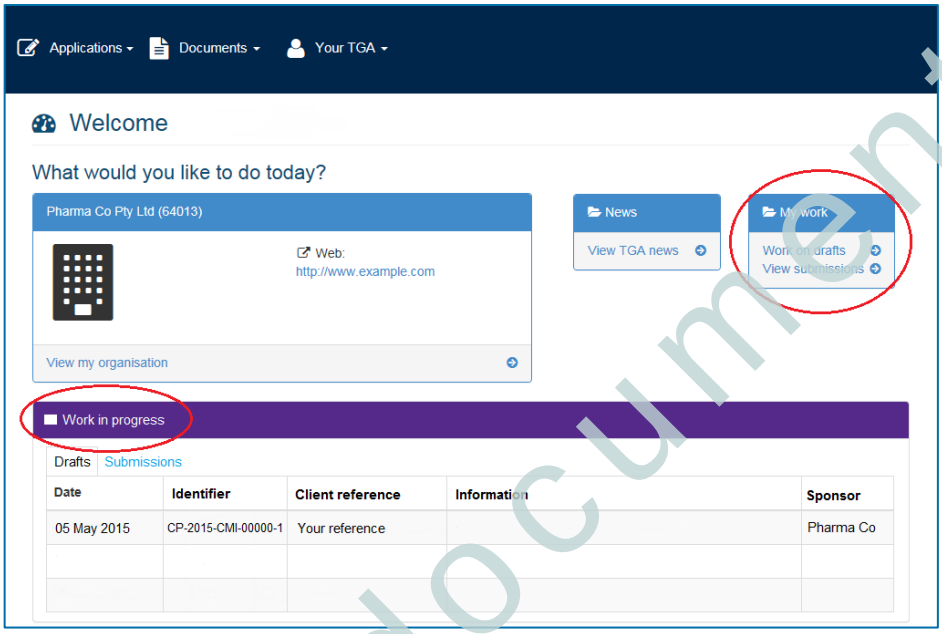


Editing a draft

You can edit your drafts at any time **prior to submitting them**.

Opening a saved draft

You can see a list of the drafts you have saved in the ***Work in progress*** list. To open a draft, select ***Work on drafts*** in the ***My Work*** menu on the dashboard.



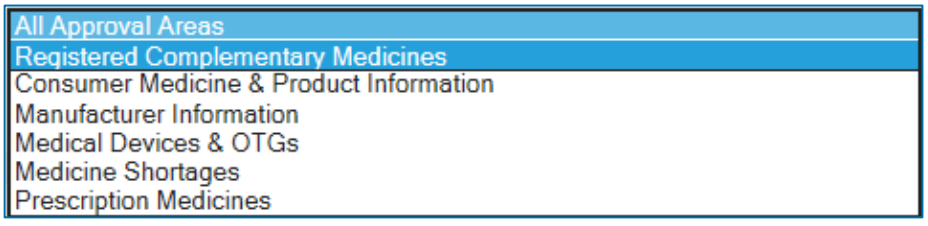
This will take you to the list of drafts for your organisation. Select the relevant entry on the list (for mouse users, a single click) to go to that draft.

Note: *Don't select the small down arrow or information icon immediately to the left of each entry on the list. These have different functions.*

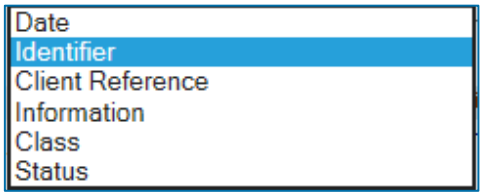
Filtering your selection

If you have a lot of drafts on your list, you can filter it to make your draft easier to find.

For example, you can filter by ***Approval Area*** using the drop down list.



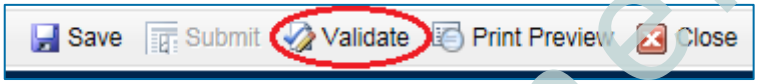
Or, you can filter by ***Date***, ***Identifier***, ***Client Reference***, ***Information***, ***Class***, or ***Status***.



Validation

The application form must pass validation before it can be submitted. (We recommend that you save your draft before selecting validate.)

To validate the form, select ***Validate*** located at the bottom right of the form.



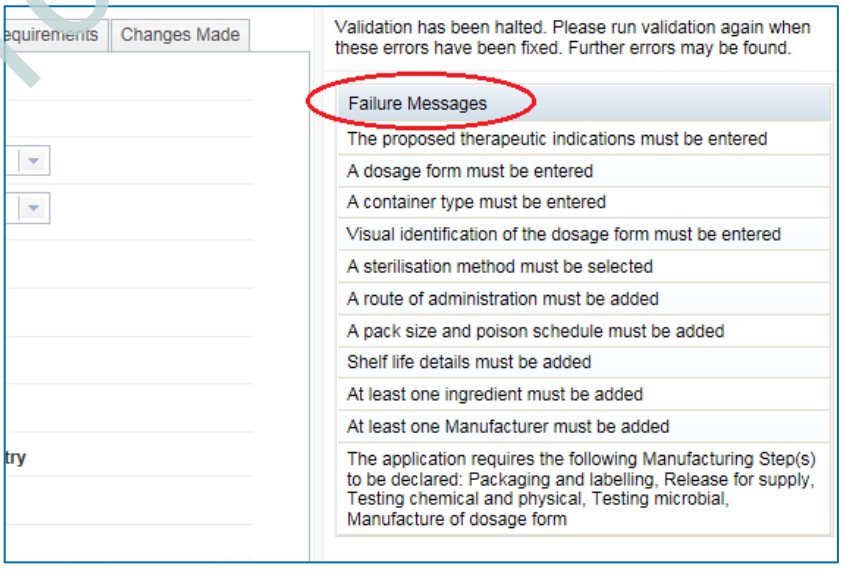
The validation process checks that all compulsory fields are completed, and that information is entered in the correct format (e.g. email addresses).

If there are no validation errors, the status of the form (top right of window) will change from ***Draft*** to ***Passed Validation***.

Validation errors

If the form won't validate, the status will remain as ***Draft***, and you will be shown the fields you need to fix (and where you need to fix them) in a list which will appear on the right hand side of the form.

Selecting each error on the list (double click for mouse users) will take you to the field that you need to correct.



Once you have corrected these fields, you should save the form before trying to validate again. Further validation checks may uncover additional errors that need attention.

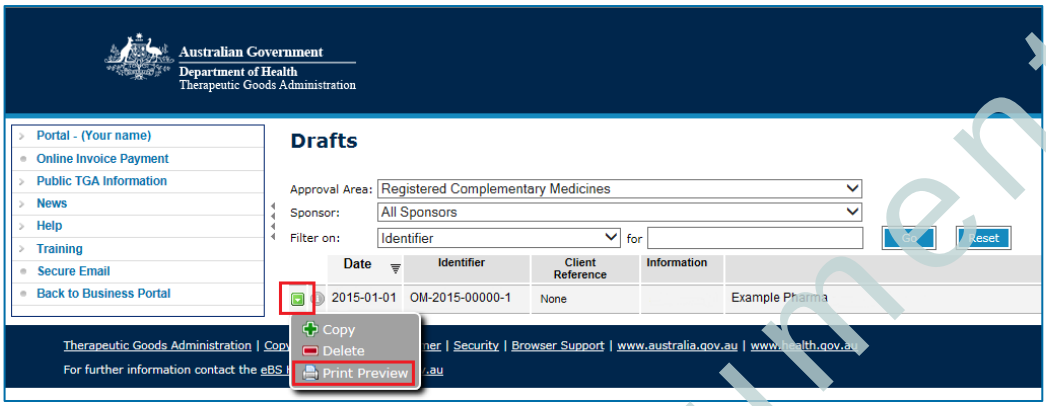
If you have issues with your application, you can contact the TGA by email: complementary.medicines@health.gov.au or by phone: 1800 020 653.

Printing, deleting, and copying

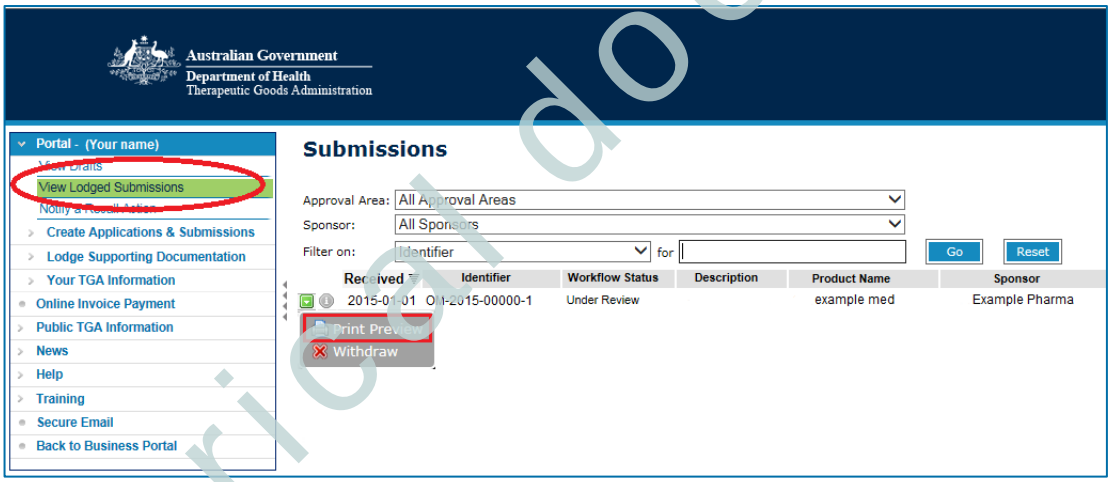
Printing

You can print the application form at any time before or after submitting it.

From the ***Drafts*** list, select the drop down arrow located at the far left of each draft, and then select ***Print Preview*** from the list.



From the ***View Lodged Submissions*** list, select the drop down arrow as above, and then click ***Print Preview***.



You will then see a preview of the draft or submission you want to print, and you have the option to either print or close the window.

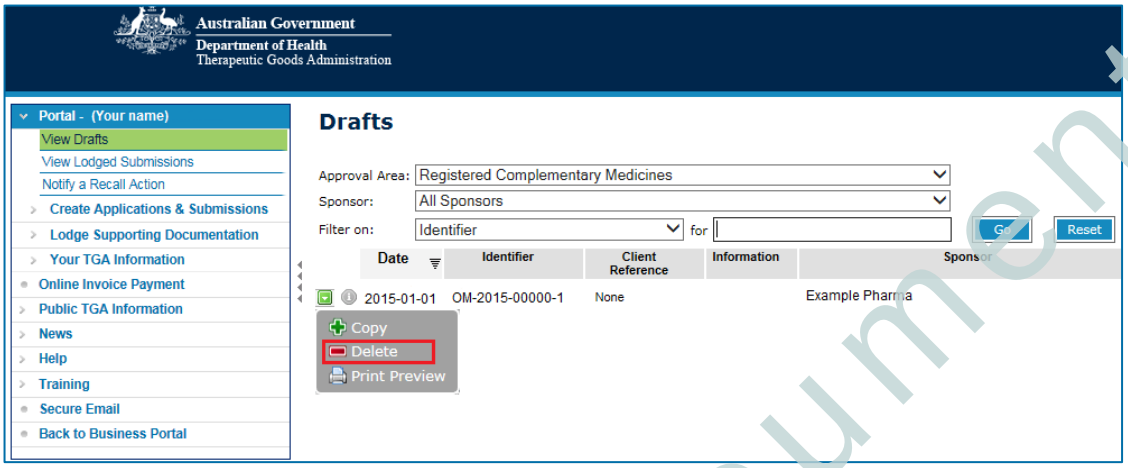
- Pressing ***Print*** brings up the printing options on your computer.
- Pressing ***Close*** takes you back to the list.

Deleting

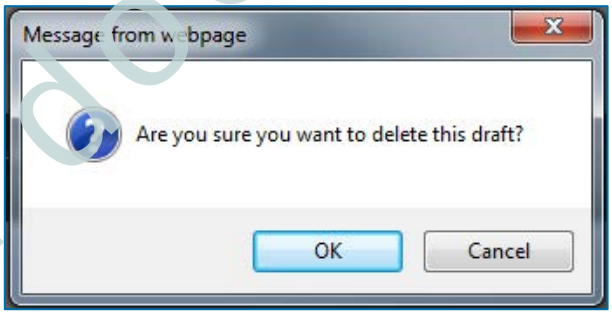
You can delete a draft application at any point up until the time you submit it.

To do this, select ***View Drafts*** near the top of the ***Portal*** menu.

Select the drop down arrow (located at the far left of each entry – it will turn green when selected), then select ***Delete***.



You will be asked to confirm that you want to delete the draft.



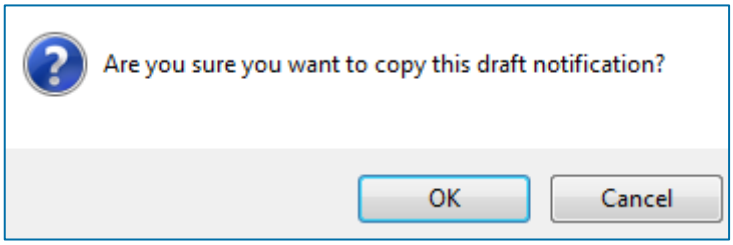
Select the ***OK*** button if you wish to proceed, or ***Cancel*** to go back to the ***Drafts*** list.

Copying

You can copy any draft application form to create a new draft. Information from the copied draft is retained for every field.

Go to the draft list, located via the ***View Drafts*** link in the ***Portal*** menu.

Select the drop down arrow located at the far left of the listing, and then select ***Copy***. A dialog box will ask if you are sure you want to copy this draft notification.



Selecting ***OK*** creates a new draft application form, and selecting ***Cancel*** takes you back to the Drafts list.

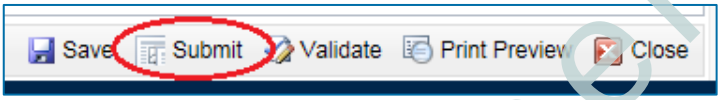
Submitting

Tip

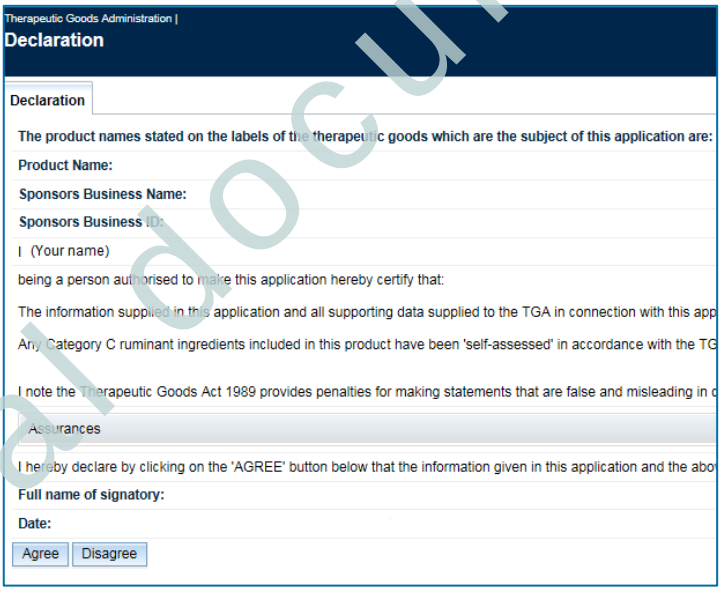
It may be worthwhile making a copy of your application before submitting it.

This would be useful in cases where you need to temporarily withdraw an application, as doing so removes all the originally submitted information and you would otherwise have to start filling in a new application from scratch.

Once validation is successful, the ***Submit*** button will fully display in the action toolbar.



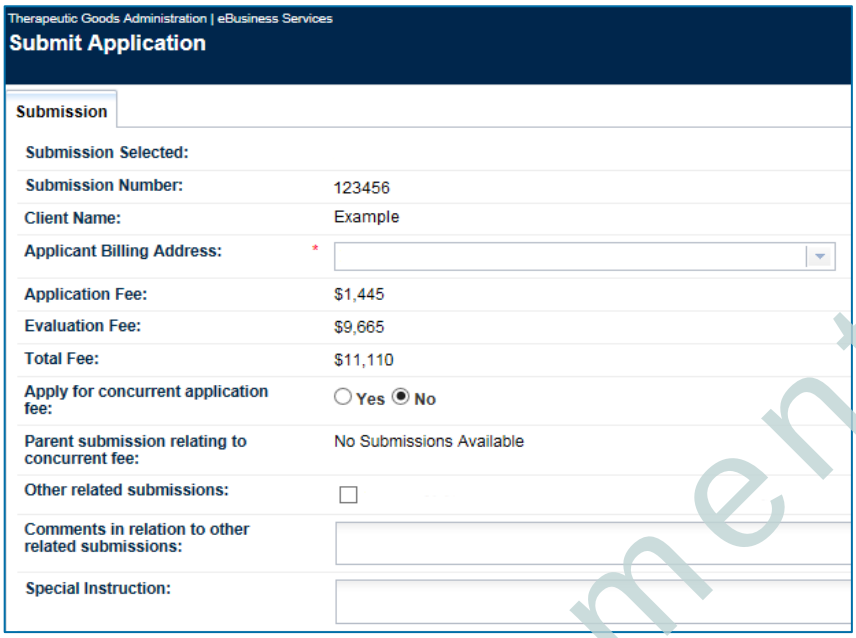
Selecting ***Submit*** will first take you to the ***Declaration page***. The full text of the Declaration can be found below.



Selecting ***Disagree*** will take you back to the application form.

Selecting ***Agree*** takes you to the next submission step, which allows you to:

- confirm basic submission details
- add any extra comments or instructions
- see the total fee (application + evaluation fee)



Once completed, select ***Submit*** (bottom right hand corner of the form), and you will be taken to a final ***checklist*** to confirm some basic administrative information.

If everything is correct, select ***Submit*** again (bottom right hand corner of the form), and your application will be submitted to us.

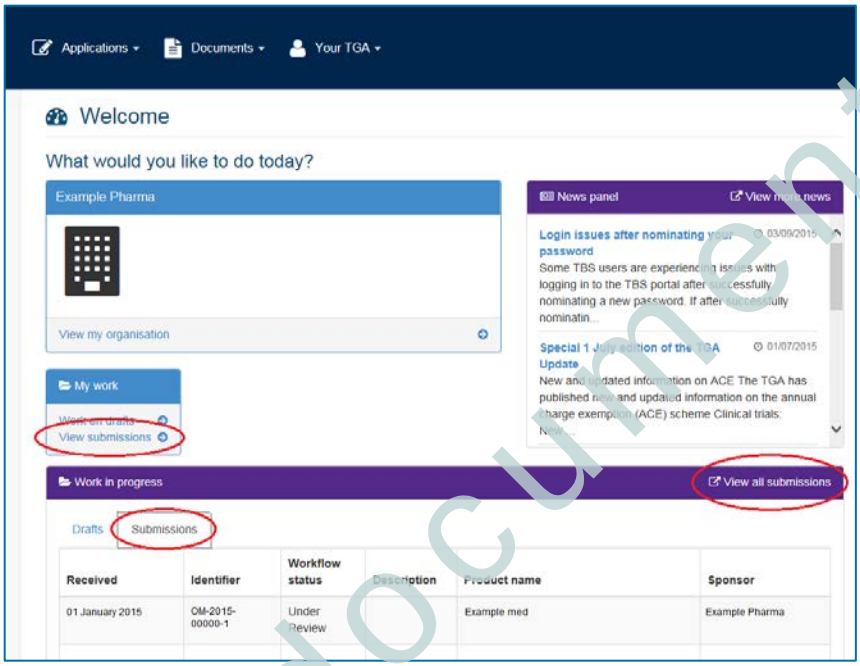
A notification page then displays which:

- confirms a successful submission
- provides your submission number
- gives instructions for printing your invoice

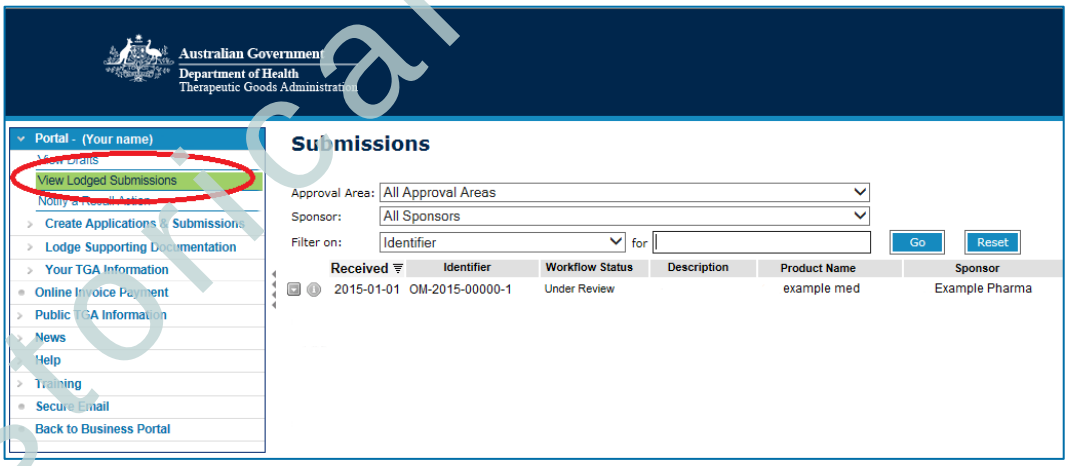
View lodged applications

From the dashboard view, there are two ways to get to your submissions list:

- Select ***View submissions*** from the ***My work*** menu
- Select the ***Submissions*** tab in the ***Work in progress*** list, then select ***View all submissions***



If you are in the eBS view, select ***View Lodged Submissions*** in the ***Portal*** menu on the left of the screen.



Any of these will take you to the list of submissions for your organisation. Select the relevant entry on the list (for mouse users, a single click) to go to that application.

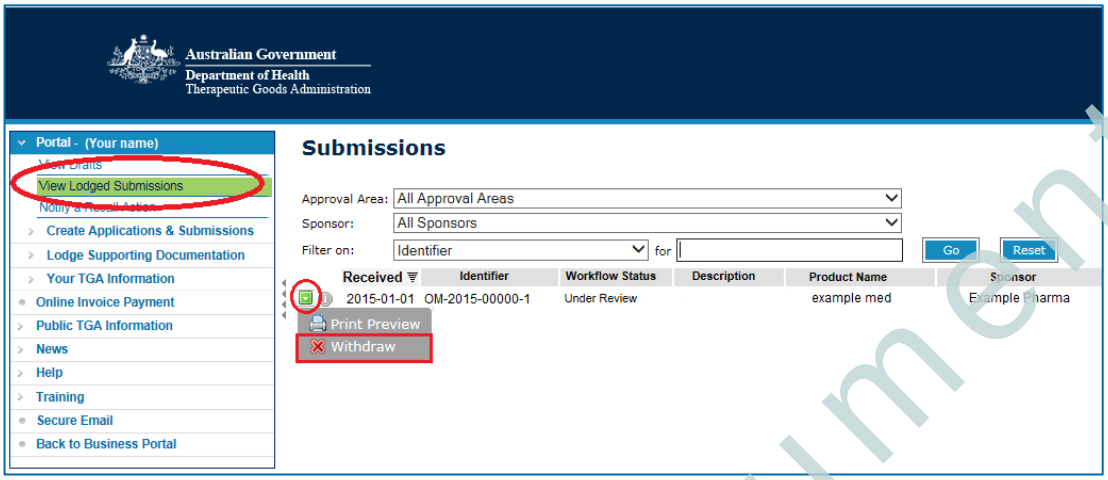
Note: *Don't select the small down arrow or information icon immediately to the left of each entry on the list. These have different functions.*

You can filter the list in the same ways as described in Filtering your selection (Editing your draft section).

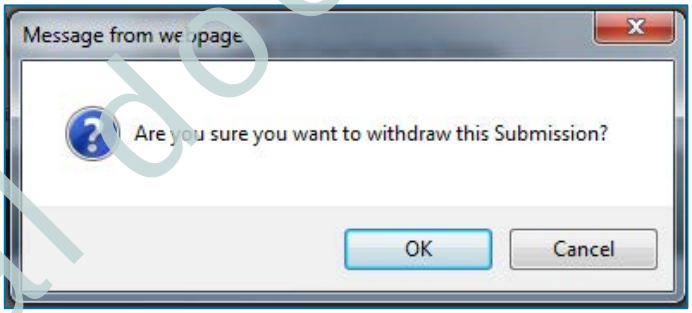
Withdrawing a submission

If you wish to withdraw an application, go to your ***Submissions*** list and select the down arrow to the left of the relevant entry.

