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Department of Health
Therapeutic Goods Administration

Australian regulatory guidelines for complementary medicines

ARGCM

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TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

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

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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 While the revised document does not introduce any new procedures or procedural changes, the ARGCM V4.2 contained outdated information which has been amended to reflect current regulatory practice.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

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Abbreviations

Refer to the TGA acronyms & glossary for terms, definitions & 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 (for a list of consultants, refer to the [Complementary Medicines Australia](#), the [Australian Self Medication Industry](#) and the [Association of Therapeutic Goods Consultants](#)).

The ARGCM May 2015 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.

Information is provided on:

- what complementary medicines are
- legislation applicable to complementary medicines
- the different types of complementary medicines and ingredients
- approved terminology
- exempt medicines
- practitioner medicines and exemptions
- medicine presentation
- changes to information in the Australian Register of Therapeutic Goods (ARTG) for complementary medicines
- post market regulatory activity
- complementary medicine interface issues
- appeal mechanisms for decisions made under the *Therapeutic Goods Act 1989*.

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.

Information is provided on:

- ingredients and indications permitted for use in listed medicines
- legislative requirements for listed medicines
- quality of listed medicines
- guidance on how to list a medicine on the ARTG.

Part C: Evaluation of new complementary medicine substances 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.

Information is provided on:

- the substances that are eligible for evaluation as a new complementary medicine substance
- the application phases
- the information required to be submitted in an application for evaluation for a new complementary medicine substance.

Part D: Registered complementary medicines

Part D provides guidance on the evaluation process for registered complementary medicines. This guidance is for sponsors, manufacturers and applicants of/for proposed new registered complementary medicines.

Information is provided on:

- what complementary medicines can be registered on the ARTG
- the application phases
- the information to be submitted in an application for registration of a new complementary medicine.

ARGCM additional guidance

The following additional guidance is provided for sponsors, manufacturers and applicants on technical details and requirements relevant to the procedural information:

1. Compositional guidelines for complementary medicine substances
2. Finished product specifications, certificates of analysis
3. Guidance on use of the term 'quantified by input' for listed complementary medicines
4. Literature search and evaluation
5. Changes tables for 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:

- [Required Advisory Statements for Medicine Labels](#) (RASML).
- [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, in writing, 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, for example; the BP, Ph Eur, USP or TGOs. Such requests incur an [application fee](#).

Sponsors must explain why the standard(s) cannot be met and provide justification that the quality and safety of the medicine will not be compromised. Justification and details of proposed alternative(s) must also be provided.

Requests are considered on a case by case basis. A Delegate of the Secretary will review the request and you will be advised in writing of the decision. Any consent that is provided by the Delegate may have conditions attached to that decision and approvals may be time limited (imposed under sections 15 and 15A of the Act).

Under section 14 of the Act, the Secretary must, as soon as practicable after making a decision to give consent, publish particulars of the decision to be published in the [Government Notices Gazette](#). These particulars will usually include the following information:

- sponsor name
- name of therapeutic goods or class of therapeutic goods
- ARTG number
- the applicable standard and clause to which the consent to supply applies
- the conditions applicable to the consent to supply
- the time period for which consent is given.

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.



At the Standing Council on Health (SCoH) meeting of 14 June 2013, Ministers agreed in principle that a national Code of Conduct for unregistered health practitioners should be made by regulation in each Australian state and territory with statutory enforcement powers. To give effect to these decisions, on 27 January 2015, Ministers have asked the Australian Health Ministers Advisory Council (AHMAC) to undertake a public consultation on the terms of the first national Code of Conduct and proposed policy parameters—refer to the [Council of Australian Governments \(COAG\) Health Council](#).

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. This product is referred to as a 'dispensing pack' in Therapeutic Goods Order No. 69—General requirements for labels for medicines ([TGO 69](#)):

'in relation to complementary healthcare, [dispensing pack] means a pack which is to be supplied solely to complementary healthcare practitioners for supply to a person after affixing an instruction label following a consultation with that person.'

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)]. 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.

However, regardless of whether the label includes the statement, 'for practitioner dispensing only', 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 TGO 69 and the [Therapeutic Goods Advertising Code](#) (unless the appropriate exemption or approval to do otherwise has been granted).

Exemptions for advertising directed to health professionals

Section 42AA of the Act provides for sponsors to advertise directly and exclusively to health professionals¹ 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 [CHC Codes of Practices](#) on the [Complementary](#)

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

[Medicines Australia](#) website and the [Australian Self Medication Industry \(ASMI\) Code of Practice](#).

Approved terminology for complementary medicines

A searchable database of all Australian approved names (chemical, biological and herbal) is accessible via the [TGA Business Services](#) website. The list of other approved terminology for medicines (routes of administration, dosage forms etc.) are located in the Code Tables on the TGA Business Services website. Instructions on searching the database are provided in ARGCM Part B: [TGA Business Services ingredient database](#).



The publication [TGA Approved Terminology for Medicines](#) provides Australian approved terminology. In May 2013, we [sought comments](#) on an update to this document in consideration of the international harmonisation of ingredient names. A new version of this document, with guidance on approved terminology policies, will be published once finalised.

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'.

- **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. An 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, an HCN will not be assigned for ubiquitous non-phytochemical components of herbal species, for example: compounds that commonly occur in plant materials. An 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.

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. That is, assignment of a name does not mean