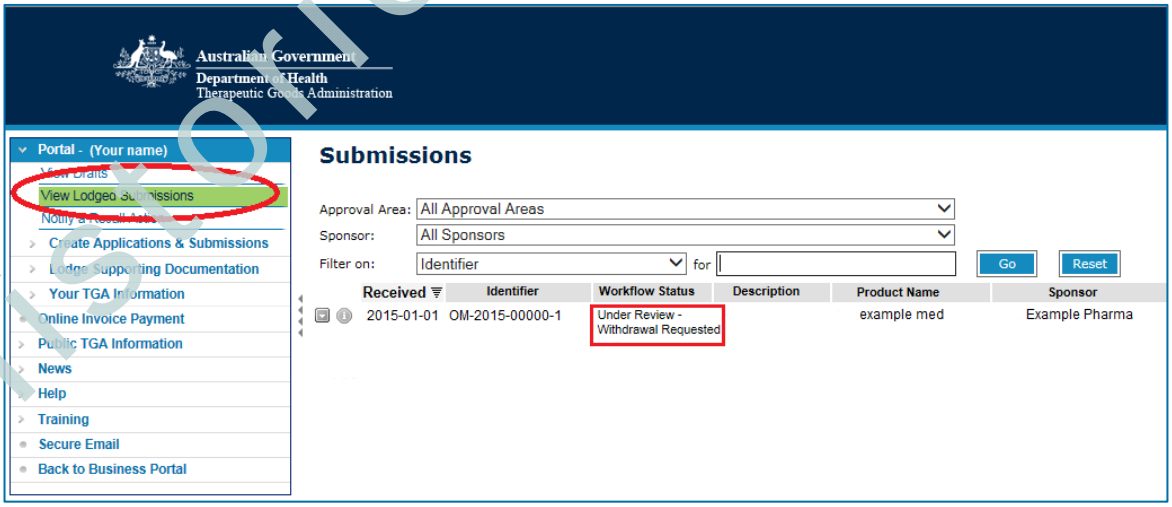
Then select ***Withdraw*** from the available options.



You will be asked to confirm if you want to withdraw the submission. Select the ***OK*** button if you wish to proceed, or ***Cancel*** to go back to the submissions list.



If you select ***OK***, the ***Workflow Status*** for that entry will have *'Withdrawal Requested'* added.



Full text of Declaration

The product names stated on the labels of the therapeutic goods which are the subject of this application are:

Product Name:

Sponsors Business Name:

Sponsors Business ID:

I …….. being a person authorised to make this application hereby certify that:

The information supplied in this application and all supporting data supplied to the TGA in connection with this application, or as revised by TGA and presented here for my verification, is current and correct.

Any Category C ruminant ingredients included in this product have been 'self-assessed' in accordance with the TGA's "Supplementary requirements for therapeutic goods for minimising the risk of transmitting transmissible spongiform encephalopathies (TSE's)" and comply with those requirements.

I note that the *Therapeutic Goods Act 1989* provides penalties for making statements that are false and misleading in connection with an application for registration of therapeutic goods.

Assurances

I hereby declare by clicking on the 'AGREE' button below that the information given in this application and the above statements on this declaration form are current and correct.

Full name of signatory:

Date:

Completing the online application form for RCMs

Help

- If you require specific help with your registered complementary medicine application, please contact the Complementary and OTC Medicines Branch (COMB).
- For further information about registering and using the TGA Business Services website go to TGA Business Services (TBS).

Fields in the application form

The information below will assist you in providing the required information for completing (and submitting) an online application for a Registered Complementary Medicine (either for new ARTG entries or changes to existing ARTG entries).

- **Ensure you complete ALL fields**, indicating 'nil' or 'not applicable' if required.
- Simple fields (e.g. phone numbers) will not have any further explanation in this guidance.

Application details tab

Applicant name

This field is pre-populated based on the TBS logon ID used.

Billing address

Select address recorded in TBS for this sponsor (drop-down list).

Regulatory correspondence address

Select address recorded in TBS for this sponsor (drop-down list).

Contact person

Contact for this application.

This application is to:

This defaults to 'Create a new ARTG entry' when you first begin.

If you are changing a current ARTG entry, selecting this button will open additional fields for you to complete.

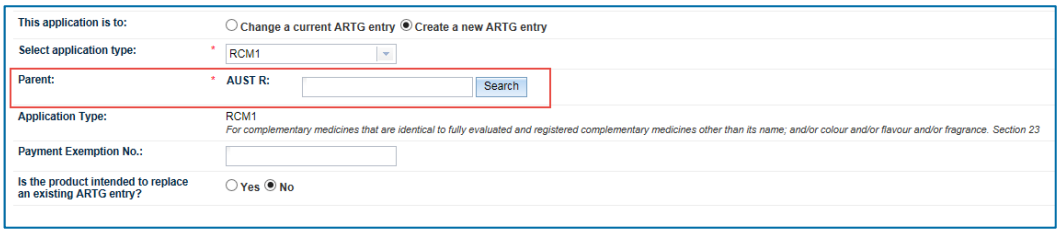
Select application type: new registered complementary medicines

These use the 'RCM' application type:

- **RCM1**: An application for a fragrance/flavour/colouring variant of a fully evaluated originator medicine.

  If your application type is RCM1

  In this case, an additional field (***Parent***) will appear requiring you to select the AUST R number of the fully evaluated parent medicine.



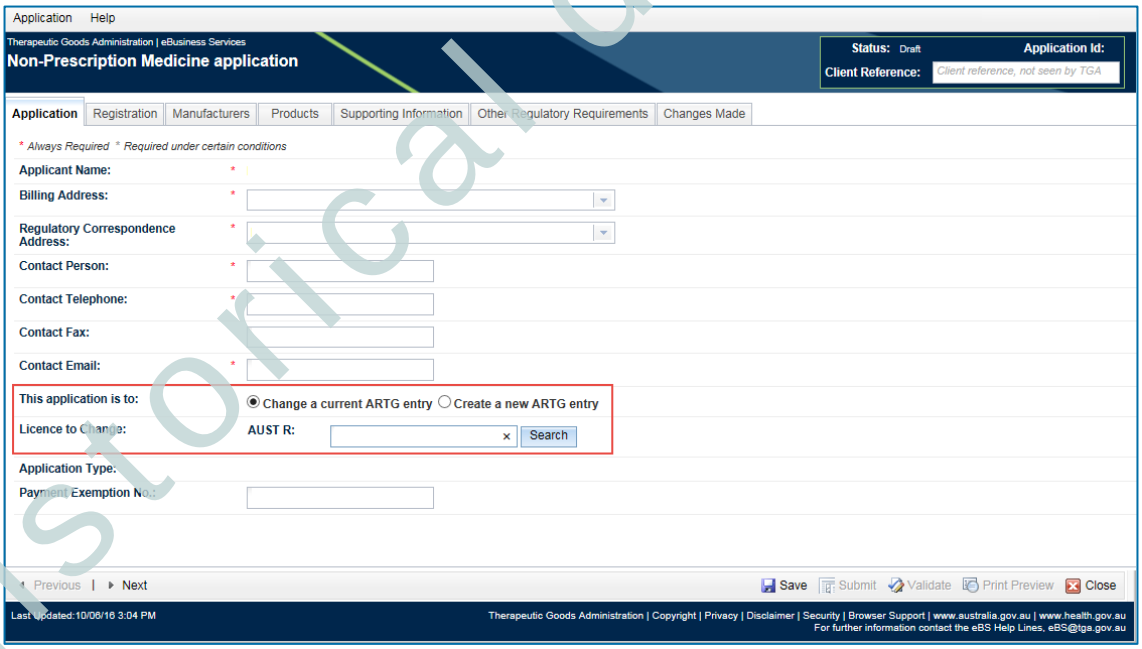
Searching and selecting the relevant parent medicine will create a new draft copy of the application, based on the details of the parent medicine.

- **RCM2**: An application for a medicine which complies with a RCM monograph, as described in the guidance documents.
- **RCM3**: For complementary medicines where previous evaluation by TGA (or comparable regulatory authority) has demonstrated their safety and efficacy.
- **RCM4**: For complementary medicines where one or two out of quality, safety and efficacy has been established.
- **RCM5**: For new complementary medicines to be registered on the ARTG that have not been previously evaluated to demonstrate quality, safety and efficacy.

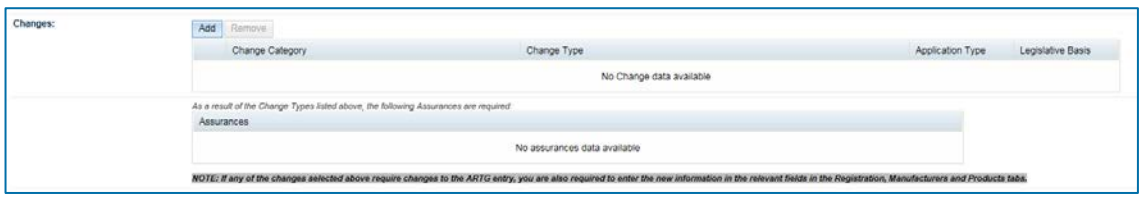
Select application type: changes to registered complementary medicines

These use the 'C' application type, and will be classified as C1 to C4 depending on requirements.

After you select ***Change a current ARTG entry***, enter the ARTG number of the entry you want to change in the ***Licence to Change*** field. Then select the ***Search*** button.

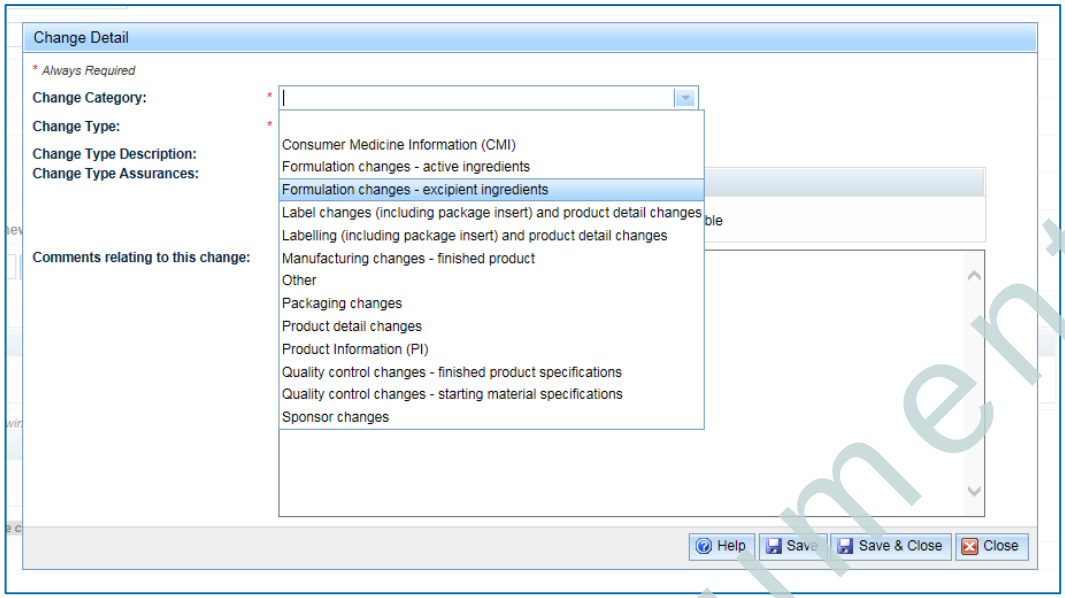


New ***Changes*** fields will then appear in the ***Application tab***.

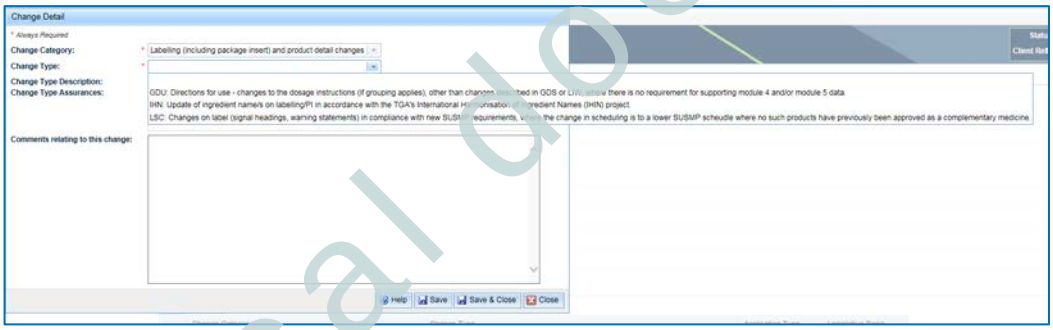


Select the ***Add*** button to begin adding changes. This will open the ***Change Detail*** window.

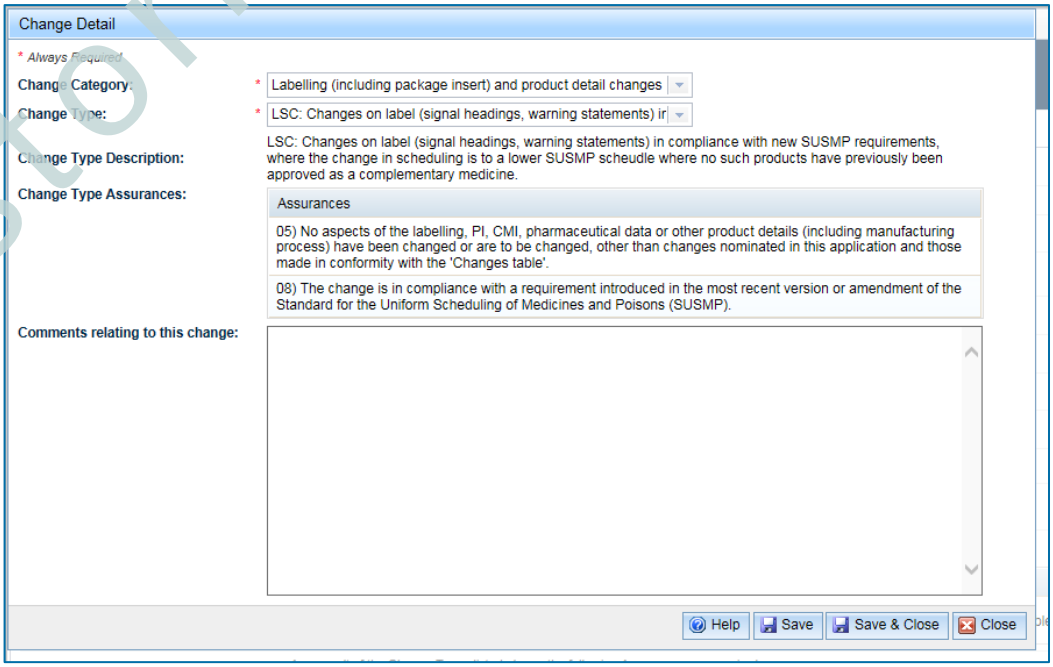
Select the relevant ***Change Category*** from the drop down list (in this example, Labelling and product detail changes).



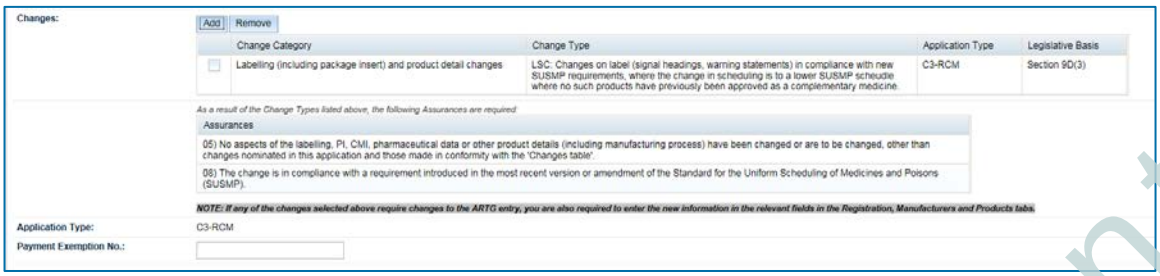
Next, select the ***Change Type*** from the drop down list. (Note: the list will only contain the change types relevant to the change category you selected).



When you select the relevant ***Change Type***, the ***Description*** and ***Assurances*** fields will be populated with the relevant information, and you will be able to add comments.



If you want to add another change category, select the ***Save*** button to add the change to the ***Changes list*** (on the main form), and then select another change category to start adding another change. Once you have added all the desired changes, select ***Save & Close*** to go back to the main form.



Payment exemption number

Exemption from payment is only available upon application. Please send your request to complementary.medicines@health.gov.au.

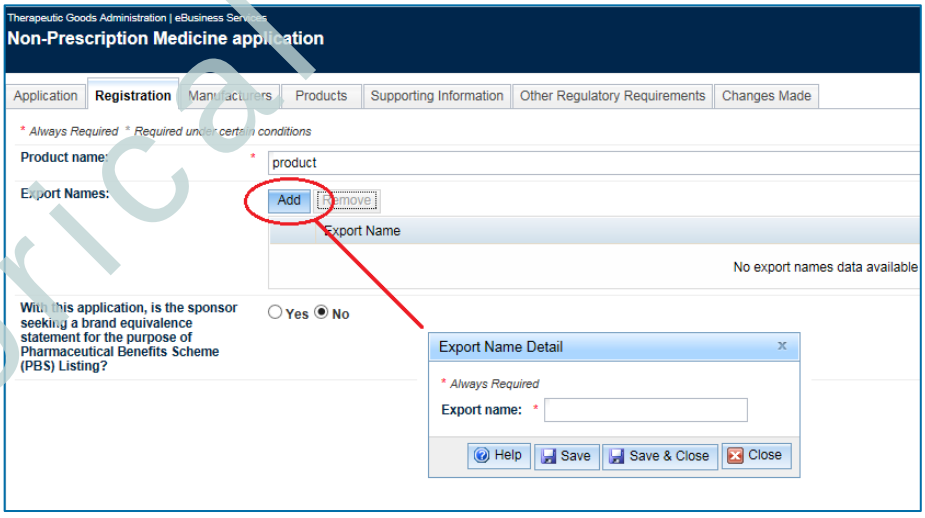
Registration details tab

Product name

For a new registration application, enter the proprietary name as it appears on the product label. For a change application, only amend this field if proposing a change to the proprietary name.

Export names

To add export names, select the ***Add*** button, which will then display a free text box to insert the export name.



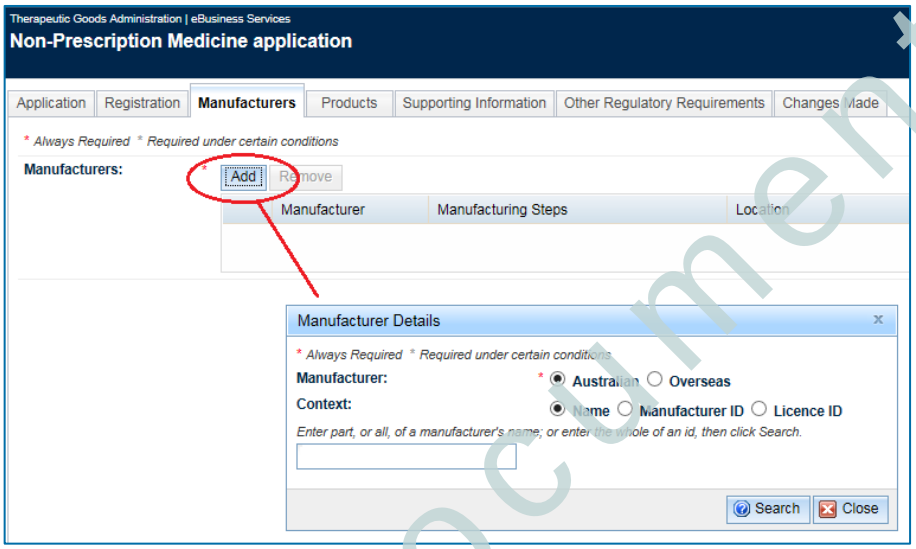
If you want to enter more than one name here, select ***Save*** to add each one to the list. When you have entered the last (or only) name, select ***Save & Close*** to return to the main form.

Manufacturer details tab

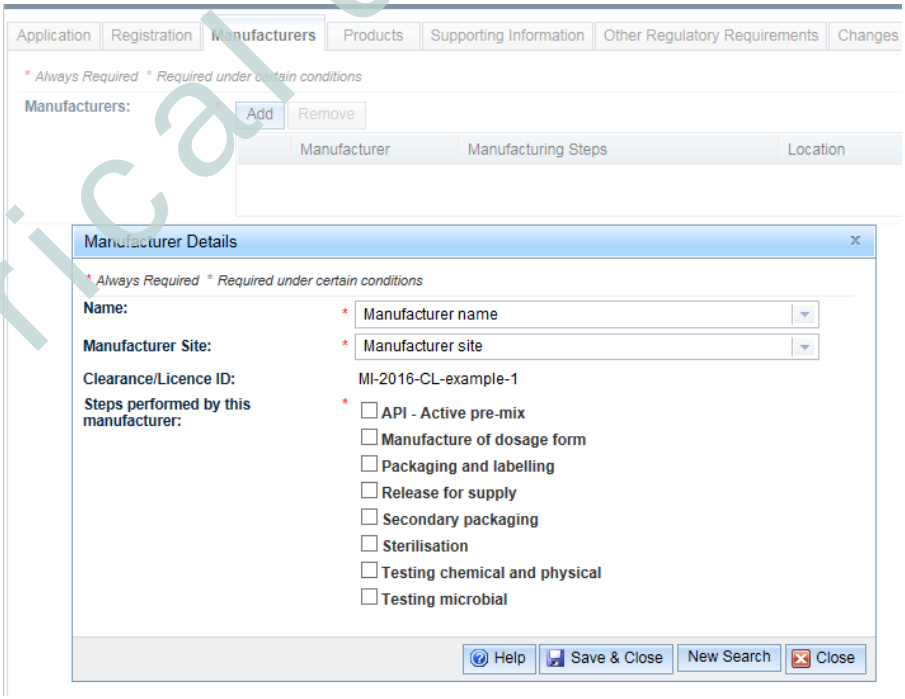
Note: For change applications, this tab will be pre-populated with the details of the ARTG entry you wish to change.

Manufacturers

To add manufacturers, select the ***Add*** button, which will then display a box to insert more specific manufacturer information.



Once you have successfully searched for the relevant manufacturer, another information box will appear. All fields in this box are required.



For the manufacturer name and site, the details will be pre-populated, but other selections may be possible using the drop-down lists in these fields. Please confirm the details are correct.

Once complete, select ***Save & Close*** to add the details to the Manufacturers list.

To remove manufacturers, simply select the check box next to the entry you wish to delete, and select the ***Remove*** button.

Product details tab

Note: For change applications, the fields in this tab will be pre-populated with the information from the ARTG entry you've selected to change.

Proposed therapeutic indications

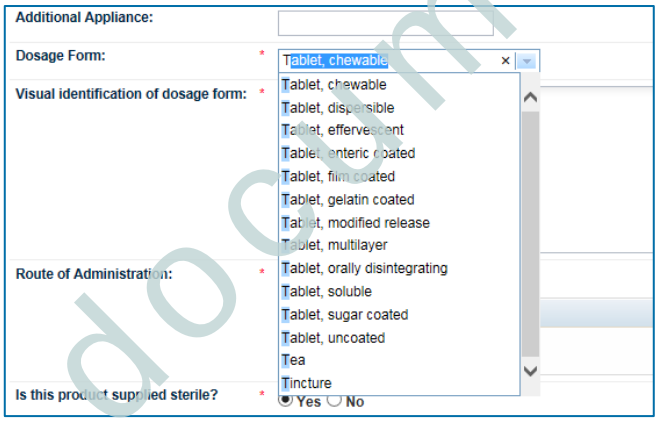
The proposed indications for the medicine (which will be used in the ARTG if approved).

Additional appliance

Include details here if your product contains an additional appliance, e.g. a measuring device.

Dosage form

To add a dosage form, you can either select a route from the drop down list, or begin entering your proposed route, which will then display a filtered list of possible options from the available list.



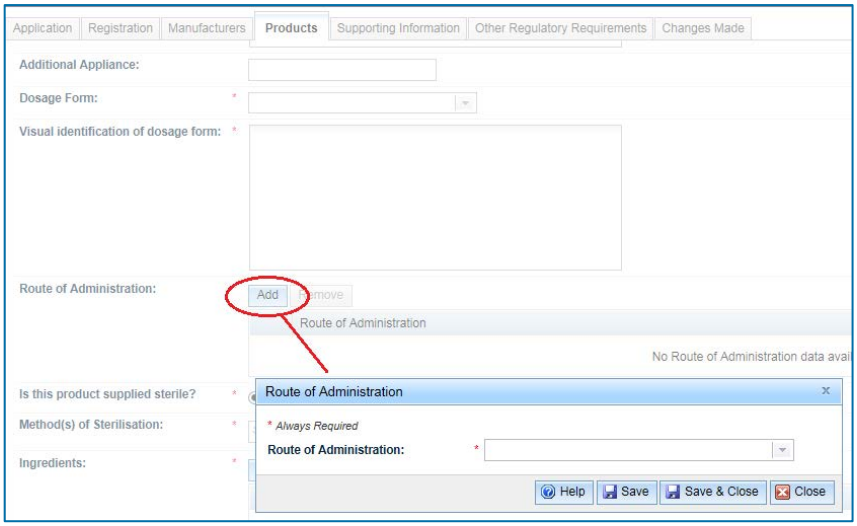
Visual identification of dosage form

What you enter here must be consistent with the description of the medicine's visual appearance (visual ID), as specified in the medicine's Finished Product Specifications document, e.g.:

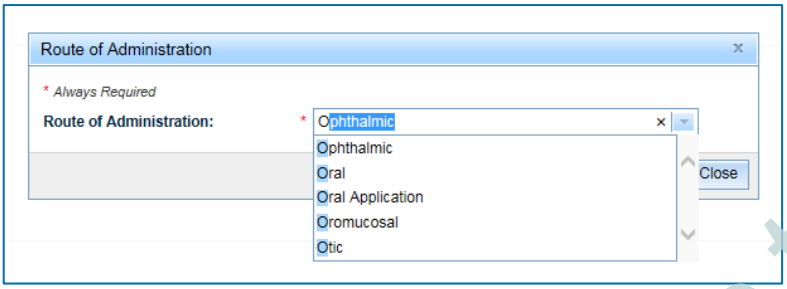
- white, circular, biconvex tablets

Route of administration

To add a route of administration, select the ***Add*** button in this section, which will open a drop down list.



You can either select a route from the drop down list, or begin entering your proposed route, which will then display a filtered list of possible options from the available list.

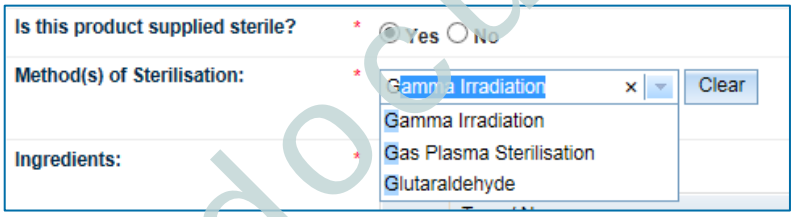


Is the product supplied sterile?

Yes or No.

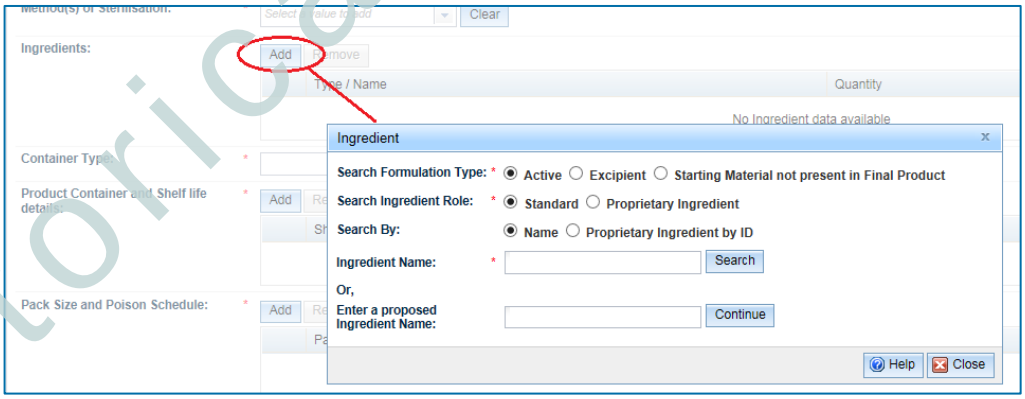
If Yes, go to the next section **Method(s) of Sterilisation** and select the relevant methods from the drop down list. You can also begin entering the sterilisation method which will then display a filtered list of possible options.

If No, the default requirement for **Method(s) of Sterilisation** will be removed.



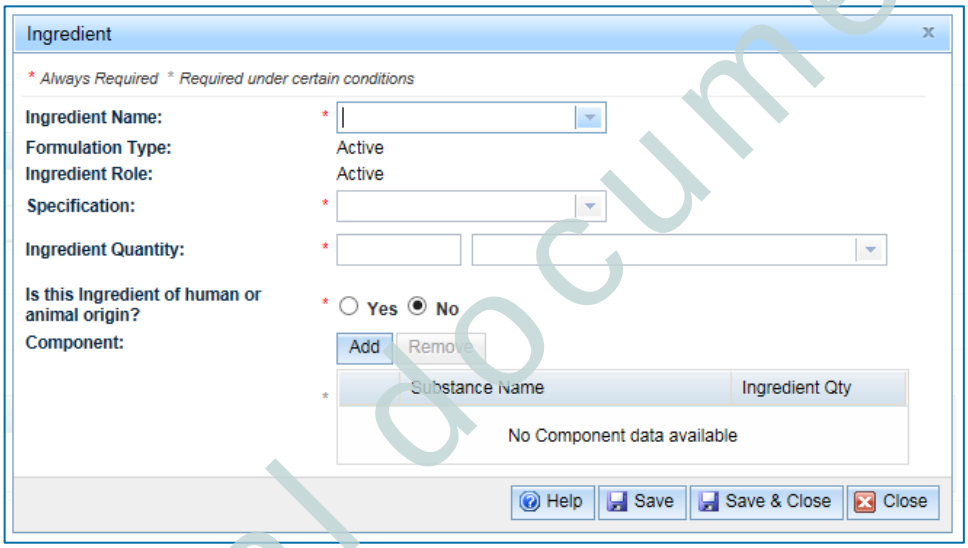
Ingredients

To add the product's ingredients, select the ***Add*** button in this section, which will then open the ***Ingredient*** selection/search box.

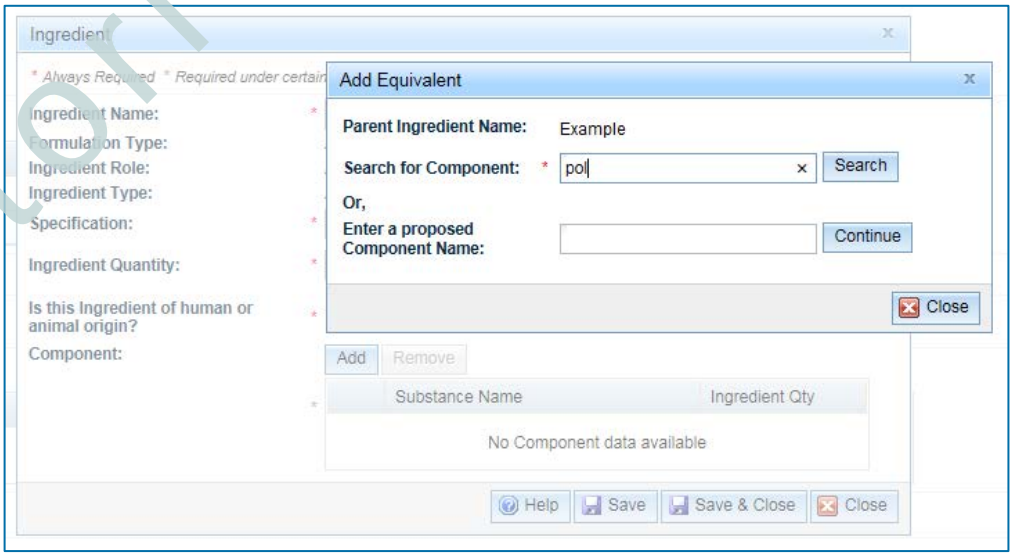


For **each ingredient to be added to the Ingredients list**, you'll need to complete the following process:

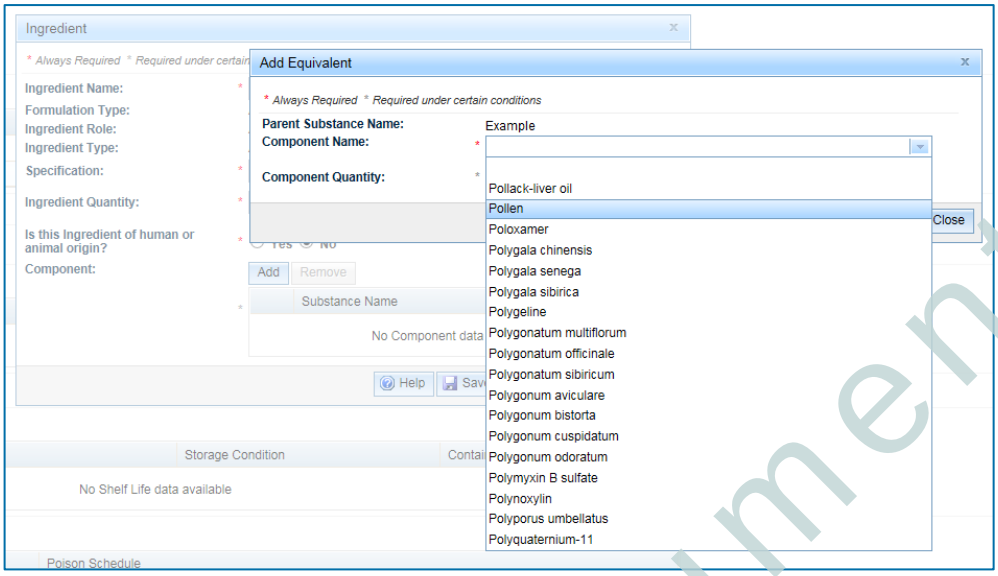
1. In the Ingredient selection/search box, select the appropriate combination of ***Formulation Type*** and ***Ingredient Role***.
2. Select to search by name or proprietary ingredient ID.
3. Enter either:
    a. the Ingredient Name you wish to search
    b. a proposed ingredient name
4. If you are searching for an ingredient name, enter your search term and select the ***Search*** button. This will open the Ingredient details box, and all fields are required.



If a component needs to be added, select the ***Add*** button in the ***Component*** section. This will open the ***Add Equivalent*** search box to either search for a component, or enter a proposed component name.



When searching for a component (in this example, pollen), you can enter either a full or partial term to search.



Once your component name is selected, enter the quantity of the component.

If you want to enter more than one component here, select ***Save*** to add each one to the list. When you have entered the last (or only) component, select ***Save & Close*** to return to the ***Ingredient*** details box.

Then, select ***Save & Close*** in the ***Ingredient*** details box to add the ingredient to the list.

Container type

Select the container type from the drop-down list.

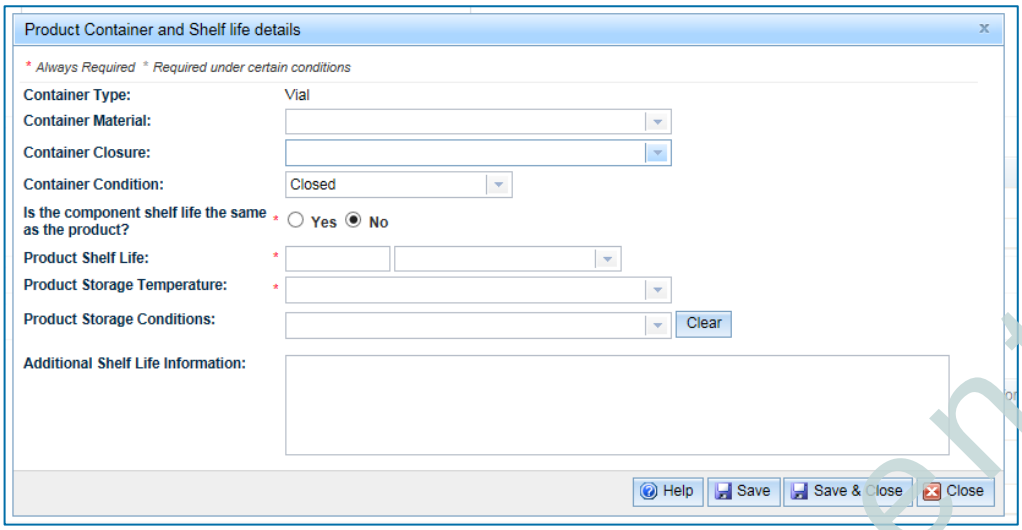
(We have used *vial* for this example.)

Product container and shelf life details

Select the ***Add*** button to open the ***Product Container*** and ***Shelf life details*** box.

Enter details for:

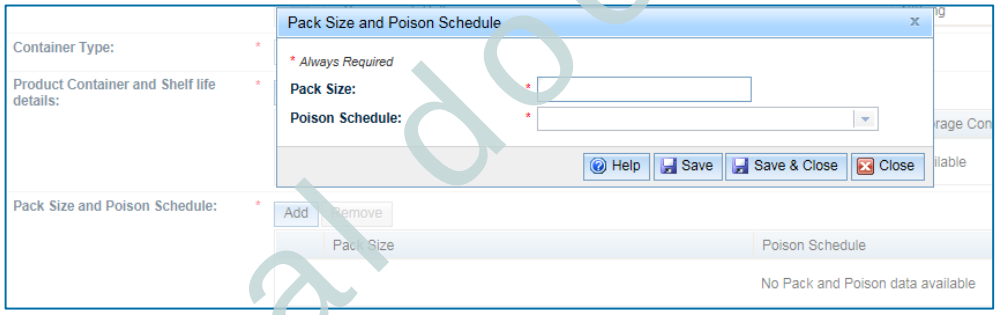
- Container material
- Container closure
- Container condition
- Product shelf life
- Product storage conditions
- Additional shelf life information



If you want to enter the details of more than one container, select ***Save*** to add each one to the list. When you have entered the last (or only) container, select ***Save & Close*** to return to the main form.

Pack size and poison schedule

Select the ***Add*** button to open the ***Pack Size and Poison Schedule details*** box.



Pack size: Select the ***Help*** button if you need any information on pack size.

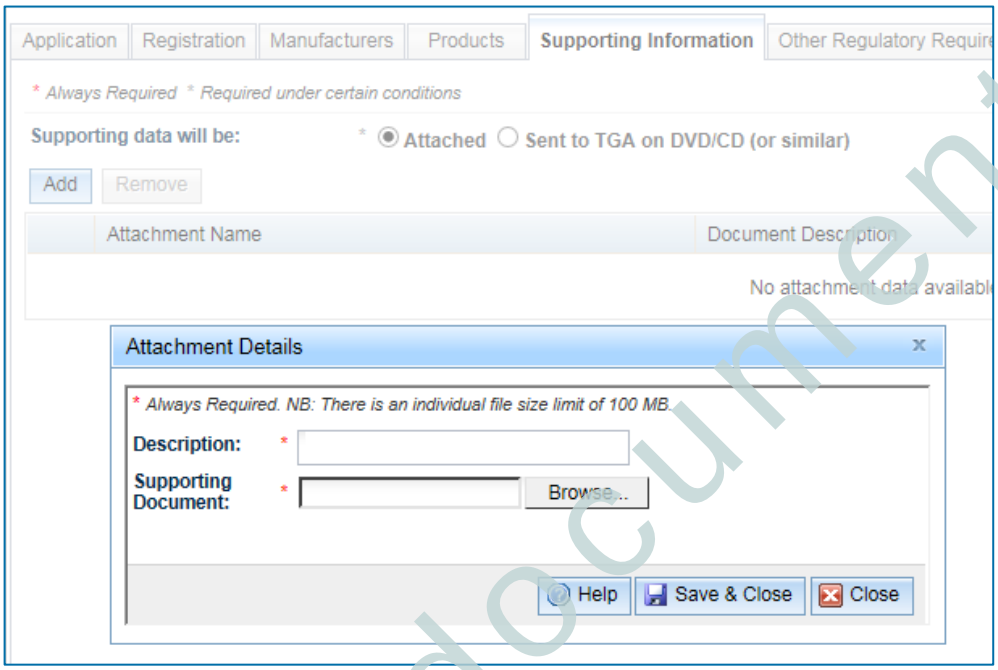
Poison schedule: Select the appropriate entry from the drop down list.

Note: If you want to enter the details of more than one pack size/schedule, select ***Save*** to add each one to the list. When you have completed the last (or only) entry, select ***Save & Close*** to return to the main form.

Supporting information tab

Supporting data/information should be attached (preferably) as a single zipped file (individual file sizes are limited to 100 Megabytes).

For further explanation on this, select the ***Help*** button within the ***Attachment details*** pop-up box.



Description

Enter the title of the document.

Supporting document

Selecting the ***Browse*** button will open ***Windows Explorer*** on your computer, which then allows you to search and select the relevant file to upload.

Select ***Save & Close*** to attach the file to your online application.

Sending supporting information to TGA on DVD/CD (or similar)

Select this option if you intend to provide your supporting information separately to this form (e.g. on CD).

Once your application has been submitted

Invoice and payment

Once you have submitted your application, an invoice will be raised comprised of:

- an application fee (non-refundable)
- a pre-determined base evaluation fee (refer to Summary of fees and charges).

For options on how to make your payment, refer to Payment options.

Your application will not proceed until both the application fee and base evaluation fees have been paid.

Pre-evaluation assessment

We will review your application dossier to determine:

- if the dossier is acceptable for evaluation, and
- that the appropriate evaluation fee has been paid.

We will start the evaluation process once we confirm the submitted information is satisfactory, and the evaluation fee has been paid in full.

We will notify you (in writing) if your application has been accepted (or not) for evaluation.

Total evaluation fee

We will determine the total evaluation fee for your application.

In some cases, this may exceed the base evaluation fee initially invoiced, for example:

> If your application dossier consists of clinical and toxicological data that exceeds the base evaluation fee page count (that is, 51 pages or more) then you will be invoiced for an additional supplementary fee once a pre-evaluation assessment has been performed by the TGA.

Requesting a reduction of the 'base' evaluation fee

In certain circumstances, you may have adequate justification to request a reduction of your evaluation fee under Regulation 45 of the Therapeutic Goods Regulations 1990.

If so, attach this request to your TGA Business Services application (or include your request in your covering letter).

If successful, the base evaluation fee will be adjusted and a refund may be provided.

Target evaluation timeframes

As part of the Government's complementary medicine reforms, TGA will be consulting on target evaluation timeframes for registered complementary medicines in late 2017.

Application categories

This guidance provides descriptions and examples of the five categories for registered complementary medicines applications. If your proposed application is not captured by an example, determine the appropriate application category by considering the data requirements for quality, safety and efficacy, which are submitted in Module 3 (quality), Module 4 (nonclinical) and Module 5 (clinical). Please refer to Common Technical document (CTD) for further information on the modules.

As part of the Government's complementary medicine reforms, TGA will be consulting on application category types for registered complementary medicines in late 2017.

Category 1 (RCM 1)

For complementary medicines that are identical to a fully evaluated registered complementary medicine (the originator medicine[5]) other than its name, colour, flavour and/or fragrance.

Conditions for RCM 1 applications

- Originator medicines must be registered on the ARTG and have been fully evaluated for safety, quality and efficacy (cannot be a 'grandfathered' medicine). If in doubt, check the list of evaluated registered complementary medicines.
- Label, indications and formulation must reflect the fully evaluated originator medicine.
- Originator medicines must comply with current requirements including RASML, the Poisons Standard, relevant Therapeutic Goods Orders (e.g. TGO 69, TGO 77, TGO 78, TGO 80, TGO 92) and default pharmacopoeial standards.
- The sponsor of the originator medicine must authorise the TGA to access the information on the originator medicine files and ARTG record for the purpose of the RCM 1 application.

Related guidance

- Permitted differences from the parent medicine

Although the 'Permitted differences for the parent medicine' provides guidance for OTC medicines and refers to a 'parent' medicine rather than an 'originator' medicine, the guidance also applies to RCM1 application.

[5] An originator medicine (sometimes referred to as the 'innovator' or 'parent' medicine) is one that has been approved for marketing in Australia following the evaluation of a full dossier.

Data requirements for RCM 1

RCM 1 applications have reduced requirements for supporting data as the proposed medicine is almost identical to an originator medicine. However, adequate data and/or justification to support any permitted differences between the proposed and originator medicine must be provided.

You need to provide Module 1: registered complementary medicines including:

- a letter of authorisation from the sponsor of the originator medicine to access the medicine information under 'Letters of authorisation' (1.5.5)
- assurance that all quality aspects of the proposed medicine are identical to the originator medicine, other than differences that are specifically permitted (as listed in the permitted differences guidance) under 'Assurances' (1.5.7).

Additionally, if the proposed product includes a new flavour, fragrance or printing ink, you need to provide:

Module 3 (quality):

- the proposed specifications and details of the test methods for the new flavour/fragrance/colours(s) under 'control of excipients' (3.2.P.4).

Category 2 (RCM 2)

For complementary medicines that comply with a TGA complementary medicine monograph.

There are no TGA complementary medicine monographs available at the time of writing.

Data requirements for RCM 2

Module 1: registered complementary medicines including a letter of assurance the medicine meets a TGA complementary medicine monograph under 'Assurances' (1.5.7).

Category 3 (RCM 3)

For complementary medicines where previous evaluation by the TGA or a comparable regulatory authority (CRA) has demonstrated their safety and efficacy. Applications in this category include:

- generic complementary medicine
- medicine evaluated by a comparable regulatory authority.

Generic complementary medicine

In comparison to the fully evaluated (not grandfathered) originator medicine, the proposed generic medicine must have the same:

- amount of active ingredient with similar quality
- pharmaceutical form and be appropriately justified to be therapeutically equivalent through the use of bioequivalence data
- safety and efficacy properties.

Conditions

- Any justification for not providing bioequivalence data must meet the conditions described in the guidance for Generic registered complementary medicines.
- The safety and efficacy data provided with the originator medicine must not be 'protected' (refer to Section 25A of the *Therapeutic Goods Act 1989*).

NOTE: Generic complementary medicines applications that require submission of bioequivalence data will be RCM 4.

Medicine evaluated by a comparable regulatory authority

Provide full safety and efficacy evaluation reports (in English) from the CRA, and information on relevant quality assessment of all active ingredients (or the proposed medicine).

The definition of a comparable regulatory authority (CRA) is under consideration at the time of writing.

Further considerations

- Reports must be complete, unredacted and included in Module 1: registered complementary medicines under 'Foreign evaluation reports' (1.11.4). To meet the evidence requirements the TGA will accept multiple evaluation reports on the proposed medicine. For example one report may cover all safety aspects, excluding genotoxicity studies, but a separate report from another CRA on the same product may cover genotoxicity and efficacy data.
- Evidence submitted to and reviewed by the CRA must be equivalent to the evidence requirements for Module 4 (nonclinical) and Module 5 (clinical).
- There must be no new indications proposed beyond what the report considered.
- The proposed medicine formulation must be the same as the medicine considered in the reports (formulation changes for fragrance, flavour and colouring variants are permitted).

Conditions

- A full Module 3 (quality) dossier must be provided, even if quality has been considered in the evaluation report(s).
- There must be no new contradictory clinical data available beyond what the evaluation report has considered.
- No contrary regulatory evaluation reports must exist.
- An application for the proposed medicine must not have been withdrawn in response to technical questions from a regulator or rejected in any other jurisdiction.

Please arrange a pre-submission meeting prior to submission to discuss the suitability of the evaluation reports.

Data requirements for RCM 3

- Module 1 (complementary medicines)
- Module 3 (quality)

NOTE: Complementary medicines using active ingredients permitted for use in listed medicines with higher level indications will be either RCM 4 or RCM 5, depending on the data requirements.

Category 4 (RCM 4)

For complementary medicines where one of quality, safety or efficacy has been established.

For all RCM 4 applications, submit Modules 1 and 2. Submit the relevant technical modules out of Module 3 (quality), Module 4 (nonclinical) and Module 5 (clinical). For more information about the modules see Common Technical document (CTD).

Examples of application category RCM4 are included in the tables below. Please note that these tables are not extensive and sponsors should seek advice from the TGA if required.

Examples of application category RCM 4 requiring Module 4 and/or Module 5

Example of RCM 4	Further considerations	Conditions
New therapeutic indication	Only if grouping does not apply. If grouping applies, refer to the registered complementary medicines changes tables.	Must not result in a change in the target population
Wider target population	A reduction in the class of person for whom the goods are suitable is considered a C1 change (change code CDS)	-
Decrease in the strength	Determined per dosage unit	-
New directions for use	For example, change in recommended daily dose	Only if grouping does not apply. If grouping applies, refer to the registered complementary medicines changes tables.
Medicines requiring a PI and CMI	Applications requiring a PI and CMI are considered RCM 4 or RCM 5 applications; as a minimum Module 4 and Module 5 data are required	-

Examples of application category RCM 4 requiring Module 3 and Module 5

Example of RCM 4	Further considerations
Generic medicine application requiring bioequivalence data	Excluding enteric-coated tablets and capsules. Further information is provided in the Generic complementary medicine guidance)
Generic modified-release dose forms	Excluding enteric-coated tablets and capsules
Deletion of an active ingredient	-
RCMs using active ingredients permitted for use in listed medicines with higher level indications	-

A combination of RCM 4 applications may result in an RCM 5 application due to the increased data requirements (quality, safety and efficacy).

Category 5 (RCM 5)

For new complementary medicines to be registered on the ARTG that have not been previously evaluated for quality, safety and efficacy. Application examples include:

- new registered complementary medicine – where no aspect have been previously evaluated
- new active ingredient
- increase in the strength of an active ingredient
- new dosage form (as defined in TGA approved terminology for medicines)
- addition of an excipient not currently in use in complementary medicine
- contains a greater amount of an excipient

Data requirements for RCM 5

A complete Common Technical document (CTD):

- Module 1 (complementary medicines)
- Module 2
- Module 3
- Module 4
- Module 5.

Cover letter for registered complementary medicines

This guidance is to assist applicants to register a complementary medicine on the ARTG.

A letter of application (cover letter) is part of your application to register or to change the ARTG entry for your complementary medicine. In your cover letter, provide useful information regarding the nature and scope of the application.

This guidance relates to steps 2, 3, 5, 7 and 10 in the complementary medicine registration process and is to be included in Module 1 of your dossier[6], which you will prepare in Step 7 of the registration process and submit to us in Step 9 for evaluation.

Cover letter basics

Ensure your cover letter is on company letterhead and includes:

- the purpose of the application
- the medicine name
- the proposed therapeutic indications
- the contact person and sponsor name
- the date of submission and submission ID (if known)
- whether payment of fees has been forwarded directly to TGA finance
- the electronic format of the dossier (e.g. DVD/CD/USB)
- the rationale for selecting the application category. Include information that is significant for determining the application category and technical data requirements.
- other relevant background information, such as overseas regulatory status.

Make sure the cover letter is signed by a person authorised to liaise with us on your behalf.

When to provide additional information

The cover letter also needs to notify us if:

- you are providing a detailed scientific justification for not complying with technical data requirements and/or not adhering to guidelines and the location of each justification in your dossier
- the medicine is a reformulation of a currently registered medicine
- the medicine contains a new substance; state the date that you submitted the relevant application form for proposing a name
- you have submitted a request to extend or renew a GMP clearance including
  - the date of the request
  - whether your request is a clearance extension or renewal
  - any other relevant details
- you are requesting:
  - a reduction or waiver of the evaluation fees
  - any exemptions (e.g. S14 exemptions, advertising exemptions)

[6] Dossier: a collection of files and documents that contains data (administrative, quality, nonclinical and clinical) relating to a therapeutic good

Data requirements matrix for RCMs

The registered complementary medicines data requirements matrix (the 'matrix') provides a summary of the documents required for:

- new registered complementary medicines
- changes to existing registered complementary medicines.

Common technical document (CTD)

The Common Technical Document (CTD) sets out the format for an application when applying to register a medicine on the ARTG. The minimum requirements for the format and structure of registered complementary medicines dossier is described within the Minimum requirements section of this guidance.

CTD specifies the:

- organisation of the information across 5 modules:
  - Module 1: Administrative information and prescribing information for Australia
  - Module 2: Summaries of quality, safety and clinical data
  - Module 3: Quality
  - Module 4: Non-clinical data (safety)
  - Module 5: Clinical data (efficacy)
- order in which information must appear so they:
  - are grouped logically
  - can be easily located.

Under the CTD format:

- Each dossier is a collection of documents grouped into 5 modules.
- The actual content of the dossier will vary according to the application category.
- The format of Module 1 is described in CTD module 1: registered complementary medicines.
- The format of Modules 2, 3, 4 and 5 is described in the relevant adopted CTD guidelines.

The General dossier requirements apply to complementary medicines registration applications.

Minimum requirements (registered complementary medicines)

The actual content of the dossier will vary according to the application category.

If you are unable to submit a full CTD dossier, the minimum structural requirement for registered complementary medicine dossiers consists of a single pdf document for each module.

To maintain this structure, organise the document content using the CTD headings (combination of module number and module name). Further information on CTD modules, including CTD heading can be found at: Common Technical Document (CTD).

For electronic dossiers, headings must be bookmarked and/or hyperlinked to the module table of contents and the entire document must be text searchable (generated from electronic source documents and not from scanned material).

Where information is required but not available

Where data or literature-based evidence is required, but not available for a particular CTD heading, provide a scientific justification under that heading to explain why it hasn't been included.

We will assess the content and merit of a justification (i.e. whether the alternative approach is in fact valid) during the evaluation phase.

For some complementary medicine registration applications, certain parts of the CTD are not relevant. The data requirements matrix indicates documents that are not relevant; no justification is required in these instances.

How to use the matrix

After you have determined the appropriate application category, use the matrix to obtain an 'at a glance' indication of which documents you need to provide.

The information included in CTD Module 1 guidance will also provide assistance in determining whether the documents will be required.

The references in the matrix are:

- **R** (red): the document(s) and/or appropriate scientific justification for not providing document(s) are required for a valid application.
- **D** (green): the document(s) is dependent on the kind of application in a particular category for the particular dossier. For example 'D' is listed for Product information in Module 1.
- **O** (blue): the document(s) is optional. There is no requirement for the document to be submitted with the application. However, the document(s) can be provided if the applicant considers the information is relevant to the application.
- Where there is no reference (blank): the document(s) are not relevant and should not be submitted.

For full folder names, refer to ICH guidance: Appendix 3: General Consideration for the CTD Modules.

New registration: data requirements matrix

Module 1

Please review in combination with the CTD Module 1: registered complementary medicines.

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
1.0	**Correspondence**	R	R	R	R	R	100-correspondence
1.0.1	**Cover letter**	R	R	R	R	R	1001-cover
1.1	**Table of Contents**	R	R	R	R	R	101-toc
1.2	**Administrative information**	D	D	D	D	D	102-admin-info
1.2.3	Patent certification	D	D	D	D	D	1023-pat-cert
1.2.5	Form for approval to use a restricted representation	O	O	O	O	O	1025-res-rep
1.2.6	Form for proposing a name for a new substance	O	O	O	O	O	1026-new-sub
1.3	Medicine information and labelling	D	D	D	D	D	103-med-info
1.3.1	**Product Information and package insert**	D	D	D	D	D	1031-pi
1.3.1.1	Product information – clean	D	D	D	D	D	10311-pi-clean
1.3.1.2	Product information – annotated	D	D	D	D	D	10312-pi-annotated
1.3.1.3	Package insert	D	D	D	D	D	10313-pack-ins
1.3.2	**Consumer Medicine Information (CMI)**	D	D	D	D	D	1032-cmi
1.3.2.1	CMI – clean	D	D	D	D	D	10321-cmi-clean
1.3.2.2	CMI - annotated	D	D	D	D	D	10322-cmi-annotated

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
1.3.3	Label mock-ups and specimens	R	R	R	R	R	1033-mock-ups
1.4	**Information about the experts**			R	R	R	104-experts
1.4.1	Quality			R	D	R	1041-quality
1.4.2	Non-clinical				D	R	1042-nonclinical
1.4.3	Clinical				D	R	1043-clinical
1.5	**Specific requirements for applications**	D	D	D	D	D	105-specific
1.5.1	Literature-based submission documents				D	D	1051-lit-based
1.5.5	Letters of authorisation	D					1055-co-marketed
1.5.7	CM medicine assurances	R	R	D	D	D	1057- assurance
1.5.8	Umbrella branding assessment				D	D	1058-umbrella-br-assess
1.7	**Compliance with meetings and pre-submission processes**	D	D	D	D	D	107-compliance
1.7.1	Details of compliance with pre-submission meeting outcomes	D	D	D	D	D	1071-pre-sub-outcomes
1.7.2	Details of any additional data to be submitted	D	D	D	D	D	1072-additional-data
1.8	**Information relating to pharmacovigilance**			D	D	D	108-pharmacovigilance
1.9	**Summary of biopharmaceutic studies**				D	D	109-biopharm

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
1.9.1	Summary of bioavailability or bioequivalence study			D	D	D	1091-ba-be
1.11	**Foreign regulatory information**	D	D	D	D	D	111-foreign
1.11.1	Foreign regulatory status	D	D	D	D	D	1111-status
1.11.2	Foreign product information	O	O	D	D	D	1112-pi
1.11.3	Data similarities and differences	O	O	D	D	D	1113-similarities
1.11.4	Foreign evaluation reports	O	O	D	D	D	1114-eval-reports

Module 2

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
2	**CTD Summaries**						m2
2.2	**Introduction**			O	O	O	22-intro
2.3	**Quality overall summary**				D	R	23-qos
2.4	**Nonclinical overview**				D	R	24-nonclin-over
2.5	**Clinical overview**				D	R	25-clin-over
2.6	**Nonclinical written and tabulated summaries**				O	O	26-nonclin-sum
2.7	**Clinical summary**				O	O	27-clin-sum

Module 3

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3	Quality			R	D	R	m3
3.2.S	**Drug substance**						32s-drug-sub
3.2.S.1	General Information						32s1-gen-info
3.2.S.1.1	Nomenclature			R	D	R	nomenclature
3.2.S.1.2	Structure			R	D	R	structure
3.2.S.1.3	General Properties			R	D	R	general-properties
3.2.S.2	**Manufacture**						32s2-manuf
3.2.S.2.1	Name address and responsibility of each manufacturer			O	D	O	manufacturer
3.2.S.2.2	Description of manufacturing process and process controls			O	D	O	manuf-process-and-controls
3.2.S.2.3	Control of materials			O	D	O	control-of-materials
3.2.S.3	**Characterisatio n**			R	D	R	32s3-charac
3.2.S.3.1	Elucidation of structure and other characteristics			R	D	R	elucidation-of-structure
3.2.S.3.2	Impurities			R	D	R	impurities
3.2.S.4	**Control of Drug Substance**			R	D	R	32s4-contr-drug-sub
3.2.S.4.1	Specification			R	D	R	32s41-spec
3.2.S.4.2	Analytical Procedures			R	D	R	32s42-analyt-proc

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.S.4.3	Validation of analytical procedures			R	D	R	32s43-val-analyt-proc
3.2.S.4.4	Batch analysis			R	D	R	32s44-batch-analys
3.2.S.4.5	Justification of Specification			R	D	R	32s45-justif-spec
3.2.S.5	**Reference standards or materials**			R	D	R	32s5-ref-stand
3.2.S.6	**Container closure**			R	D	R	32s6-cont-closure-sys
3.2.S.7	**Stability**			R	D	R	32s7-stab
3.2.S.7.1	Stability summary and conclusion			R	D	R	stability-summary
3.2.S.7.3	Stability data			R	D	R	stability-data
3.2.P	**Drug product**			R	D	R	32p-drug-prod
3.2.P.1	**Description and composition of the drug product**			R	D	R	2p1-desc-comp
3.2.P.2	**Pharmaceutical development**			R	D	R	32p2-pharm-dev
3.2.P.2.1	Components of the drug product (heading)			R	D	R	
3.2.P.2.1.1	Drug Substance compatibility			R	D	R	
3.2.P.2.1.2	Choice of the excipients listed in 3.2.P.1			R	D	R	
3.2.P.2.2	Drug Product (heading)			R	D	R	
3.2.P.2.2.1	Formulation development			R	D	R	

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.P.2.2.2	Overages			R	D	R	
3.2.P.2.2.3	Physicochemical and biological properties			R	D	R	
3.2.P.2.3	Manufacturing process development			R	D	R	
3.2.P.2.4	Container Closure System			R	D	R	
3.2.P.2.5	Microbiological attributes			R	D	R	
3.2.P.2.6	Compatibility			R	D	R	
3.2.P.3	**Manufacture**			R	D	R	2p3-manuf
3.2.P.3.1	Manufacturers			R	D	R	manufacturers
3.2.P.3.2	Batch formula			R	D	R	batch-formula
3.2.P.3.3	Description of manufacturing process and process controls			R	D	R	manuf-process-and-controls
3.2.P.3.4	Control of critical steps and intermediates			R	D	R	control-critical-steps
3.2.P.3.5	Process validation and/or evaluation			R	D	R	process-validation
3.2.P.4	**Control of excipients**	D		R	D	R	32p4-contr-excip
3.2.P.4.1	Specifications	D		R	D	R	specifications
3.2.P.4.2	Analytical procedures	D		R	D	R	analytical-procedures
3.2.P.4.3	Validation of analytical procedures	D		R	D	R	validation-analyt-procedures

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
3.2.P.4.4	Justification of specifications	D		R	D	R	justification-of-specifications
3.2.P.4.5	Excipients of human or animal origin	D		R	D	R	excipients-human-animal
3.2.P.4.6	Novel excipients	D		R	D	R	novel-excipients
3.2.P.5	**Control of drug product**			R	D	R	32p5-contr-drug-prod
3.2.P.5.1	Specifications			R	D	R	32p51-spec
3.2.P.5.2	Analytical procedures			R	D	R	32p52-analyt-proc
3.2.P.5.3	Validation of analytical procedures			R	D	R	32p53-val-analyt-proc
3.2.P.5.4	Batch analysis			R	D	R	32p54-batch-analys
3.2.P.5.5	Characterisation of impurities and requirements for non-pharmacopoeial products			R	D	R	32p55-charac-imp
3.2.P.5.6	Justification of specifications			R	D	R	32p56-justif-spec
3.2.P.6	**Reference standards or materials**			R	D	R	32p6-ref-stand
3.2.P.7	**Container closure system**			R	D	R	32p7-cont-closure-sys
3.2.P.8	**Stability**			R	D	R	32p8-stab
3.2.P.8.1	Stability summary and conclusion			R	D	R	stability-summary
3.2.P.8.3	Stability data			R	D	R	stability-data

Module 4

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
4	**Nonclinical (safety)**						m4
4.1	**Table of contents**	O	O	O	O	O	41-toc
4.2	**Nonclinical study reports**				D	R	42-stud-rep
4.2.1	**Pharmacology**				D	R	421-pharmacol
4.2.1.1	Primary pharmacodynamics				D	R	4211-prim-pd
4.2.1.2	Secondary pharmacodynamics				D	R	4212-sec-pd
4.2.1.3	Safety pharmacology				D	R	4213-safety-pharmacol
4.2.1.4	Pharmacodynamic drug interactions				D	R	4214-pd-drug-interact
4.2.2	**Pharmacokinetics**				D	R	422-pk
4.2.2.1	Analytical methods and validation reports				D	R	4221-analyt-met-val
4.2.2.2	Absorption				D	R	4222-absorp
4.2.2.3	Distribution				D	R	4223-distrib
4.2.2.4	Metabolism				D	R	4224-metab
4.2.2.5	Excretion				D	R	4225-excr
4.2.2.6	Pharmacokinetic drug interactions				D	R	4226-pk-drug-interact
4.2.2.7	Other pharmacokinetic studies				D	R	4227-other-pk-stud
4.2.3	**Toxicology**				D	R	423-tox
4.2.3.1	Acute toxicity				D	R	4231-acute-tox
4.2.3.2	Repeat dose toxicity				D	R	4232-repeat-dose-tox
4.2.3.3	**Genotoxicity**				D	R	4233-genotox
4.2.3.3.1	In vitro				D	R	42331-in-vitro

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
4.2.3.3.2	In vivo				D	R	42332-in-vivo
4.2.3.4	**Carcinogenicity including supportive toxicokinetics evaluations**				D	R	4.2.3.4
4.2.3.4.1	Long-term studies				D	R	42341-lt-stud
4.2.3.4.2	Short or medium term studies				D	R	42342-smt-stud
4.2.3.5	**Reproductive and developmental toxicity**				D	R	4235-repro-dev-tox
4.2.3.5.1	Fertility and early embryonic development				D	R	42351-fert-embryo-dev
4.2.3.5.2	Embryo-foetal development				D	R	embryo-fetal-dev
4.2.3.5.3	Prenatal and postnatal development				D	R	42353-pre-postnatal-dev
4.2.3.5.4	Studies in the offspring (juvenile animals are dosed and /or further evaluated)				D	R	42354-juv
4.2.3.6	**Local tolerance**				D	R	4236-loc-tol
4.2.3.7	**Other toxicity studies**				D	R	4237-other-tox-stud
4.2.3.7.1	Antigenicity				D	R	42371-antigen
4.2.3.7.2	Immunotoxicity				D	R	42372-immunotox
4.2.3.7.3	Mechanistic studies				D	R	42373-mechan-stud
4.2.3.7.4	Dependence				D	R	42374-dep
4.2.3.7.5	Metabolites				D	R	42375-metab
4.2.3.7.6	Impurities				D	R	42376-imp
4.3	**Literature references**				D	R	43-lit-ref

Module 5

Module	Name	RCM 1	RCM 2	RCM 3	RCM 4	RCM 5	File or folder name
5	**Clinical**						m5
5.1	**Table of contents**				O	O	51-toc
5.2	**Tabular listing of all clinical studies**				D	R	52-tab-list
5.3	**Clinical study reports**				D	R	53-clin-stud-rep
5.3.1	Reports of biopharmaceutic studies				D	R	531-rep-biopharm-stud
5.3.2	Reports of studies pertinent to pharmacokinetic using human biomaterials				D	R	532-rep-stud-pk-human-biomat
5.3.3	Reports of human pharmacokinetic studies				D	R	533-rep-human-pk-stud
5.3.4	Reports of human pharmacodynamic studies				D	R	534-rep-human-pd-stud
5.3.5	**Reports of efficacy and safety studies (header)**				D	R	535-rep-effic-safety-stud
5.3.5.1	Study reports of controlled clinical studies pertinent to the claimed indication				D	R	5351-stud-rep-contr
5.3.5.2	Study reports of uncontrolled clinical trials				D	R	5352-stud-rep-uncontr
5.3.5.3	Reports of analysis of data from more than one study				D	R	5353-rep-analys-data-more-one-stud
5.3.5.4	Other clinical study reports				D	R	5354-other-stud-rep
5.3.6	Reports of Post-Marketing Experience				D	D	536-postmark-exp
5.4	**Literature references**				D	R	54-lit-ref

Change to existing ARTG entry: data requirements matrix

Module 1

Module	Name	C1	C2	C3	C4	File or folder name
1.0	Correspondence	R	R	R	R	10-correspondence
1.0.1	**Cover letter**	R	R	R	R	101-cover
1.1	Table of Contents	R	R	R	R	11-toc
1.2	**Administrative information**	D	D	D	D	102-admin-info
1.2.3	**Patent certification**	D	D	D	D	123-pat-cert
1.2.5	Form for approval to use a restricted representation	O	O	O	O	125-res-rep
1.3	Product information and package insert	D	D	D	D	103-med-info
1.3.1	**Product Information and package insert**	D	D	D	D	131-pi
1.3.1.1	Product information – clean	D	D	D	D	1311-pi-clean
1.3.1.2	Product information – annotated	D	D	D	D	1312-pi-annotated
1.3.1.3	Package insert	D	D	D	D	1313-pack-ins
1.3.2	**Consumer Medicine Information (CMI)**	D	D	D	D	132-cmi
1.3.2.1	CMI – clean	D	D	D	D	1321-cmi-clean
1.3.2.2	CMI - annotated	D	D	D	D	1322-cmi-annotated
1.3.3	**Label mock-ups and specimens**	D	D	D	D	133-mock-ups
1.4	**Information about the experts**			D	D	14-experts
1.4.1	Quality			D	D	141-quality
1.4.2	Non-clinical			D	D	142-nonclinical
1.4.3	Clinical			D	D	143-clinical
1.5	**Specific requirements for applications**	D	D	D	D	15-specific

Module	Name	C1	C2	C3	C4	File or folder name
1.5.1	Literature-based submission documents			D	D	151-lit-based
1.5.5	letters of authorisation					155-co-marketed
1.5.7	CM medicine assurances					157- assurance
1.5.8	Umbrella branding assessment			D	D	158-umbrella-br-assess
1.7	**Pre-submission outcomes**	D	D	D	D	1-7-compliance
1.7.1	Details of compliance with pre-submission meeting outcomes					1071-pre-sub-outcomes
1.7.2	Details of any additional data to be submitted					1072-additional-data
1.8	**Information relating to pharmacovigilance**			D	D	18-pharmacovigilance
1.9	**Summary of biopharmaceutic studies**		D	D	D	19-biopharm
1.9.1	Summary of bioavailability or bioequivalence study			D	D	191-ba-be
1.11	**Foreign regulatory information**	D	D	D	D	111-foreign
1.11.1	Foreign regulatory status	D	D	D	D	1111-status
1.11.2	Foreign product information	D	D	D	D	1112-pi
1.11.3	Data similarities and differences	D	D	D	D	1113-similarities
1.11.4	Foreign evaluation reports	D	D	D	D	1114-eval-reports

Module 2

Module	Name	C1	C2	C3	C4	File or folder name
2	CTD Summaries					m2
2.2	Introduction			O	O	22-intro
2.3	Quality overall summary					23-qos
2.4	Nonclinical overview			O	O	24-nonclin-over
2.5	Clinical overview			D	D	25-clin-over
2.6	Nonclinical written and tabulated summaries			D	D	26-nonclin-sum
2.7	Clinical summary			D	D	27-clin-sum

Module 3

Module						
3	**Quality**		D	D		m3
3.2.S	**Drug substance**					32s-drug-sub
3.2.S.1	**General Information**					32s1-gen-info
3.2.S.1.1	Nomenclature					nomenclature
3.2.S.1.2	Structure					structure
3.2.S.1.3	General Properties		D	D		general-properties
3.2.S.2	**Manufacture**					32s2-manuf
3.2.S.2.1	Name address and responsibility of each manufacturer		D	D		manufacturer
3.2.S.2.2	Description of manufacturing process and process controls		D	D		manuf-process-and-controls
3.2.S.2.3	Control of materials		D	D		control-of-materials
3.2.S.3	**Characterisation**		D	D		32s3-charac
3.2.S.3.1	Elucidation of structure and other characteristics		D	D		elucidation-of-structure

Module	Name	C1	C2	C3	C4	File or folder name
3.2.S.3.2	Impurities		D	D		impurities
3.2.S.4	**Control of Drug Substance**	O	D	D		32s4-contr-drug-sub
3.2.S.4.1	Specification	O	D	D		32s41-spec
3.2.S.4.2	Analytical Procedures	O	D	D		32s42-analyt-proc
3.2.S.4.3	Validation of analytical procedures	O	D	D		32s43-val-analyt-proc
3.2.S.4.4	Batch analysis	O	D	D		32s44-batch-analys
3.2.S.4.5	Justification of Specification	O	D	D		32s45-justif-spec
3.2.S.5	**Reference standards or materials**		D	D		32s5-ref-stand
3.2.S.6	**Container closure**		O	O		32s6-cont-closure-sys
3.2.S.7	**Stability**		D	D		32s7-stab
	Stability summary and conclusion		D	D		stability-summary
	Stability data		D	D		stability-data
3.2.P	**Drug product**					32p-drug-prod
3.2.P.1	**Description and composition of the drug product**		D	D		2p1-desc-comp
3.2.P.2	**Pharmaceutical development**		D	D		32p2-pharm-dev
3.2.P.2.1	Components of the drug product (heading)		D	D		
3.2.P.2.1.1	Drug Substance compatibility		O	O		
3.2.P.2.1.2	Choice of the excipients listed in 3.2.P.1		O	O		
3.2.P.2.2	Components of the drug product (heading)		D	D		
3.2.P.2.2.1	Formulation development		D	D		
3.2.P.2.2.2	Overages	D	D	D		

Module	Name	C1	C2	C3	C4	File or folder name
3.2.P.2.2.3	Physicochemical and biological properties		D	D		
3.2.P.2.3	Manufacturing process development		D	D		
3.2.P.2.4	Container Closure System	D	D	D		
3.2.P.2.5	Microbiological attributes		D	D		
3.2.P.2.6	Compatibility		D	D		
3.2.P.3	**Manufacture**					2p3-manuf
3.2.P.3.1	Manufacturers	D	D	D		manufacturers
3.2.P.3.2	Batch formula		D	D		batch-formula
3.2.P.3.3	Description of manufacturing process and process controls	D	D	D		manuf-process-and-controls
3.2.P.3.4	Control of critical steps and intermediates		D	D		control-critical-steps
3.2.P.3.5	Process validation and/or evaluation		D	D		process-validation
3.2.P.4	**Control of excipients**					32p4-contr-excip
3.2.P.4.1	Specifications	O	D	D		specifications
3.2.P.4.2	Analytical procedures	O	D	D		analytical-procedures
3.2.P.4.3	Validation of analytical procedures	O	D	D		validation-analyt-procedures
3.2.P.4.4	Justification of specifications	O	D	D		justification-of-specifications
3.2.P.4.5	Excipients of human or animal origin		D	D		excipients-human-animal
3.2.P.4.6	Novel excipients		D	D		novel-excipients
3.2.P.5	**Control of drug product**					32p5-contr-drug-prod
3.2.P.5.1	Specifications	O	D	D		32p51-spec
3.2.P.5.2	Analytical procedures	O	D	D		32p52-analyt-proc

Module	Name	C1	C2	C3	C4	File or folder name
3.2.P.5.3	Validation of analytical procedures	O	D	D		32p53-val-analyt-proc
3.2.P.5.4	Batch analysis		D	D		32p54-batch-analys
3.2.P.5.5	Characterisation of impurities and requirements for non-pharmacopoeial products		D	D		32p55-charac-imp
3.2.P.5.6	Justification of specifications	O	D	D		32p56-justif-spec
3.2.P.6	**Reference standards or materials**		D	D		32p6-ref-stand
3.2.P.7	**Container closure system**		D	D		32p7-cont-closure-sys
3.2.P.8	**Stability**		D	D		32p8-stab
3.2.P.8.1	Stability summary and conclusion		D	D		stability-summary
3.2.P.8.3	Stability data		D	D		stability-data

Module 4

Module	Name	C1	C2	C3	C4	File or folder name
4	**Nonclinical (safety)**			D	D	m4
4.1	**Table of contents**			D	D	41-toc
4.2	**Nonclinical study reports**			D	D	42-stud-rep
4.2.1	**Pharmacology**			D	D	421-pharmacol
4.2.1.1	Primary pharmacodynamics			D	D	4211-prim-pd
4.2.1.2	Secondary pharmacodynamics			D	D	4212-sec-pd
4.2.1.3	Safety pharmacology			D	D	4213-safety-pharmacol
4.2.1.4	Pharmacodynamic drug interactions			D	D	4214-pd-drug-interact
4.2.2	**Pharmacokinetics**			D	D	422-pk
4.2.2.1	Analytical methods and validation reports			D	D	4221-analyt-met-val
4.2.2.2	Absorption			D	D	4222-absorp
4.2.2.3	Distribution			D	D	4223-distrib

Module	Name	C1	C2	C3	C4	File or folder name
4.2.2.4	Metabolism			D	D	4224-metab
4.2.2.5	Excretion			D	D	4225-excr
4.2.2.6	Pharmacokinetic drug interactions			D	D	4226-pk-drug-interact
4.2.2.7	Other pharmacokinetic studies			D	D	4227-other-pk-stud
4.2.3	**Toxicology**			D	D	423-tox
4.2.3.1	Acute toxicity			D	D	4231-acute-tox
4.2.3.2	Repeat dose toxicity			D	D	4232-repeat-dose-tox
4.2.3.3	**Genotoxicity**			D	D	4233-genotox
4.2.3.3.1	In vitro			D	D	42331-in-vitro
4.2.3.3.2	In vivo			D	D	42332-in-vivo
4.2.3.4	**Carcinogenicity**			D	D	4.2.3.4
4.2.3.4.1	Long-term studies			D	D	42341-lt-stud
4.2.3.4.2	Short or medium term studies			D	D	42342-smt-stud
4.2.3.5	**Reproductive and developmental toxicity**			D	D	4235-repro-dev-tox
4.2.3.5.1	Fertility and early embryonic development			D	D	42351-fert-embryo-dev
4.2.3.5.2	Embryo-foetal development			D	D	embryo-fetal-dev
4.2.3.5.3	Prenatal and postnatal development			D	D	42353-pre-postnatal-dev
4.2.3.5.4	Studies in the offspring (juvenile animals are dosed and /or further evaluated)			D	D	42354-juv
4.2.3.6	**Local tolerance**			D	D	4236-loc-tol
4.2.3.7	**Other toxicity studies**			D	D	4237-other-tox-stud
4.2.3.7.1	Antigenicity			D	D	42371-antigen
4.2.3.7.2	Immunotoxicity			D	D	42372-immunotox
4.2.3.7.3	Mechanistic studies			D	D	42373-mechan-stud
4.2.3.7.4	Dependence			D	D	42374-dep
4.2.3.7.5	Metabolites			D	D	42375-metab

Module	Name	C1	C2	C3	C4	File or folder name
4.2.3.7.6	Impurities			D	D	42376-imp
4.3	**Literature references**			D	D	43-lit-ref

Module 5

Module	Name	C1	C2	C3	C4	File or folder name
5	Clinical					m5
5.1	**Table of contents**			D	D	51-toc
5.2	**Tabular listing of all clinical studies**			D	D	52-tab-list
5.3	**Clinical study reports**			D	D	53-clin-stud-rep
5.3.1	Reports of biopharmaceutic studies			D	D	531-rep-biopharm-stud
5.3.2	Reports of studies pertinent to pharmacokinetic using human biomaterials			D	D	532-rep-stud-pk-human-biomat
5.3.3	Reports of human pharmacokinetic studies			D	D	533-rep-human-pk-stud
5.3.4	Reports of human pharmacodynamic studies			D	D	534-rep-human-pd-stud
5.3.5	**Reports of efficacy and safety studies (header)**			D	D	535-rep-effic-safety-stud
5.3.5.1	Study reports of controlled clinical studies pertinent to the claimed indication			D	D	5351-stud-rep-contr
5.3.5.2	Study reports of uncontrolled clinical trials			D	D	5352-stud-rep-uncontr
5.3.5.3	Reports of analysis of data from more than one study			D	D	5353-rep-analys-data-more-one-stud
5.3.5.4	Other clinical study reports			D	D	5354-other-stud-rep
5.3.6	Reports of Post-Marketing Experience			D	D	
5.4	**Literature references**			D	D	54-lit-ref

CTD Module 1: registered complementary medicines

Module 1of the Common Technical Document (CTD) has been tailored to accommodate the needs and requirements for complementary medicines.

It is a standardised format for collating and organising the administrative information part of the dossier to support an application to either:

- register a complementary medicine under section 23 of the *Therapeutic Goods Act 1989* by following the complementary medicine registration process
- change the details of an ARTG entry for a complementary medicine under section 9D of the *Therapeutic Goods Act 1989* by following the process to change a complementary medicine.

Sections intentionally deleted

We have deleted the following sections as they do not apply to complementary medicine applications:

- 1.6 Master files and certificates of suitability
- 1.8 Pharmacovigilance
- 1.10 Information relating to paediatrics
- 1.12 Antibiotic resistance data

Make sure all the document(s) meet the general dossier requirements.

1.0 Correspondence

Use this section to include:

- Your application cover letter.
- Your responses to our requests we make for information during the screening (Step 10) or during evaluation (Step 11 of the registration process).
- Any other correspondence you may have received from us before submitting your application. For example, an email from us about:
  - data requirements for a registration application
  - using a particular code and application level for a change application
  - format for the application as agreed at the pre submission meeting.

Cover letter (letter of application)

Follow the guidance for the cover letter.

Make sure the cover letter is on company letterhead and:

- includes the information required of your application
- is signed by a person listed in your company details as authorised to conduct business with us. The 'AU eCTD specification: Module 1 and regional information' contains information about electronic signatures.

Include the cover letter in Module 1.0.1 for all applications.

Make sure the new document(s) meet the general dossier requirements.

1.1 Comprehensive table of contents

Locate the main table of contents in the top level folder of the dossier.

The comprehensive table of contents is a complete list of all documents in the dossier, arranged by module, and with location references for each document.

The table of contents can have hyperlinks that navigate to the individual files (documents) in the dossier.

1.2 Administrative information

This section contains the patent certification documents for medicine applications.

Do not include:

- application forms for complementary medicines in Module 1.

1.2.3 Patent certification

Provide either a patent certification or patent notification under section 26B(1) of the *Therapeutic Goods Act 1989* for all new registrations, including:

- formulation changes
- changes in trade name
- extensions of indications
- changes to the directions for use.

Submit the relevant patent certification or notification:

- Certification in relation to patents required in relation to registration or listing under Sections 25, 26 and 26A of the *Therapeutic Goods Act 1989*
- Notification to the Secretary that certification under section 26B(1) of the *Therapeutic Goods Act 1989* is not required.

You can either:

- Include the certification or notification in Module 1.2.3, if you are able to provide it when you submit your dossier.
- Send the certification or notification to complementary.medicines@health.gov.au at any time after you lodge the application with the submission ID clearly visible and clearly identified as Module 1.2.3 Patent certification.

1.2.5 Form for approval to use a restricted representation

If you are using a restricted representation on your medicine label, include in Module 1.2.5:

- Application for approval to use a restricted representation in advertising

Please note that approval for the use of a restricted representation can only be considered once the complementary medicine is registered on the ARTG.

1.3 Medicine information and labelling

This section holds documents relating to the presentation and packaging of the medicine including:

- Product Information and package insert
- Consumer Medicine Information
- labels.

You can also include labelling and product documentation of other medicines in Module 1.3. For example:

- labelling of the originator medicine (RCM 1 applications)
- labels of other medicines included in the dossier to assist the evaluator.

1.3.1 Product Information and package insert

Module 1.3.1 is for both the Product Information (PI) and the package inserts.

Product Information

The PI contains technical information intended for healthcare practitioners and must not include promotional material.

For more information, go to:

- Product information for information about what is required
- Guidance on Product Information.

A PI is required for restricted medicines, which are those registered complementary medicines that are:

- subject to Schedule 3 of the Poisons Standard

  OR

- contained in a therapeutic good mentioned in Part 1 of Schedule 10 to the *Therapeutic Goods Regulations 1990* (other than in items 1(b) and 14).

Include Product Information (PI) with your application when you:

- intend to supply a PI for the medicine
- submit a RCM 1 application and the originator medicine includes a PI. For these applications also:
  - include a copy of the most recently approved PI of the originator medicine in Module 1.3.1
- apply to change a registered complementary medicine that involves a change to the PI. For example, an update to the adverse events section of the PI

Even where a PI is not mandatory, you may choose to include one to provide more information on the medicine. However, the requirements for PI documents are the same.

Product information based on an approved PI

If your PI is based on an existing one, provide both the clean and marked –up versions.

The clean version of the PI

Include the 'clean' copy of the PI in Module 1.3.1.1.

This copy incorporates all the proposed changes, but has no version marks and comments.

The 'marked-up' PI

Include the marked-up version in Module 1.3.1.2.

This copy contains all the track changes including changes, additions and deletions.

Justify any differences between the existing and the proposed PI. You can include the justification for the differences as either comments within the document (i.e. as part of the tracked changed document) or a table in the cover letter.

Identify the location within the dossier of the evidence to support the differences.

Package insert

All package inserts for registered medicines are part of product labelling and require TGA approval.

Include a package insert with:

- Applications for medicines that either:
  - need a package insert. For example, when labelling information does not fit on the label.
  - involve changing the existing package insert. Include both the current package insert of the medicine and a draft copy of the new package insert.
- RCM 1 applications where the originator medicine includes a package insert. In this case you need to include both:
  - the package insert for the proposed medicine
  - the most recently approved package insert of the originator medicine.
- Applications where you intend to supply a package insert with the medicine.

Highlight the differences between the current and proposed package insert.

Justify any differences between the current and proposed package insert – Include the justification either:

- as comments within the document (i.e. as part of the tracked changed document)
- in a table in the cover letter.

Identify the location within the dossier of the evidence to support the differences.

Product Information and package inserts for other medicines

If your application refers to Product Information and/or package inserts of other relevant medicines, include these documents in Module 1.3.1.

For example, if your Product Information is based on the PI of another medicine, include the PI of that medicine in Module 1.3.1.

1.3.2 Consumer Medicines Information

The CMI:

✓ contains general information about the medicine

✓ is written in plain English (for the consumer)

✓ must be consistent with the PI

✓ must comply with the requirements specified in Schedule 13 of the *Therapeutic Goods Regulations 1990* (although the information does not have to be set out in the same order as the Schedule).

✘ cannot include promotional material.

Include a CMI when your application is for a:

- new ARTG entry
- separate and distinct good[7] (e.g. changing the proprietary name of an existing medicine that is in Schedule 3 of the Poisons Standard)
- medicine that falls under Schedule 3 of the Poisons Standard
- a change that affects the CMI (for example, an application to include important safety information in the PI which needs to be reflected in the CMI)
- a RCM 1 application and the originator medicine includes a CMI. Include the most recently approved CMI of the originator medicine in Module 1.3.2.

Consumer medicine information based on an existing CMI

If the CMI is based on an existing CMI, include two versions of the CMI, include:

- The 'marked-up' CMI in Module 1.3.2.2.

[7] A separate and distinct good is defined under section 16 of the Therapeutic Goods Act as:
a different formulation, composition or design specification; strength or size, dosage form or model; name; indications; directions for use; container type (disregarding container size).

  - Identify all additions, deletions or changes using 'track changes'.
  - Justify any differences between the existing and the proposed CMI.
- A 'clean' CMI in Module 1.3.2.1. The 'clean' copy incorporates all the changes proposed but removes the version marks and comments.

Consumer medicine information for other medicines

If your application refers to the CMI of other relevant medicines, include those CMI documents in Module 1.3.2.

1.3.3 Label mock-ups and/or specimens

Include copies of all draft medicine labels with all applications to either:

- register new complementary medicines
- change the labelling of a registered complementary medicine.

When the quantity is the only difference in labels for different pack sizes:

- submit one set of labels.
- include an assurance that this is the only difference between the pack sizes.

Application involving a change to the medicine label

Include both the current label and a draft copy of the new label and:

- highlight the differences between the current and proposed labels
- justify any differences between the current and proposed labels
- include the justification for the differences in a table in the cover letter
- identify the location within the dossier of the evidence to support the differences.

Labels of other medicines

Include labels of other relevant medicines in Module 1.3.3 when the application:

- is a RCM 1 (include copies of the most recently approved originator labels)
- refers to labels of other medicines.

1.4 Information about the experts

This section holds documents about the experts who reviewed the supporting data for the application, and prepared the summaries and overviews that constitute Module 2.

Include information about the:

- quality expert in Module 1.4.1 for applications that include any subsection of Module 2.3 in the dossier.
- safety nonclinical expert in Module 1.4.2 for applications that include any subsection of Module 2.4 and/or 2.6 in the dossier.
- clinical expert in Module 1.4.3 for applications that include subsection of Module 2.5 and/or 2.7 in the dossier.

Expert reports

Include expert reports which:

- are cross-referenced by page number or hyperlinked to the submission
- provide separate critical appraisals of both the:
  - quality and manufacturing
  - nonclinical and clinical efficacy and safety of the medicine.

Related guidance

- Module 2 guidance and Module 2 of the CTD.

Authors of expert reports

The author of an Expert Report should have appropriate qualifications and experience relevant to the subject matter. E.g. the expert for a mineral or vitamin supplement application should have qualifications and expertise in nutritional epidemiology.

For each expert responsible for compiling Module 1, provide:

- A declaration completed and signed by the expert that both:
  - declares the extent, if any, of their professional or other involvement with the dossier owner.
  - confirms that the report has been prepared by them or if not, any assistance provided and by whom.
- A curriculum vitae (CV) outlining the expert's educational background, training and occupational experience.

You may find the Module 1.4 form useful for this purpose.

1.5 Requirements for different applications

This section holds documents required for specific types of applications.

You can include the optional OTC analytical validation summary form, form for an approval of a restricted representation and request for section 14 exemptions in Module 1.5.

We have intentionally omitted subsections 1.5.2, 1.5.3 and 1.5.4.

1.5.1 Literature based submission documents

This section applies to applications that partially or completely rely on literature based data.

Follow the guidance on literature based submissions.

Prepare and include the following in Module 1.5.1:

- methodology of the literature search, including complete details of database search strategies.
- the complete search output.

Include the overview summary reports in Module 2.5.

1.5.5 Letters of authorisation

This section holds documents that authorise TGA to both:

- access information of a third party sponsor for the benefit of the applicant e.g. a cross-licensing agreement between the applicant and a third party sponsor
- use the proprietary information for the applicant's medicine e.g. a third party sponsor authorises the use of their logo on the applicants medicine labelling.

Include a letter of authorisation in Module 1.5.5 when your application refers to, or relies on, the data or information held on file of an originator medicine.

What to include in a letter of authorisation

If your application is for an RCM1, or refers to or relies on the data or information of an originator medicine, make sure the letter from the sponsor of the identical medicine:

- Is on company letter head and includes the full name and signature of a person authorised to conduct business on behalf of the applicant. The person must be in our client database and may be a company employee or an agent
- Authorises TGA to use information in their registration file on behalf of the applicant of the new application
- Identifies the medicine by stating its full ARTG name and AUST R number.

1.7 Pre-submission meetings

This section of Module 1 is for documents relating to pre-submission meetings and identifies how you have addressed any issues raised during the meeting in the dossier.

1.7.1 Pre-submission meeting outcomes

Only include information in this section if you had a pre-submission meeting with us (Step 7 of the registration process) and there were issues that you needed to address as part of your application.

Include a copy of the pre-submission meeting outcomes.

In preparing the details of how you have addressed any issues that arose from the pre submission meeting, you need to identify:

- The date(s) of the meeting(s)
- The outcomes arising from the meeting(s) requiring applicant action
- How the outcomes from the meeting(s) have been addressed in the dossier
- Any agreements reached at the meeting.

Meetings include all relevant meetings in any format (i.e. face to face, teleconference or videoconference) requested by either an applicant or TGA.

Ensure the information in Module 1.7.1 accurately reflects the meeting(s) and any outcomes you need to address in your application.

All meetings provide guidance only and outcomes are without prejudice and are not considered binding on TGA.

1.7.2 Details of any additional data

We usually only accept additional data if the medicine is critical to the Australian community to address emergency or safety situations.

You should only need to submit relevant safety data and data that we may request during the evaluation of an application.

If we agree to accept additional data during the evaluation in Step 11 of the registration process, include:

- A copy of our agreement to accept the additional data
- The agreed date for sending the data
- Details of the additional data we agreed to accept.

The additional data:

✓ needs to be well defined and relate to a particular and limited aspect of the application

? may affect target timeframes

✘ are not intended to facilitate inadequate or premature applications.

1.9 Summary of biopharmaceutic studies

1.9.1 Bioavailability or bioequivalence

Include the summary of a bioavailability or a bioequivalence study for RCM 4 and RCM 5 applications that includes a bioavailability or bioequivalence study in the dossier.

To prepare a summary of a bioavailability or bioequivalence study:

- Download the Summary of a bioavailability or bioequivalence study form
- Complete a separate form for each study
- Include the form(s) in Module 1.9.1.

Justifications when you do not have data

You can submit a scientific justification when biopharmaceutic studies are required but not provided under the Module 5 Reports of biopharmaceutic studies (5.3.1).

Ensure you:

- Address all the relevant points in your justification for not submitting biopharmaceutic data
- Include any other relevant information
- Include any references used to support the justification in Module 5.

1.11 Foreign regulatory information

This section holds documents relating to foreign regulatory information for a new medicine, or significant changes to a registered medicine.

It is not usually needed for complementary medicines but it may be relevant in certain circumstances. For example, an application for a new medicine with a new active ingredient (a category RCM5 application) where simultaneous applications are being submitted in other countries.

We may ask you to provide information on the foreign regulatory status during the screening or evaluation phase of an application.

1.11.1 Foreign regulatory status

Details of the foreign regulatory status may be included if the same or similar applications have been submitted in other countries or the medicine is marketed in other countries.

Include:

- a list of countries in which a similar application has been submitted
- a list of countries where the proposed medicine or a similar medicine(s) is marketed
- details of approvals, deferrals, withdrawals or rejections of the application in other countries.

1.11.2 Foreign product information

You may include foreign product information for some RCM4, RCM5, C3 or C4 level applications if the same or similar applications have been submitted in other countries or the medicine is marketed in other countries.

Include a copy of the equivalent overseas document to the Australian Product Information. For example, a data sheet from New Zealand or the prescribing information from USA.

1.11.3 Data similarities and differences

You may include data similarities for some category RCM4, RCM5 or level C3 or C4 applications if the same or similar applications submitted in other countries or the medicine is marketed in other countries.

Prepare a summary of the similarities/differences between the data in this application and the data packages submitted in the overseas country.

Identify and account for any significant differences.

1.11.4 Foreign evaluation reports

As part of the Government's complementary medicine reforms, TGA will be consulting on the acceptance of reports from comparable overseas regulators for registered complementary medicines in late 2017.

You may include a foreign evaluation report for some category RCM4, RCM5 or level C3 or C4 applications if another regulatory authority in another country has evaluated the same or similar applications and the evaluation report is available.

Obtain a copy of the relevant evaluation report and include a complete copy of the report.

Module 2: registered complementary medicines

This guidance provides assistance with compiling Module 2 for an application to register a complementary medicine on the ARTG.

It relates to steps 4, 5, and 7 in the registration process for complementary medicines.

Ensuring consistency with the CTD format

Ensure you present an overall quality summary, and overviews of nonclinical and clinical safety and efficacy data, consistent with CTD Module 2.

To assist you, we have provided the general points mainly collated from the CTD guidance documents under the relevant subheadings.

For a complete description of all requirements, refer to the guidelines for Module 2: Common technical document summaries.

Please note

There is no single CTD guidance document that explains all of the content for Module 2.

The guidance for Modules 3, 4, and 5 each include a section on the information that must be provided in Module 2.

When required

This guidance should be reviewed in combination with the registered complementary medicines data requirements matrix.

For RCM4 applications, only a Quality overall summary (included in Module 2) is required and overviews only are required for Module 4 (nonclinical) and module 5 (clinical).

For example an RCM 4 application for a medicine that includes a new therapeutic indication would require a nonclinical overview and a clinical overview including risk benefit analysis of the medicine to support the module 4 and 5 data.

Expert summaries and overviews

Include separate expert reports for:

- quality overall summary
- nonclinical overview (safety)
- clinical overview (efficacy)

For more information about what is required within each module see Common Technical document (CTD).

Quality summary (Module 2.3)

Provide a critical scientific summary explaining how you established the quality of the medicine.

When preparing your summary:

- You should normally not exceed 40 pages of text (excluding tables and figures).
- The structure of the summary should follow the scope and outline of the body of data in module 3 and should include an introduction.
- Include sufficient information from each section to provide an overview of module 3.
- Include discussion of key issues, integrating information for module 3 with supporting information from other modules of the dossier (e.g. qualification of impurities via toxicological studies), including cross references.
- Do not include information, data or justification that was not already included in module 3 or other parts of the dossier.
- Include proprietary name, non-proprietary name of the substance, company name, dosage from, strength, route of administration and proposed indications in the introduction.
- Emphasise key product parameters and justification where guidelines were not followed.
- Refer to quality overall summary – module 2 and 3 for detailed guidance.

Nonclinical overview (Module 2.4)

Provide an integrated and critical assessment of the pharmacological, pharmacokinetic and toxicological data for the medicine.

When preparing your nonclinical overview:

- You should normally not exceed 30 pages.
- Present the nonclinical overview in the following order: overview of nonclinical testing strategy, pharmacology, pharmacokinetics, toxicology, integrated overview and conclusions, list of literature references.
- Discuss and justify the nonclinical testing strategy.
- Interpret the nonclinical data, clinical relevance of the findings and cross-link with quality aspects and implications of the nonclinical findings for the safe use of the product.
- Consider the total amount of the active ingredient from both the medicine and other sources of the active ingredient such as food supply of the target population.
- Take into account the relevant scientific literature and properties of related products.
- Provide an appropriate justification that reviews the design of studies and any deviation from guidelines where you are using scientific literature instead of nonclinical studies.
- Discuss information of the quality of batches of drug substance used in referenced studies.
- Discuss inconsistencies in the data.
- Use consistent units throughout the overview.
- Detailed guidance on the sequence and content of the nonclinical overview is described in the guidance for nonclinical summaries of module 2 under section 2.4 nonclinical overview.

Clinical overview including risk benefit analysis of the medicine (Module 2.5)

Provide a critical scientific analysis of the clinical data.

When preparing your clinical overview:

- You should normally not exceed 30 pages.
- Present the clinical overview in the following order: product development rationale, overview of biopharmaceutics, overview of clinical pharmacology, overview of efficacy, overview of safety, benefits and risks conclusion, literature references.
- Include the proposed therapeutic indications, the target population, strength, dosage, duration and frequency of use, route of administration and pack size in the section on product development rationale.
- Describe the overall approach to establishing safety and efficacy of the medicine in its intended use.
- Take into consideration the history of use of the medicine and any traditional use of the medicine as subheadings of the product development rationale section.
- Present the conclusions and implications of the clinical data to create a succinct discussion and interpretation of both:
  - the clinical findings
  - any other relevant information (e.g. animal data or product quality issues that may have clinical implication).
- Present strengths and limitations of the development program and study results, including important limitations such as:
  - absence of information in some patient populations
  - use in combination with other products.
- Discuss each of the following:
  - positive and negative outcomes
  - adverse events (both serious and non-serious) noting any causal relationships.
- Analyse the benefits and risks of the medicine in its intended use, including interpretation of how efficacy and safety findings support the proposed dose and indication (in form of a critical scientific assessment).
- Provide a separate explanation on how the data supports each indication and claim.
- Address particular efficacy or safety issues encountered, and how they have been evaluated and resolved.
- Explore any unresolved issues and:
  - explain why they should not be considered as barriers to approval
  - describe plans to resolve them.

Further guidance on clinical overviews is provided under section 2.5 clinical overview of the ICH guideline on clinical efficacy.

History of use of the medicine

Provide information on the history of use of the medicine as a subsection in module 2.5.1 (product development rationale) of the clinical overview.

Provide a summary of human exposure data, dietary, traditional and commercial use in Australia and internationally.

Provide (and categorise) the estimated number of people exposed to the medicine since the start of supply by each of the following:

- indication
- dosage and route of administration
- treatment duration
- geographical location.

Traditional use

- Provide information on the history of use of the medicine as a subsection in module 2.5.1 (product development rationale) of the clinical overview.
- When applying evidence of traditional use, the traditionally used medicine described in this evidence and the proposed medicine must have the same:
  - traditional preparation – ensuring consistent characteristics
  - use (including dose, route of administration and duration of use).

Although long-term traditional use does not fully establish the safety and efficacy of a proposed medicine, we will consider the evidence as part of the safety evaluation.

Quality information for a new registered complementary medicine

Present the data on quality in an application for evaluation of a new registered complementary medicine in a manner consistent with the European Medicines Agency (EMA) CTD module 3: ICH M4Q CTD for the registration of pharmaceuticals for human use - Quality. Presentation of data in the CTD format is not mandatory, but it is encouraged.

Quality issues relating to the active ingredient(s) and the finished product should be addressed. A list of the scientific guidelines on quality matters that have been adopted in Australia is available on the TGA website.

You should ensure that the data address the key aspects provided in the following guidance.

As part of the Government's complementary medicine reforms, TGA will be consulting on the data requirements for registered complementary medicines in late 2017.

Active ingredient quality information

The data required to be submitted for an active ingredient in a new registered complementary medicine is comparable to those required for an application for a new complementary medicine substance—refer to Information required for an application for evaluation of a new complementary medicine substance.

Nomenclature of active ingredient(s)

All the components of the proposed medicine should be identified using Australian approved terminology—refer to Approved terminology for medicines.

Structural formula of active ingredient(s)

For simple substances and any nominated characterised constituents, provide the molecular formula, molecular weight and Chemical Abstracts Service (CAS) Registry Number or similar information that will demonstrate identity.

For complex substances, where applicable, provide a description of the constituents with known therapeutic activity or markers and other constituents.

General properties of active ingredient(s)

Provide information about the physico-chemical properties relevant to the characterisation of the substance or that may be important for the manufacture, performance or stability of its intended final dosage form, for example: solubility, particle size. Provide qualitative and quantitative particulars of the substance, including information on all physical properties such as appearance, colour, texture and smell.

Manufacturing details of active ingredient(s)

List of manufacturer(s) of active ingredient(s)

Provision of the active ingredient manufacturer's name and address, while not mandatory, will assist the TGA in the evaluation process.

Description of manufacturing process and process controls for the active ingredient(s)

A description of the manufacturing process and process controls for the active ingredient (including, for example: source and control of starting materials, reprocessing, control of critical steps and intermediates) with a flow diagram should be provided.

Where an active ingredient is derived from a herbal material, specifications for the herbal material should be provided. For control of herbal materials refer to the ICH guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2.

If a manufacturer is unwilling to release information required in an application to you, this information can be submitted directly to the TGA, with written authorisation from you.

Characterisation of active ingredient(s)

Identify the physical and chemical properties of the active ingredient(s).

Control of active ingredients - specifications of raw materials

Under current Australian legislation, if an ingredient is subject to a specific monograph in a default standard, it must comply with the requirements of that monograph. If there is a default standard for a finished product, the active ingredient must comply with the same default standard, for example: BP, USP. If the finished product is subject to more than one monograph, the manufacturer may nominate which will be applied. In the absence of a monograph, specifications to ensure consistent quality will need to be developed.

Typically, the manufacturer of the active ingredient will develop and apply quality specifications. The finished product manufacturer is also expected to ensure that the active ingredient is of appropriate quality before including it in the manufacture of the finished product. If there are any differences between the active ingredient specifications used by the active ingredient manufacturer and the finished product manufacturer, these should be identified and discussed.

If the ingredient is herbal, the botanical species, plant part and, if an extract, the amount of the extract, the strength of the extract, extracting solvent and the equivalent amount of dried plant should be provided. Guidance on the identification of herbal materials and extracts is provided in the document titled Identification of herbal materials and extracts - Questions & answers.

Specifications of active ingredient(s)

The active ingredient acceptance specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality.

The development of the specifications for the active ingredient should be guided by the following scientific guidelines:

- Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances CPMP/ICH/367/96.
- Guideline on specifications: Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2820/00 Rev. 2.

Where there is a TGA default standard for the ingredient, and if no additions have been made to the requirements of that standard, reference to the current version of the pharmacopoeia is sufficient. It is not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph; or
- adopt an earlier edition of the pharmacopoeial monograph or standard.

In some cases, the pharmacopoeial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient and applicants may include additional tests.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided, together with a justification. The justification should outline how the specifications ensure that the ingredient used in a medicine formulation is of consistent quality. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient should be addressed.

Impurities and incidental constituents of active ingredient(s)

For guidance refer to Impurities and incidental constituents of complementary medicine substances. For solvent impurities refer to the scientific guideline: Note for Guidance on Impurities: Residual Solvents CPMP/ICH/283/95.

Batch certificates of analysis for active ingredient(s)

Certificates of analysis should be provided for at least two recent commercial-scale production batches to demonstrate routine compliance with the specifications or monograph.

Certificates of analysis should also be provided for any batches of material used in toxicity tests, stability studies and clinical trials reported in support of the application. This will assist the TGA in determining whether the substance intended for supply is the same as that for which safety or stability data have been provided. If certificates of analysis are not available, justification as to why they have not been supplied must be provided.

Reference standard for active ingredient(s)

Provide information about the reference standards used in the tests for, for example: identification, assay and impurities. Information should also be provided about how these reference substances were established, and where applicable, how their potencies were assigned. Where 'in-house' reference materials are used, provide information on how the reference material has been characterised.

Stability of active ingredients

Stability data should be provided for active ingredient(s). The data can assist in identifying any particular degradants that may be formed and should be monitored as part of the overall stability program. For guidance, refer to the scientific guideline: Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products CPMP/QWP/122/02 rev 1 corr.

Product quality information

Description and composition of the product

Provide the medicine name and a description of the finished product that includes a visual description of the dosage form, including any special characteristics, for example: modified release.

Product development

Formulation details for the product

Include a table of all the ingredients in the product (using Australian approved name (AAN) terminology) which details:

- the purpose of each ingredient in the formulation, for example: active, disintegrant, antimicrobial preservative
- amount of each ingredient on a per unit basis
- any overages (additional amounts of ingredients, over the amounts nominated in the product's formulation, added during manufacture)
- a reference to the quality standard for each of the ingredients, for example: a pharmacopoeial monograph reference or manufacturer's specifications number.

Each excipient ingredient included in a formulation must have a justifiable excipient role and be used in appropriate amounts to achieve its technical purpose.

Formulation development

Information on the development of the medicine should be provided, including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container.

Overages and batch to batch variation

If an overage of an active ingredient (an additional amount of an ingredient added during manufacture and greater than the amount nominated in the product's formulation) is used during manufacture, details and justification of the overage used should be included in the medicine development summary.

For some active ingredients, such as herbal substances, the weight of the active raw material used in a batch of the formulated product may vary according to the content of a standardised component. The formulation given in the application should have an annotation indicating that the actual weight of active raw material will vary according to its estimated amount, and a formula should be provided showing how the amount of adjustment will be calculated. Validation data should be provided for the extremes of proposed ranges. Critically, where the product is a tablet or capsule, the validation data should include dissolution or disintegration data, using the test method in the proposed finished product specifications.

It is recognised that it may be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during manufacturing. Table D6 lists the changes to the nominal amounts of certain excipients that may be made in the manufacture of immediate release registered complementary medicines.

Table D6: Allowed changes to the nominal amounts of certain excipients

Excipient type	Range
pH adjusting ingredients	qs
Volume adjusting fluids	qs
Quantity of ingredients whose function is to contribute to viscosity	+/– 10%
Colour in tablet coating (but not in body of tablet)	qs
Solvent in granulating fluid	qs
Granulating fluid (fixed composition)	+/– 10%
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25%
Coating solution	qs*
Talc and water-soluble lubricants and glidants	–25% to +100%
Water-insoluble lubricants and glidants, except talc (e.g. magnesium stearate)	+/– 25%
Filler (bulking agent) in hard gelatine capsules	+/– 10%
Polishing agents	qs
Carriers and potency-adjusting ingredients for materials of biological, herbal origin	+/– 10%
Filler (bulking agent) in tablets and soft gelatine capsules to account for the changes in the item above	+/– 10%

*Does not apply to modified release products – approval is required for any variation from the registered formulation

qs – quantum satis or 'as required'

Physiochemical and biological properties

Where a medicine has modified release characteristics or an unusual method of manufacture, the medicine development summary should include a detailed discussion of the development of those characteristics or method and any relationship with the finished product specifications. For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be discussed and related to the dissolution test in the finished product specifications.

Manufacturing process development

The selection and optimisation of the manufacturing process, particularly its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Describe any significant changes made to the manufacturing process of the medicine used in producing scale-up, pilot and production-scale batches that may affect the composition of the substance.

Container closure system

The suitability of the container closure system used for the storage, transportation (shipping) and use of the medicine should be discussed. The discussion should consider such things as choice of material, protection from moisture and light.

Microbiological attributes

Where appropriate, microbiological attributes of the dosage form should be discussed, including such things as the rationale for not performing microbial limits testing for non-sterile products. For sterile products, the integrity of the container closure system to prevent microbial contamination should be discussed.

Compatibility

Where applicable, the compatibility of the medicine with reconstituent diluents or dosage devices should be addressed to provide appropriate and supportive information for the labelling.

Product manufacture

Manufacturer information name(s)

All medicines must be manufactured in accordance with the principles of good manufacturing practice. The manufacturer of each step in the manufacture of the medicine that occurs in Australia must be licensed to perform that step. If a step in manufacture is carried outside Australia then the manufacturing and control procedures used in the manufacture must be acceptable.

Australian manufacturers must comply with the PIC/S Guide to Good Manufacturing Practice for Medicinal Products.

The TGA has produced guidance for sponsors who rely on international manufacturers for any part of their production process. Refer to:

- GMP clearance guidance
- Questions & answers on the code of good manufacturing practice for medicinal products.

Batch formula

A batch formula should be provided in a table format. It should include all of the components that will be used in the manufacture of the finished product and their amounts on a per batch basis (including any overages).

Description of manufacturing process and process controls

Details of the manufacturing process for the finished product should be provided for each manufacturing site. Typically, these steps may include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for supply. The manufacturing details should include a manufacturing formula and also information on:

- solvents that are used, even if they are evaporated from the medicine during manufacture
- polishing agents that do not appear in the formulation.

Control of critical steps and intermediates

Tests and acceptance criteria that are applied to critical steps or intermediates in the manufacture of the finished product should be provided, such as: manufacturing acceptance criteria for a tablet granulation or in-process controls for pH during mixing of a syrup.

Process validation and/or evaluation

Description, documentation and results of the validation and/ or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process.

Control of excipients

Excipient ingredients subject to a specific monograph in a default standard must comply with the requirements of that monograph. If there is no relevant monograph for the ingredient, full details of the specifications for each excipient are required.

Note that there are additional restrictions and requirements for ingredients that are of animal or human origin or that are genetically modified organisms or genetically modified products.

Colours permitted in oral medicines are specified in the guidance 'Colourings used in medicines for topical and oral use' is available on the TGA website. While topical products may include colours other than those listed in this document, the specifications for colourings used in topical products should be comparable with those permitted for oral use.

In the absence of a default standard, colours should generally conform either to the specifications in the FAO/WHO Compendium of Food Additive Specifications or to those defined in the European Commission Directive 95/45/EC.

Specifications

The specifications of excipients should be provided.

Analytical procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

Analytical validation information, including experimental data for the analytical procedures used for testing the excipients should be provided, where appropriate.

Justification of specifications

Justification for the proposed excipient specifications should be provided, where appropriate.

Excipients of human or animal origin

For excipients of human or animal origin, information should be provided regarding adventitious agents.

Novel excipients

For excipients used for the first time in a medicine or by a new route of administration, full details of manufacture, characterisation and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the medicine ingredient format.

Control of the finished product

Specifications

The finished product specifications should be provided. Refer to Finished product specifications, certificate of analysis for guidance on the information required in a finished product specification.

The specification should include both the batch release and expiry specifications. Where the expiry specifications differ from the batch release specifications, this should be noted. The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life. The limits applied at batch release should be discussed in terms of their ability to ensure this.

The specifications should take into account any overages and the results obtained in the stability studies.

Where the product is subject to a default standard the expiry specifications must include all of the tests and limits therein. If the applicant considers that nominated test methods are unsuitable for the product, the applicant may propose other, appropriately validated, methods.

Useful guidance on the development of product specifications is provided in the following scientific guidelines:

- Specifications: Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances CPMP/ICH/367/96

For demonstration of quality for herbal complementary medicines, the following scientific guidelines provide useful guidance:

- Quality of herbal medicinal products/ traditional herbal medicinal products EMA/CPMP/QWP/2819/00 Rev. 2
- Test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/ traditional herbal medicinal products CPMP/QWP/2820/00 Rev. 2
- Quality of combination herbal medicinal products/ traditional herbal medicinal products EMEA/HMPC/CHMP/CVMP/214869/06

Specifications should also take into account Australian legislative requirements for finished products.

The general monographs of the BP, Ph. Eur. and USP are also relevant, for example: the BP monograph for oral liquids, which includes requirements for dose and uniformity of dose of oral drops and also uniformity of delivered dose from multidose containers. The most recent edition of the cited pharmacopoeia should be used.

Where a finished product does not comply with Australian legislative requirements, for example: Therapeutic Goods Order No. 78 - Standard for Tablets and Capsules (TGO 78), a consent to supply the product is required—refer to Consent to supply goods that are not compliant with prescribed standards.

Analytical procedures

Details of analytical methods should be provided for all tests proposed in the specifications. Appropriately validated methods should be used.

Details of the analytical method validation should also be provided in the dossier.

Batch certificates of analysis

You must provide at least three certificates of analysis for the final product to demonstrate compliance with batch release specifications. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured. In such a case, you should identify any differences between the trial process and the manufacturing process and undertake to provide certificates of analysis for at least two production batches after registration has been achieved.

Residual solvents in non-pharmacopoeial products

It is necessary to consider the total amount of residual solvents that may be present in the finished product. This includes solvent residues resulting from the manufacture of the finished product. Depending on the amounts and types of solvent residues, it may be appropriate to include a test and limits for residual solvents in the finished-product specifications. Tests and limits in the specifications, or justification for not including them, should be based on the BP Appendix VIIIL – Residual Solvents.

Impurities in non-pharmacopoeial products

The specifications for finished products for which there is no default standard, should include tests and limits for impurities related to the active ingredient. For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the amount and types of impurities that were detected in the stability studies should be consistent with the expiry specifications and the proposed shelf life. Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

Where the active ingredient is a chemical entity, guidance on the amount and type of information needed on degradation products of the active ingredient can be found in the scientific guideline: Note for Guidance on Impurities in New Drug Products CPMP/ICH/2738/99.

Microbiological requirements for non-sterile products

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and expiry specifications. The Therapeutic Goods Order No. 77 - Microbiological Standards for Medicines (TGO 77) specifies the minimum microbiological requirements with which a medicine must comply throughout its shelf life.

It is not a requirement that every batch of a product (with a low risk of contamination) be tested at batch release. Once it has been demonstrated, by testing a number of routine production batches to establish a product history, that the manufacturing processes do not permit contamination by excessive numbers of microorganisms, testing may be reduced to once every 6 to 12 months or some other selected basis, for example: every tenth batch.

Products with significant water content (for example: creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

For products containing an antimicrobial preservative, both the batch release and expiry specifications should include physicochemical tests and limits for content of preservatives. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH that will ensure preservative efficacy. The expiry limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

Microbiological requirements for sterile products

The official requirements for sterility tests in Australia are those specified in the current default standards. The TGA Guidelines for sterility testing of therapeutic goods provide guidance for sterility testing of sterile therapeutic goods supplied in Australia for human use. These guidelines, however, are not mandatory for industry.

Generally, products that are required to be sterile (for example: for ophthalmic use) will require extremely stringent microbiological specifications together with detailed information on manufacturing steps that ensure sterility.

Justification of finished product specifications

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with reference to relevant standards, the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product.

Reference standards or materials

Information on the reference standards or reference materials used for testing of the medicine should be provided, if not previously provided.

Container closure system

A description of the container and closure system should be provided, including the materials used. The suitability of the container should be discussed in terms of its compatibility with the medicine and also its performance in protecting the medicine physically, including from exposure to moisture and light.

In the case of 'standard' package types, it may be sufficient to simply describe the packaging. Many applicants provide diagrams of the packaging material, identifying bottle or box dimensions, and this is helpful. If the packaging material is unusual, very detailed information should be provided on its composition, as well as an assessment of the potential for undesirable material to be leached from the packaging into the medicine.

Child resistant closures

TGO No. 80 – Child-Resistant Packaging Requirements for Medicines (TGO 80) specifies requirements relating to the use of child-resistant packaging (CRP) for medicines which may present a significant risk of toxicity to children if accidentally ingested and also specifies the performance requirements that packaging must meet in order to be considered child-resistant. TGO 80 applies to medicines containing any of the ingredients specified in the First Schedule to the Order, as well as other medicines that imply, through their presentation, that the packaging is child-resistant. Presentations considered to indicate child-resistant packaging include closures with the push-down and turn graphics, typically used on child-resistant caps, and label statements referring to the closure as being child-safe or designed to prevent access by children.

Tamper-evident packaging

Tamper-evident packaging (TEP) of therapeutic goods that may be vulnerable to tampering (either deliberate or accidental) is important in ensuring consumer safety and the integrity of the goods. Where sponsors may choose to apply TEP to therapeutic products, the products should meet the requirements of the Tamper-evident packaging (TEP) code of practice. This code of practice refers to therapeutic goods that are unscheduled or in Schedule 2 or 3 to the Poisons Standard and are administered transdermally, orally or come into contact with mucous membranes.

Measuring devices

Under current Australian legislation some measuring devices or dose delivering devices may be considered as Class 1 medical devices—please refer to the Australian Regulatory Guidelines for Medical Devices (ARGMD) for further guidance.

Finished product stability

Stability summary and conclusion

The types of studies conducted, protocols used and the results of the studies should be summarised. The summary should include, for example: conclusions with respect to shelf life and, if applicable, in–use storage conditions and shelf-life.

Stability data

The stability data must be sufficient to demonstrate, or indicate with a high probability, that the medicine intended for market will remain safe, of consistent quality and efficacious throughout the its shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions. Refer to the scientific guideline: Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products CPMP/QWP/122/02 rev 1 corr.

Post-registration requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to the PIC/S Guide for Good Manufacturing Practice for Medicinal Products).

Where a shelf life has been allocated on the basis of:

- accelerated testing
- data generated on a related formulation
- data generated on the same formulation in a different container; or
- data generated on batches other than production batches.

It is a requirement to provide an assurance that full stability testing will begin on at least the first two production batches and continue for the full period of the product's shelf life (at the recommended storage condition) and that any adverse trends will be reported to the TGA.

Data may be requested for review at any time or followed up by the TGA's inspectors during GMP inspections of the manufacturing site. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken, which may include cancellation of the medicine's registration.

Stability protocol for self-assessable shelf life extension

A medicine's shelf life may be extended on the basis of stability testing conducted according to a protocol specifically approved for this purpose. For a stability protocol to be considered for the purpose of self-assessable shelf life extensions, it is normally necessary for at least twelve months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing or one that is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a stand-alone document, which includes:

- a statement of the intended purpose (for example: 'This protocol is intended for notification of shelf life increases of up to x years following self-assessment of stability data')

- a statement of the criteria for notifying a shelf-life increase (for example: 'Full-term stability data will be generated using two production batches stored at x°C'. All analytical results obtained will comply with the protocol acceptance criteria; otherwise, the TGA will be notified immediately')
- the precise formulation of the medicine (if overages are included, this should be stated and a justification provided)
- the immediate container specifications
- the storage conditions to be included on the label
- the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test)
- a statement of the proposed tests and validated test methods (validation data should be included if it has not already been supplied to the TGA)
- a matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study.

Shelf life extensions according to an approved protocol

Provided that a protocol for self-assessable shelf life extensions has been approved by the TGA for a particular product, the shelf life extension for that medicine may be implemented following notification to the TGA, provided that:

- all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol
- no other changes to the information previously provided to the TGA about this medicine (other than as specified in the notification) have been made, or are currently proposed to be made
- a stability testing protocol has been approved and a copy of the approval letter is attached to the notification
- at least two full production batches of the Australian formulation packed in the approved container have been used in the studies
- the shelf life is not longer than the time for which stability data meeting the approved protocol are available, and in any case is not longer than five years.

Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are as follows:

- the existing shelf life should be at least two years
- stability data should be available to the TGA which validate the existing shelf life
- a recent (less than two months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release
- the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is intended as a purely one-off event to ensure continued supply.

Prospective extensions of more than six months, or to a shelf life of more than five years, are not normally acceptable.

Generic registered complementary medicines

This guidance is to assist applicants to register a generic complementary medicine on the ARTG.

Quality data is required in support of generic complementary medicines to ensure:

- consistency and quality of the manufacturing process for the medicine
- the quality of the ingredients and the final product
- the combination of ingredients used to make the final medicine product.

In most cases you do not need to provide safety data in support of generic complementary medicines. However, in most cases you need to provide efficacy data (bioequivalence or therapeutic equivalence data) to demonstrate bioequivalence with the originator medicine.

Applications for new generic complementary medicines can be one of two application categories:

- RCM 3: generic complementary medicines for which you can provide an appropriate scientific justification for not providing bioequivalence data
- RCM 4: generic complementary medicines when bioequivalence studies are necessary

When bioequivalence data is required

Bioequivalence date is required:

- for all generic modified release dose forms (excluding enteric-coated tablets or capsules)
- if there is reason to believe that the bioavailability of the proposed medicine may differ from the originator medicine, which may adversely impact on efficacy and/or safety of the medicine
  - For example, if the medicine contains excipient(s) or has novel properties that could significantly affect gastric passage, absorption, *in vivo* solubility or *in vivo* stability of the active substance

Requirements for bioequivalence data

Include biopharmaceutic study reports in module 5.3.1 and complete the Summary of a Bioavailability or Bioequivalence Study form for each study and include in module 1.9.1 of the dossier.

When bioequivalence data is not required

There may be cases where a justification for not providing bioequivalence data is appropriate. These should be discussed at a pre-submission meeting. In your justification:

- include an explanation as to why the requirement is not being met
- detail the proposed alternative approach and a scientific justification for why the proposed approach is valid (with reference to any supporting documents)

Include your justifications for not providing bioequivalence data in Module 1.9.2 of the dossier.

Refer to Biopharmaceutic studies guidance, section 15.9 for more information on what to include in the justification.

Related guidance

- ARGPM guidance 15: Biopharmaceutic studies
- Guideline in the investigation of bioequivalence
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms – section 6, abridged application for modified release forms refer to a marketed modified release form
- CTD Module 5: Efficacy (clinical study reports) - section 2.7.1 and 5.3.1 provide information on bioequivalence.

RCMs using active ingredients permitted in listed medicines

A registered medicine can contain active ingredients permitted for use in listed medicines when the indications are at a higher level than those permitted for listed medicines.

The Therapeutic Goods (Permissible Ingredients) Determination provides a comprehensive list of ingredients permitted for use in listed medicine, along with requirements applying to the use of particular ingredients included in listed medicines.

When each active ingredient is in compliance with the requirements stated in the Therapeutic Goods (Permissible Ingredients) Determination, safety data is usually not required.

Conditions

- No new safety data available beyond what was considered to establish safety for listed medicines
- No changes to the quality of the active ingredient

Data requirements

- Module 3 (quality)
- Module 5 (clinical) - clinical data is required to support all the indications and can be presented as clinical trial study reports or literature based evidence or a mixture of both.

Note: Safety (non-clinical) data is required when the medicine contains excipients (that are not approved for use in listed medicines.

Related guidance and information

- Therapeutic Goods (Permissible Ingredients) Determination
- Module 3: Quality
- Module 5 Efficacy (clinical study reports)
- Literature based submissions

Safety and efficacy information for a new registered complementary medicine

Well documented ingredients/medicines

If an ingredient or medicine is well described and appropriately referenced in reputable texts or publications (for example: Martindale-The Complete Drug Reference) the TGA will consider these sources in the assessment of safety and efficacy where these are provided in the application. Indications, dosage and route of administration must be consistent with the reference provided. For guidance for applicants choosing to submit a literature-based submission, see Literature-based submissions for complementary medicines.

For other new medicines, that are not well described in literature, nonclinical and clinical data will be required to support the safety and efficacy of the medicine. Safety and efficacy data should be presented as 'nonclinical' and 'clinical' data modules (consistent with the CTD Modules 4 and 5).

Data that demonstrate the safety of the medicine include information on history and pattern of use, biological activity, toxicology, clinical data and reports of adverse reactions. The overall safety of the medicine is dependent upon its formulation, its intended therapeutic purpose, dosage, method or route of administration, duration of use, the target patient group (such as children or the elderly) and the potential for interaction with other medicine(s).

Safety may be established by detailed reference to the published literature and/or the submission of original study data. Where there is sufficient evidence based on human experience to support safety, the absence of extensive nonclinical investigations may be justifiable. Note that anecdotal or limited clinical reports of efficacy alone are not considered evidence of efficacy and safety.

Nonclinical data

Pharmacology

Primary pharmacodynamics: in vitro and in vivo

Studies on primary pharmacodynamics should be provided and evaluated.

Secondary pharmacodynamics: in vitro and in vivo

Studies on secondary pharmacodynamics should be provided by organ system, where appropriate, and evaluated.

Safety pharmacology

Safety pharmacology studies should be provided and evaluated. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they assess potential adverse effects in humans.

Pharmacodynamic drug interactions

Where they have been performed, pharmacodynamic drug interactions should be provided.

Pharmacokinetics

Analytical methods and validation reports

Provide the methods of analysis for biological samples, including the detection and quantification limits of analytical procedures.

Absorption

Provide data on the extent and rate of absorption (*in vivo* and *in vitro* studies) and kinetic parameters, bioequivalence and/or bioavailability.

Distribution

Where available, provide data tissue distribution studies, protein binding and distribution in blood cells and placental transfer studies.

Metabolism

Where available, provide data on:

- chemical structures and quantities of metabolites in biological samples
- possible metabolic pathways
- pre-systemic metabolism
- in vitro metabolism including P450 studies
- enzyme induction and inhibition.

Excretion

Where available provide data on routes and extent of excretion and excretion in breast milk.

Pharmacokinetic drug interactions (nonclinical)

If they have been performed, provide nonclinical pharmacokinetic drug interaction studies (*in vitro* and *in vivo*).

Provide details of any contraindications or interactions with conventional and non-conventional medicines.

Other pharmacokinetic studies

If studies have been performed in nonclinical models of disease they should be provided and evaluated.

Toxicology

Single dose toxicity

The single dose data should be provided in order of species, by route and evaluated.

Repeat dose toxicity

Studies should be provided in order of species, by route and by duration and evaluated.

Genotoxicity: in vitro and in vivo

Where available, *in vitro* and *in vivo* mammalian and non-mammalian cell system genotoxicity studies should be provided and evaluated.

Carcinogenicity: long term studies and short or medium term studies

Where available, carcinogenicity studies should be provided and evaluated.

Reproductive, developmental toxicity

Where available, provide and evaluate studies on:

- fertility and early embryonic development
- embryo-foetal development
- prenatal and postnatal development
- studies in offspring.

Local tolerance

If local tolerance studies have been performed, these should be provided and evaluated.

Other toxicity studies

Provide any other studies such as: antigenicity, immunotoxicity, mechanistic studies, dependence, metabolites and impurities.

Clinical data

Clinical data should preferably be presented as specified in Modules 2.5 Clinical Overview, 2.7 Clinical Summary and Module 5 Clinical Study Reports of the CTD format. The clinical overview provides a critical analysis of the clinical data in the dossier while the clinical summary is provides a detailed, factual summarisation of the clinical information.

Pharmacology studies

Pharmacokinetics

Include information on the mechanism of action, if known. Include information to justify the proposed dose and dose interval and any information that may be relevant to formulation differences in the submitted studies and to possible interactions with other medicinal products.

Pharmacodynamics

Include data on the action of the medicine on the body including absorption, distribution, metabolism and elimination of the medicine.

Efficacy studies

Controlled and uncontrolled efficacy clinical trials

Provide and evaluate any published and unpublished efficacy clinical trials.

Australian Clinical Trials provides information for sponsors developing clinical trials for a medicine or a new complementary medicine substance.

Efficacy-related PI/CMI comments (where applicable)

Where the medicine has a PI or CMI document, provide any comments related to the efficacy clinical studies.

Safety studies

Controlled and uncontrolled safety clinical trials

Provide and evaluate any published and unpublished safety clinical trials.

Safety-related PI/CMI comments (where applicable)

Where the medicine has a PI or CMI document, provide any comments related to the safety clinical studies.

Post-marketing data

The application should include all relevant post-market data, including published and unpublished data. Any safety issues identified following marketing should be highlighted and any regulatory action relating to safety taken by an international regulatory agency should be detailed. The data should be presented as a tabulation of the adverse events that have been reported, including any serious adverse events and any potentially serious interactions with other medicines.

A Periodic Safety Update Report (PSUR) report is acceptable as post-marketing data.

Changes for registered complementary medicines

The information below is for sponsors planning to change a registered complementary medicine. It:

- contains the complementary medicines changes tables, which are a tool to help you obtain essential regulatory information about your change including:
  - whether approval is needed to make the change
  - notification requests
  - the section of the Therapeutic Goods Act 1989 you are applying under
  - the relevant change codes; these are required to complete your application
  - the application level for the change.
- explains how to use the complementary medicines changes tables.

Related information and guidance

- Completing the online application form for RCMs
- Notifications process: requests to vary registered medicines where quality, safety and efficacy are not affected

Change application levels

Applications to change an ARTG entry for a registered complementary medicine are categorised into five levels (CN–C4) based on increasing risk.

It is important that you select the correct change codes in the change code tables as these will determine the application level for you.

Notification request (CN)

Notification changes are those changes where their implementation would not affect the established quality, safety or efficacy of the medicine. These have been determined by TGA to pose a very low risk.

Notifications include changes to the quality and non-quality aspects of a medicine and do not require assessment of safety, efficacy and/or quality data (or a justification for not providing such data). After making an application to TGA requesting the variation and receiving an automated acknowledgment of acceptance of the submission, sponsors can implement the changes immediately.

Notification changes identified in the Changes Table as application level N (CN).

As part of the Government's complementary medicine reforms, TGA will be consulting on change application levels C1-C4 for registered complementary medicines in late 2017.

Application level 1 (C1)

Changes identified in the Changes Table as application level C1.

C1 applications do not need safety, efficacy and/or quality data or a justification for not providing the data.

Application level 2 (C2)

Changes identified in the Changes Table as application level C2.

C2 applications:

- may require assessment of quality data
- do not need safety and/or efficacy data or a justification for not providing the data

Application level 3 (C3)

Changes identified in the Changes Table as application level C3.

C3 applications:

- include changes to the quality, safety and/or efficacy of a medicine
- include changes to the medicine name where the new name requires a higher level of assessment, such as where there is an identified risk associated with an umbrella branding segment
- require assessment of supporting safety and/or efficacy data or a justification for not providing the data

Application level 4 (C4)

Changes identified in the Changes Table as application level C4.

C4 applications:

- include changes to the safety and/or efficacy aspects of the medicine
- require assessment of safety and/or efficacy data (clinical and/or toxicological) to support the proposed changes or a justification for not providing the data

Identifying changes in the tables

Before you make a change to your complementary medicine, you will need to locate each planned change in the Changes tables so that you can:

- determine whether prior approval is required
- identify the change codes necessary to complete your application and determine the application level

Ensure that you identify all changes that you intend to make, including changes that are consequential to the primary change.

Check that you meet any conditions associated with the change, including those listed in the changes table under 'Assurance codes'.

Make sure you make the assurances corresponding to the assurance code when you submit your application in TGA Business Services.

If you cannot find your proposed change in the changes table or you cannot meet the conditions for the change, go to Changes not in the table.

Example

If you are planning to delete an indication and as a consequence you need to change the directions for use, identify both the change to the indications and the directions for use.

There are several alternative changes to indications and directions for use described in the changes table, which have different conditions. You need to check which conditions apply in order to identify the correct change.

Determining if approval is needed

To determine if your proposed change requires prior TGA approval, check the status codes associated with each change in the changes tables.

Changes requiring approval

You need TGA approval before changing the medicine if the status code for the proposed change is one of the following:

- SRR (safety related request). Application made under subsection 9D(2) of the *Therapeutic Goods Act 1989*
- SAR (self-assessable request). Application made under subsection 9D(1) or 9D(3) of the *Therapeutic Goods Act 1989*
- A (approvable changes). Application made under subsection 9D(3) or section 23 of the *Therapeutic Goods Act 1989*

It is important that you identify all applicable change codes as you will need these to complete your application and to determine the application level.

Each coded change that requires TGA approval corresponds to a particular application level based on risk. If a change requires TGA approval, you must wait to receive approval before making that change.

Making more than one change in one application

If you are making more than one change to your medicine, the application level is determined by the change that attracts the highest application level (CN RCM being the lowest level and C4 RCM the highest).

Example

You lodge an application where you change three aspects of the ARTG entry: two C1 level changes and a C3 level change. Submit the application as a C3 level application.

How to apply for approval to change a registered complementary medicine

To apply for approval to make the change, follow the online applications for registered complementary medicines guidance.

Changes not requiring approval

If the status code for a change is 'O', you can make the change without submitting an application for TGA approval.

You cannot select changes with status code 'O' when you complete an application in TGA Business Services because you do not need TGA approval.

Changes requiring a new ARTG entry

If the status code is NEW (new application required), you will need to apply for a new ARTG entry under section 23 of the *Therapeutic Goods Act 1989*.

Separate and distinct good

Some changes may result in a medicine being treated as a separate and distinct good from the medicine currently in the Australian Register of Therapeutic Goods (ARTG) under Section 16(1) of the *Therapeutic Goods Act 1989*.

The 'new' (separate and distinct) good must be entered separately in the ARTG. However, depending on the nature of the change, the provisions of the Therapeutic Goods (Groups) Order No. 1 of 2001 (the Groups Order) may allow the AUST R number to be retained for the new medicine.

Applications to which the Groups Order applies are made under Section 23 of the *Therapeutic Goods Act 1989* and require TGA approval before you can make the change(s). (Most are status code A.)

If a new complementary medicine is separate and distinct from the existing medicine and the provisions of the Groups Order do not apply, you will need to submit an application to register a new complementary medicine and obtain a new AUST R number.

Changes not in the tables

If the change you plan to make is not listed in the changes tables, contact Complementary medicines because absence of a code does not mean you can make the change to the ARTG record without notifying the TGA.

If we determine that the change you propose needs to be approved by us first and there is not an appropriate code in the changes tables, we will email you:

- endorsing the use of the 'other' change code
- advising you of the appropriate level for the application and the section of the *Therapeutic Goods Act 1989* that applies to the change

In your application, you need to:

- refer to this email in your application cover letter
- include our email in the dossier

Changes tables

These changes tables are for registered complementary medicines.

More information is available on:

1. Status codes
2. Assurance codes
3. Application level

'The Act' referred to in the tables is the *Therapeutic Goods Act 1989*.

Labelling (including package insert) and product detail changes

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
GPN	Proprietary name (if grouping applies) where either: • the product name does **not** include an umbrella branded name; or • if it does contain an umbrella branded name, then the umbrella segment is not categorised as requiring a higher level of assessment	A	1, 2	C2	23
GPU	Proprietary name (if grouping applies) where: • the product name includes an umbrella branded name **and** the umbrella segment is categorised as requiring a higher level of assessment and/or • the product name has been amended to include a new 'fast acting' claim e.g. 'Farracet Rapid Tablets' on the basis of Module 5 data	A	1, 2	C3	23
	Proprietary name (if grouping doesn't apply)	NEW			

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
GIN	New therapeutic indications (if grouping applies) where there is no requirement for supporting Module 4 and/or Module 5 data	A	1, 3	C2	23
GID	New therapeutic indications (if grouping applies) where supporting Module 4 and/or Module 5 data or a justification for not providing the supporting data is required	A	1, 3	C4	23
	New therapeutic indications (if grouping doesn't apply)	NEW			
LIW	Therapeutic indications or directions for use - change of wording without altering meaning	A	4, 5	C2	9D(3)
LIS	Therapeutic indications - removal of sub-set of indications from label	SRR	5	C1	9D(2)
LIR	Therapeutic indications - addition of registered indications to label	A	5	C2	9D(3)
GDS	Directions for use – involves a reduction in the class of person for whom the goods are suitable e.g. changing a statement from *"not recommended for children under 12 years"* to *"not recommended for children or adolescents under 18 years"*	SRR	5	C1	9D(2)
GDU	Directions for use - changes to the dosage instructions (if grouping applies), other than changes described in GDS or LIW, where there is no requirement for supporting Module 4 and/or Module 5 data	A	1, 3	C2	23
GDD	Directions for use - changes to the dosage instructions (if grouping applies), where supporting Module 4 and/or Module 5 data or a justification for not providing the supporting data is required	A	1, 3	C4	23

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
	Directions for use (if grouping doesn't apply)	NEW			
PSC	Recommended storage conditions - more restrictive	N	5	CN	9D(2C)
PST	Recommended storage conditions - less restrictive	A	5	C2	9D(3)
LSR	Addition of **more restrictive** safety-related statements including: • reduction in the class of person for whom the goods are suitable, e.g. changing a statement from "not recommended for children under 12 years" to "not recommended for children or adolescents under 18 years" • addition of a warning or precaution including a new RASML statement	SRR	5	C1	9D(2)
LSF	Changes on label (signal headings, warning statements) in compliance with new SUSMP (Poisons Standard) requirements, where the change in scheduling is to a lower SUSMP schedule, except where LSC applies	A	5, 8	C2	9D(3)
LSC	Changes on label (signal headings, warning statements) in compliance with new SUSMP (Poisons Standard) requirements, where the change in scheduling is to a lower SUSMP schedule where no such products have previously been approved as a complementary medicine	A	5, 8	C3	9D(3)
LSU	Changes on label (signal headings, warning statements) in compliance with new SUSMP (Poisons Standard) requirements, other than LSF or LSC	SRR / SAR	5, 8	C1	9D(2) / 9D(3)
LNT	Changes to bring a label into full compliance with the Therapeutic Goods Order No. 92 - other than changes to the proprietary name. If changing proprietary name (and where grouping applies), also use code GPN or GPU	A	5	C2	9D(3)

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
LLR	Addition of a required representation to a label (Part 2 of Schedule 2 to the *Therapeutic Goods Regulations 1990*)	SRR	5, 7	C1	9D(2)
LCF	Colour or type size change only (no change in label copy) other than where LFT applies	SAR	5	C1	9D(3)
LFT	Font or type size other than change to the type size on the main panel of the label. Does not include change in colour or label copy.	N	5	CN	9D(2C)
LGR	Introduction of new graphics/icons (other than as specified in change LSP & KSP)	A	5	C2	9D(3)
RGR	Removal of a graphic (other than as specified in change LAB for removal of sponsor logo or RGN)	SAR	5	C1	9D(3)
RGN	Removal of a graphic except where this relates to directions on how to use the product or the use of a measuring device or an applicator (see KMD and KMO)	N	5	CN	9D(2C)
LFO	Reformatting of pre-existing text (i.e.. moving or duplication of blocks of text and not rewording - see LIW, LDT, LDD) and/or movement of graphics (other than specified in LGM)	SAR	5	C1	9D(3)
LGM	Movement of graphics provided it remains on the same panel of the label and there is no change to the size, shape or colour of the graphic and does not involve the reformatting of pre-existing text.	N	5	CN	9D(2C)
LLN	Introduction of a 'new' or a 'value pack' flash – see LAB for removal of a 'new' or a 'value pack' flash	N	5	CN	9D(2C)

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
LSS	Introduction of text and / or graphics pertaining to sponsorship of a campaign or organisation, e.g. the Cancer Council's Pink Ribbon campaign or Surf Life Saving Australia	A	5	C1	9D(3)
LDT	Deletion or addition of text to the label (e.g. addition or removal of claims such as clinically proven, fast/rapid action; general claims regarding the product, its nature, mechanism of action, qualifying statements etc.)	A	5	C2	9D(3)
LDD	Deletion or addition of text to the label where supporting Module 4 and/or Module 5 data or a justification for not providing the supporting data is required. For example, including a *'fast absorption'* claim on the label on the basis of new clinical data	A	5	C3	9D(3)
KPI	Introduction of a package insert where there is no requirement for supporting Module 4 and/or Module 5 data. For example, including a CMI as a pack insert where the CMI is consistent with the product's approved product information	A	5, 29	C2	9D(3)
KRI	Removal of a package insert (other than CMI)	A	5, 30	C2	9D(3)
LSP	Changes to sponsor details including name and/or logo (inclusion of a logo or change to an existing logo) except where LAB applies	N	5	CN	9D(2C)
LAB	Minor label editorials that have no regulatory compliance impact (under the *Therapeutic Goods Act 1989*). The changes are limited to the following: • correction of misspelt words and/or deletion of a duplicated word – this does not involve rewording or the deletion of sentences or phrases • removal of a 'new', 'new formulation' or a 'value pack' flash • removal of details of sponsorship (in its entirety) of a campaign or organisation,	O	-	-	-

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
	e.g. the Cancer Council's Pink Ribbon campaign or Surf Life Saving Australia • deletion of sponsor logo provided the name and address of the sponsor or supplier of the goods are included on the label • inclusion, removal or changes to: – country of origin statement (e.g. 'Made in XX') including the statement "Made in Australia" or "Australian Made" or the Australian Made logo (gold kangaroo in a green triangle) in accordance with the requirements outlined by the *Australian Made Company* (refer www.australianmade.com.au) – sponsor address and/or contact details provided the information is consistent with the current approved product details and where the name and address of the sponsor or supplier of the goods are included on the label – supplier or manufacturer's name, address and/or contact details provided the name and address of the sponsor or supplier of the goods is included on the label – date of manufacture of a product – website, QR code and/or bar code: applies only where the information included on the website (including any direct links from that website) or incorporated into the QR code or bar code (if either links to a website then any direct links from that website) is consistent with the information approved by TGA for that product – ABN / ACN – product code number (or equivalent) or an overseas registration number – recycle logo and associated text				

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
	– tamper evident seal – wording / graphics. See also KSL and KSX – trade mark (™) or registration (®) symbols or similar, or trademark statements e.g. Company XXY is a registered trademark of Company XXZ • introduction, deletion or change of a graphic and/or text providing instruction on opening or closing a container • anti-theft device (including directly associated wording) that does not impact on or affect the readability of other label wording				
PSZ	Addition of a pack size for dosage forms other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) or as described in PSN	SAR	5, 6, 10	C1	9D(3)
PSN	Addition of a pack size for dosage forms other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) where the new pack size falls within the approved pack size range. See also PSZ.	N	5, 6, 10	CN	9D(2C)
PLS	Addition of pack size for liquids/semi-solids other than as described in PLN	SAR	5, 6, 10, 13	C1	9D(3)
PLN	Addition of pack size for liquids/semi solids where the new pack size falls within the approved pack size range. See also PLS.	N	5, 6, 10, 13	CN	9D(2C)
PMZ	Addition of pack size for metered dose aerosols	A	5,6	C2	9D(3)
PSD	Pack size - deletion	N	5	CN	9D(2C)
	Dosage form (as defined in TGA approved terminology for medicines)	NEW			

Change codes	Labelling (including package insert) and product detail changes	Status codes	Assurance codes	Application level	Applicable section of the Act
PVI	Visual identification (note that novelty shapes, e.g. animal-shaped tablets, are not acceptable)	SAR	5, 13, 19, 27	C1	9D(3)
PSL	Shelf life – increase	A	5	C2	9D(3)
PSR	Shelf life - decrease	N	5	CN	9D(2C)
PMI	Sterility status	A	5	C2	9D(3)

Sponsor changes

For the transfer of a good in the ARTG from one sponsor to another, contact TGA Business Services help desk or see Notification of a change of sponsorship.

For changes to sponsor details on the labelling see changes LAB and LSP; for changes to sponsor details in the Product Information (PI) see changes DAB and DAC.

Formulation changes - active ingredients

Change codes	Formulation changes - active ingredients	Status codes	Assurance codes	Application level	Applicable section of the Act
	Addition of active ingredient	NEW			
	Deletion of active ingredient	NEW			
	Amount of an active ingredient - See also Overages and batch to batch variation section of the ARGCM	NEW			

Change codes	Formulation changes - active ingredients	Status codes	Assurance codes	Application level	Applicable section of the Act
	Changes to herbal extracts outside the permitted variations as described within the Guidance on equivalence of herbal extracts in complementary medicines	NEW			
AOV	Overage - decrease or removal	N	5	CN	9D(2C)
AOA	Overage - increase	A	5	C2	9D(3)
GPA	Replacement of a proprietary ingredient which contains an active substance with another proprietary ingredient where the only difference between the two proprietary ingredients (other than name) is to the amount of an excipient(s) ingredient (if grouping applies)	A	1, 5	C2	23
	Replacement of a proprietary ingredient which contains an active ingredient with another proprietary ingredient, other than as above in change GPA	NEW			

Formulation changes - excipient ingredients

Change codes	Formulation changes - excipient ingredients	Status codes	Assurance codes	Application level	Applicable section of the Act
ERT	Removal of a fragrance, flavour, printing ink and/or colouring agent(s) if the total agent(s) are present at not more than 2% w/w or w/v (if grouping applies) Note: this change may result in consequential changes to labelling (including the PI/CMI) and/or specifications (e.g. deletion from the label of declared ingredients or change to visual identification) which should also be addressed in accordance with the changes table.	SAR	1, 5, 13	C1	23

Change codes	Formulation changes - excipient ingredients	Status codes	Assurance codes	Application level	Applicable section of the Act
GPI	Removal and/or addition of a fragrance, flavour, printing ink and/or colouring agent(s) (if grouping applies), other than change ERT	A	1, 5, 13	C2	23
	Removal or addition of a fragrance, flavour, printing ink or colouring agent (if grouping doesn't apply)	NEW			
GPR	The replacement of one proprietary excipient ingredient with a different proprietary ingredient where the only difference between the two proprietary ingredients (other than name) is a change to the amount of an inactive component of the proprietary ingredient and/or manufacturing process (if grouping applies) other than ERT or GPI	A	1, 5, 13	C2	23
	The replacement of one proprietary ingredient with a different proprietary ingredient other than in changes GPI or GPR	NEW			
	Addition or deletion of an excipient other than those above in change GPI	NEW			
GEX	Amount of excipient (if grouping applies) provided the content of the excipient is not higher than previously approved for the dosage form - See Overages and batch to batch variation in Part D of the ARGCM	A	1, 5, 13	C2	23
GED	Increase in the amount of an excipient (if grouping applies) where the content of the excipient is higher than previously approved for the dosage form - See Overages and batch to batch variation in Part D of the ARGCM	A	1, 5, 13	C3	23
	Amount of excipient (if grouping doesn't apply) – See Overages and batch to batch variation in Part D of the ARGCM	NEW			
EST	Type of starch (no change to quantity)	N	5, 12	CN	9D(2C)

Quality control changes - finished medicine specifications

Change codes	Quality control changes - finished medicine specifications	Status codes	Assurance codes	Application level	Applicable section of the Act
QFX	Specification limits or requirements - more restrictive	O			
QFE	Specification limits or requirements - less restrictive (except where QFA applies); where any supporting data provided consist only of Module 3 (and not Module 4) data	A	5, 27	C2	9D(3)
QFF	Specification limits or requirements – less restrictive; where supporting Module 4 (nonclinical) data or a justification for not providing the supporting data is required. For example, a sponsor wishes to widen the limits for a related substance from the level normally applied of NMT 1% to NMT 3.5% and justifies the widening of the specification on the basis of a dossier which includes preclinical studies and published toxicology papers	A	5, 27	C3	9D(3)
QFT	Addition of an extra test	O			
QFU	Deletion of an existing test where any supporting data provided consists only of Module 3 data	A	5, 27	C2	9D(3)
QFD	Deletion of an existing test where supporting Module 4 data or a justification for not providing the supporting data is required. For example, a sponsor wishes to delete a particular test for a product that would normally be required but provides supporting data in the form of preclinical studies which support the sponsor's case for removal of the test from the specifications	A	5, 27	C3	9D(3)
QFI	Frequency of testing – increase	O			
QFR	Frequency of testing - reduction	A	5, 27	C2	9D(3)

Change codes	Quality control changes - finished medicine specifications	Status codes	Assurance codes	Application level	Applicable section of the Act
QFA	Changes to the finished product specifications (test, test methods and limits/requirements) to comply with a standard as defined in the *Therapeutic Goods Act 1989* (e.g. the BP or a Therapeutic Goods Order), other than as specified in change MST. No non-pharmacopoeial test or requirements are concurrently deleted from the specification	O			
QFB	Analytical method (does not include changes to tests and limits and requirements) - which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity), other than as specified in change MST	O			
QFC	Analytical method - other than as specified in change QFA, QFB or MST	A	5	C2	9D(3)
QFP	Change from one default standard (as defined in the *Therapeutic Goods Act 1989*) to another (e.g. BP to USP) or from a 'company' or 'in-house' specification to a pharmacopoeial specification. This includes deletion of the existing pharmacopoeial tests and limits. This does not involve deletion of, or a change to, any current additional non-pharmacopoeial specifications, e.g. residual solvents in the finished product or friability.	N	5, 27	CN	9D(2C)

Quality control changes - starting material specifications

Change codes	Quality control changes—starting material specifications	Status codes	Assurance codes	Application level	Applicable section of the Act
QSX	Specification limits or requirements - more restrictive	O			
QSE	Specification limits or requirements - less restrictive (except where QSA applies); where any supporting data provided consist only of Module 3 (and not Module 4) data	A	5, 27	C2	9D(3)
QSF	Specification limits or requirements – less restrictive; where supporting Module 4 data or a justification for not providing the supporting data is required. For example, a sponsor wishes to widen the limits for a related substance from the level normally applied of NMT 1% to NMT 3.5% and justifies the widening of the specification on the basis of a dossier which includes preclinical studies and published toxicology papers	A	5, 27	C3	9D(3)
QST	Addition of an extra test	O			
QSU	Deletion of an existing test where any supporting data provided consist only of Module 3 data	A	5, 27	C2	9D(3)
QSD	Deletion of an existing test where supporting Module 4 data or a justification for not providing the supporting data is required. For example, a sponsor wishes to delete a particular test for a substance that would normally be required but provides supporting data in the form of preclinical studies which support the sponsor's case for removal of the test from the specifications	A	5, 27	C3	9D(3)

Change codes	Quality control changes—starting material specifications	Status codes	Assurance codes	Application level	Applicable section of the Act
QSA	Changes to the starting material specifications (test, test methods and limits/requirements) to comply with a standard as defined in the *Therapeutic Goods Act 1989* (e.g. the BP or a Therapeutic Goods Order). No non-pharmacopoeial test or requirements are concurrently deleted from the specification, e.g. a specification for particle size distribution	O			
QSB	Analytical method (does not include changes to test limits and requirements) - which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)	O			
QSC	Analytical method - other than as specified in change QSA or QSB	A	5	C2	9D(3)
QSM	Manufacturer of starting material (specifications unchanged)	O			
QSS	Supplier of starting material	O			
QSP	Change from one 'default standard' (as defined in the *Therapeutic Goods Act 1989*) o another (e.g. BP to USP) or from a 'company' or 'in-house' specification to a pharmacopoeial specification. This includes deletion of the existing pharmacopoeial tests and limits. This does not include deletion of, or a change to, any current additional non-pharmacopoeial specifications, e.g. particle size distribution.	N	5	CN	9D(2C)

Packaging changes

Change codes	Packaging changes	Status codes	Assurance codes	Application level	Applicable section of the Act
	Container type (as defined in TGA approved terminology for medicines)	NEW			
KBT	Container material - if the container is a bottle, the goods are a solid dosage form (e.g. tablet) and the change in material is of a type described below: • Polystyrene to PVC, polyethylene, polypropylene or glass • PVC to polyethylene, polypropylene or glass • Polyethylene to glass or polypropylene of density ≥ 0.89 • From one density of polyethylene to a higher density • Any change between glass, polyethylene of density ≥ 0.95, and polypropylene of density ≥ 0.89	N	5, 13, 16 & 25	CN	9D(2C)
KGL	Container material - clear to coloured glass	O			
KBL	Container material - if the container is a blister pack, the goods are a solid dosage form (e.g. tablet) and the change in material is of a type described below: • PVC to PVC/PVDC or to PVC/PCTFE • PVC/PVDC to PVC/PCTFE or the change to the plastic component is to a material with demonstrated lower or equivalent water permeability than the existing material (see for example USP monograph '*<671> Containers Permeation*')	N	5, 13 & 25	CN	9D(2C)
KCI	Container – increase in container wall thickness	O			
KCD	Container – decrease in container wall thickness, except where KBT, KBL	A	5	C2	9D(3)
KOT	Container material – other than in changes KBT, KGL, KBL, KCI, KCD	A	5	C2	9D(3)

Change codes	Packaging changes	Status codes	Assurance codes	Application level	Applicable section of the Act
KCL	Closure – other than changes in KCM or MDA	N	5, 13	CN	9D(2C)
KCM	Closure, where the closure also serves as a metering component (other than MDA)	A	5	C2	9D(3)
MDA	Changes in pump or pump components of meter-dose aerosol (e.g. valve material)	A	5	C2	9D(3)
KSL	Tamper evident seal - addition (including label notice to alert consumers to presence of seal). See also LAB	O			
KSX	Tamper evident seal - removal (including removal of label notice re seal). See also LAB	O			
KWA	Inert wadding material - addition, substitution or removal where stability is not affected by the action	O			
KDA	Desiccant - inclusion in container	A	5	C2	9D(3)
KDX	Desiccant - removal from container	A	5	C2	9D(3)
KPP	Specifications of primary pack except where the primary pack is also the container Does not include any other changes to the labelling such as text, graphics, colour, font, etc. Note: primary pack is defined in subsection 3(1) of the Act as *'primary pack, in relation to therapeutic goods, means the complete pack in which the goods, or the goods and their container, are to be supplied to consumers'*	O			

Change codes	Packaging changes	Status codes	Assurance codes	Application level	Applicable section of the Act
KSP	Introduction of a measuring device (e.g. spoon, cylinder) or applicator (e.g. finger cot). This change can include graphical representation (and associated wording where required) of the device on the label. A copy of current & proposed label must be supplied if the label is changed	SAR	5, 24	C1	9D(3)
KMO	Removal of a measuring device where other means of accurately measuring the dose are readily available. This change can include the deletion of graphical representation of the device (including associated wording) on the label Does not include changes to the directions for use or any other changes to labelling such as reformatting. A copy of current & proposed label must be supplied if the label is changed.	N	5	CN	9D(2C)
KMD	Changes to existing measuring device (e.g. spoon, cylinder) or applicator supplied with the goods or removal of an applicator, where other means of accurately administering the dose are readily available. This change can include changes to the graphical representation (and associated wording where required) of the device on the label. It can also include the addition or deletion of graphical representation (including associated wording) of the device on the label. A copy of current & proposed label must be supplied if the label is changed	SAR	5, 24	C1	9D(3)
KPA	Introduction of a primary pack (no new text or graphics) Note: primary pack is defined in subsection 3(1) of the Act as *'primary pack, in relation to therapeutic goods, means the complete pack in which the goods, or the goods and their container, are to be supplied to consumers'*	SAR	5, 14	C1	9D(3)
KPX	Removal of a primary pack	SAR	5, 17	C1	9D(3)
KRP	Introduction of a refill pack	A	5	C2	9D(3)
KRR	Removal of refill pack	N	5	CN	9D(2C)

Manufacturing changes - finished product

Change codes	Manufacturing changes - finished product	Status codes	Assurance codes	Application level	Applicable section of the Act
MMA	Addition of a manufacturer (includes site of manufacture), other than for sterile products where MSS or MST applies	N	5, 9	CN	9D(2C)
MMD	Deletion of a manufacturer (includes site of manufacture)	N	5	CN	9D(2C)
AMS	Addition of steps of manufacture, other than for sterile products where MSS or MST applies	N	5, 9	CN	9D(2C)
MSD	Deletion of steps of manufacture	N	5	CN	9D(2C)
MPT	Manufacturing process: tightening of in-process limits and/or introduction of an additional in-process control	O			
MPR	Manufacturing process other than for 'higher risk' complementary medicines (see MPH or MPD) or for sterile products (see MSS or MST). See also MPT	SAR	5, 13	C1	9D(3)
MPH	Manufacturing process for the following 'higher risk' complementary medicines: • microdose products (solid oral dosage forms where the active ingredient is present in an amount of less than 2mg or 2% w/w of the dosage form) • products with a sustained release characteristic (not including enteric coated products) • metered dose inhalers • where the changes to the product have been demonstrated to be equivalent to or superior to the approved manufacturing process	SAR	5, 13	C1	9D(3)

Change codes	Manufacturing changes - finished product	Status codes	Assurance codes	Application level	Applicable section of the Act
MPD	Manufacturing process for the following 'higher risk' complementary medicines: • microdose products (solid oral dosage forms where the active ingredient is present in an amount of less than 2mg or 2% w/w of the dosage form) • products with a sustained release characteristic (not including enteric coated products) • metered dose inhalers • except where MPH applies	A	5, 13	C2	9D(3)
MUP	GMP clearance number update only; no other change to the product	SAR (fee exempt)	5	C1	9D(3)
MSS	For a sterile product (other than where MST applies): • Addition of a manufacturer (includes site of manufacture) involving **only** one or more of the following steps: release for supply, secondary packaging or testing [chemical and physical or microbial] • Addition of steps of manufacture involving **only** one or more of the following steps: release for supply, secondary packaging or testing [chemical and physical or microbial]	N	5, 9	CN	9D(2C)
MST	For a sterile product: • Addition of a manufacturer (includes site of manufacture) other than where MSS applies • Addition of steps of manufacture other than where MSS applies • Change in the manufacturing process	A	5	C2	9D(3)

Consumer Medicine Information (CMI)

Change codes	Consumer Medicine Information (CMI)	Status codes	Assurance codes	Application level	Applicable section of the Act
CPI	Introduction of a CMI for a 'Pharmacist Only Medicine' (Schedule 3) product registered after 4 July 1995 where the CMI complies with Schedule 13 to the *Therapeutic Goods Regulations 1990* and is not to be included as a package insert. Note: Change KPI applies where the CMI is to be included as a package insert.	O			
CPO	Changes to an existing CMI, where the changes are consistent with all previously approved product details and the CMI is not to be included as a package insert. Note: Refer to Labelling (including package insert) and medicine detail changes on changes to a CMI where the CMI is to be included as a package insert (package inserts are treated as part of the label).	O			

Product Information (PI)

Change codes	Product Information (PI)	Status codes	Assurance codes	Application level	Applicable section of the Act
DPI	Introduction of Product Information (PI) for an existing product where there is no requirement for supporting Module 4 and/or Module 5 data. For example, where the PI is essentially the same as the PI of the originator medicine	A	5	C2	9D(3)
DPD	Introduction of Product Information (PI) for an existing product where supporting Module 4 and/or Module 5 data or a justification for not providing the supporting data is required. For example, where the PI includes information on clinical trials and Module 5 data are provided to substantiate the information included in the PI	A	5	C3	9D(3)
DAB	Minor editorial changes that have no regulatory compliance impact (under the *Therapeutic Goods Act 1989*). The changes are limited to the following: • correction of misspelt words and/or deletion of a duplicated word - this does not involve rewording or the deletion of sentences or phrases • deletion of sponsor logo provided the name and address of the sponsor is included in the PI • inclusion, removal or changes to: – country of origin statement (e.g. 'Made in XX') – sponsor address and/or contact details provided the information is consistent with the current approved product details and where the name and address of the sponsor of the goods is included in the PI – supplier/manufacturer name, address and/or contact details – ABN / ACN – product code number (or equivalent) or an overseas registration number – trade mark (™) or registration (®)symbols or similar or trademark statements e.g. Company XXY is a registered trademark of Company XXZ	O			

Change codes	Product Information (PI)	Status codes	Assurance codes	Application level	Applicable section of the Act
DAC	Updating the PI to reflect the currently approved product details or changes consequential to other changes made in the same application. Changes are limited to the following: • storage conditions • sponsor details including sponsor name and/or logo (inclusion of a logo or change of an existing logo) except where DAB applies • container or pack size details • visual identification • dosage form • route of administration • formulation details • poisons schedule • proprietary name • indications (where the wording is identical to that included on the ARTG or that proposed for the ARTG as part of the same application) Does not include changes to the directions for use	SAR	5	C1	9D(3)
DRS	Addition of **more restrictive** safety-related statements including: • reduction in the class of person for whom the goods are suitable, e.g. changing a statement from "not recommended for children under 12 years" to "not recommended for children or adolescents under 18 years" • addition of a warning or precaution including a new RASML statement or new statement required in permitted ingredient determination. (See also LSR for consequential changes to labelling)	SRR	5	C1	9D(2)
DOT	Changes (including addition or deletion of text or the rewording or reformatting of existing text) where there is no requirement for supporting Module 4 and/or Module 5 data, other than as specified in change DAB, DAC or DRS	A	5	C2	9D(3)

Change codes	Product Information (PI)	Status codes	Assurance codes	Application level	Applicable section of the Act
DOD	Changes other than the addition of more restrictive safety-related statements where supporting Module 4 and/or Module 5 data or a justification for not providing the supporting data is required. For example, updating the section on Clinical Trials where the changes made are supported by Module 5 data	A	5	C3	9D(3)
DRP	Removal of a PI where the PI is not required under section 25AA of the Act	A	5	C2	9D(3)

Other

Change codes	Other	Status codes	Assurance codes	Application level	Applicable section of the Act
CTA	Correction of ARTG record in accordance with section 9D(1) of the *Therapeutic Goods Act 1989*. Evidence to support the change is included with the application	SAR	5, 21	C1	9D(1)
CAO	Correction of ARTG record in accordance with section 9D(1) of the *Therapeutic Goods Act 1989*. An application using this change code must include written advice from the TGA advising the use of this change code for the requested change to the product	SAR (fee exempt)	5, 21, 31	C1	9D(1)
OT1	'Other' changes – application level C1. An 'other' code is used only when no other code applies. An application using OT1 must include written advice from the TGA advising the use of this change code for the requested change to the product	ASK	31	C1	Specified in advice from TGA
OT2	'Other' changes – application level C2. An 'other' code is used only when no other code applies. An application using OT2 must include written advice from the TGA advising the use of this change code for the requested change to the product	ASK	31	C2	Specified in advice from TGA
OT3	'Other' changes – application level C3. An 'other' code is used only when no other code applies. An application using OT3 must include written advice from the TGA advising the use of this change code for the requested change to the product	ASK	31	C3	Specified in advice from TGA
OT4	'Other' changes – application level C4. An 'other' code is used only when no other code applies. An application using OT4 must include written advice from the TGA advising the use of this change code for the requested change to the product	ASK	31	C4	Specified in advice from TGA
OTX	'Other changes – application level CN. This code is to be used to request CN level changes to multiple ARTG entries. This code must be used in addition to other change types that result in a CN level application. The details of the additional products, including relevant ARTG IDs must be provided. Additional processing time will be required.	N	As required for the	CN	9D(2C)

Status codes

The type of application you need to make.

Code	Prior TGA approval required?	Description
A	Yes	A change made under section 9D or section 23 of the Act
SRR	Yes	Safety Related Request: a change made under section 9D(2) of the Act
SAR	Yes	Self-Assessable Request: a change made under section 9D(1) or section 9D(3) of the Act
N	Yes	Notifications: a change made under section 9D(2C) of the Act. TGA approval is made automatically upon lodgement and payment of the application.
NEW	Yes	New application for registration required
O	No	The TGA does not need to be informed of changes subject to status code 'O' – no application is submitted. Note 1:Change codes for 'O' status changes are not included in the application portal. Note 2: Changes with status 'O' have been included in the changes table for clarity and completeness and do not imply that this information is required for evaluation of an equivalent new product.
ASK	Yes	This applies only where one of the 'other' change codes (OT1, OT2, OT3 or OT4) is used. Refer to the Changes not in the changes table

Assurance codes

Code	Description
1.	The 'new' goods are intended to replace the existing goods in use
2.	The only difference between the 'new' goods and the existing goods is the name
3.	The only differences between the 'new' goods and the existing goods are related to the indications for use and/or the directions for use
4.	No additional indications have been introduced or directions for use altered (other than change to wording)
5.	No aspects of the labelling, PI, CMI, pharmaceutical data or other product details (including manufacturing process), have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the changes table
6.	The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume
7.	The only changes made are those which bring the label into compliance with requirements of the Labelling Order, or Schedule 2 to the *Therapeutic Goods Regulations 1990*
8.	The change is in compliance with a requirement introduced in the most recent version or amendment of the SUSMP (Poisons Standard).
9.	The nominated manufacturer is licensed to manufacture goods of this type
10.	The container type (as defined in TGA approved terminology for medicines) is unchanged and container material is unchanged
11.	A stability testing protocol has been approved for this product and a copy of the approval letter is attached
12.	All of the following apply: • Neither the existing nor the new material is a modified starch. • The changeover has been validated. • At least 6 month's stability data have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 month's data at a temperature at least 10°C higher than the maximum recommended storage temperature. • Stability testing will continue for the full term of the product's shelf life and any batches not meeting specifications will be withdrawn from the market immediately and the TGA notified immediately.

Code	Description
13.	All of the following apply: • The changeover has been validated* and the Sponsor is satisfied that the change will not adversely affect the stability of the product. • Stability testing will continue for the full term of the product's shelf life and the TGA advised immediately of any batches not meeting specifications. *Note: Validation data will be provided during a GMP inspection or upon request by the TGA within 3 months following the request
14.	No new text or graphics have been introduced
15.	Intentionally blank
16.	The new container/closure system has demonstrated equal or better moisture protection in the USP test for Containers – Permeation (water vapour transmission) to that of the existing container/closure system
17.	The information on the container label is not less than the information on the primary pack
18.	Intentionally blank
19.	Manufacturing method and specifications, other than visual identification, have not been changed
20.	Two production batches have been tested according to the approved stability protocol and all results fall within the acceptance criteria, as specified in the approved stability protocol
21.	The changes are in accordance with s.9D(1) of the Act
22.	Intentionally blank
23.	Intentionally blank
24.	Where a measuring device is being introduced or changed, it includes calibrations exclusively in metric units and will allow all the doses shown on the label to be measured accurately
25.	The container type (as defined in TGA approved terminology for medicines) is unchanged
26.	Intentionally blank
27.	A copy of the current specification plus a copy of the new specification, with the changes highlighted, have been supplied

Code	Description
28.	Intentionally blank
29.	A copy of the current label of the goods together with a draft copy of the new package insert have been supplied
30.	A copy of the current label and package insert of the goods have been supplied
31.	A copy of the written advice from TGA advising the use of this change code for the requested change to the product has been supplied

Version history

Version	Description of change	Author	Effective date
V5.0	ARGCM V5 is a revision and restructure of ARGCM V4.2. Changes to the original document include formatting, corrections and clarification of information. While the revised document does not introduce any new procedures or procedural changes, the ARGCM V4.2 contained outdated information which has been amended to reflect current regulatory practice.	TGA	November 2013
V5.1	Correction of hyperlinks throughout document. Update references to Evidence guidelines for listed medicines Update information on Approved terminology for medicines. Update information on Complementary medicine interface issues. Include link to Food Medicine Interface Tool on the TGA website. Instructions for searching the ingredient database via the TGA eBusiness Services website. Clarification of information on indications for listed medicines. Insertion of reference to ARGCM Part D Table 6 in relation to changes in excipient ingredients for listed medicines. Under 'Manufacturing changes', minor modification to MUS code (GMP clearance number update). Deletion of MST code (Change to manufacturing site and/or process of sterile product).	TGA	August 2014
V5.2	Updated commercially confidential information Updated organisational names Updated hyperlinks and minor formatting changes Update information on National Code of Conduct for unregistered healthcare practitioners Update information on compositional guidelines to consolidate information available on website	TGA	May 2015
V5.3	Information on compositional guidelines updated to reflect changes in process	TGA	July 2015

Version	Description of change	Author	Effective date
V6.0	Update information referring to ingredients permitted in listed medicines to reflect changes in legislation (26 BB legislative instrument). Update references to TGO 69 to include information on new labelling order (TGO 92). Update information on Approved terminology for medicines. Update information on National Code of Conduct for unregistered healthcare practitioners. Update information on homoeopathic medicines. Review information on consent to supply goods that are not compliant with prescribed standards. Update guidance on changes to registered medicines, including updated ode tables. Updated hyperlinks and minor formatting changes.	TGA	October 2016
V7.0	Updated Part D to include notification changes Additional guidance material redistributed into other parts of the ARGCM Updated hyperlinks	TGA	October 2017
V7.1	Update to change codes to include further notifications, commencing 4 December 2017.	TGA	December 2017
V7.2	Minor update to Proprietary ingredients in complementary medicines.	TGA	February 2018

Version	Description of change	Author	Effective date
V8	Amended to incorporate legislative changes for substance evaluations. Title changed from 'New complementary medicine substance evaluation' to 'Evaluation of a substance for use in listed complementary medicines'. 'New complementary medicine substance' changed to 'substance for use in listed complementary medicines' throughout document. References to the form 'Application for evaluation of a new complementary medicine substance' changed to 'Application for evaluation of a substance for use in listed complementary medicines'. Information in overview amended to clarify that applications for substances are made under 26BE the Act. The following **new** sections have been included: • Application categories for evaluation of substances • Timeframes and fees • Exclusive use of new approved ingredients Information on safety data page count removed from the section entitled 'Phase 2: Lodgement of application' Section on 'Clarification of information' changed to 'Requests for information' and information reviewed to provide clarity on timeframes. Information on sponsor's ability to appeal decisions included under 'Phase 5: Delegate determination'. Minor updates to Chart C1 e.g. include information on market exclusivity. Table numbering amended to be consecutive C1 to C5 Table C2 (renamed C4) moved up higher in document.	TGA	April 2018

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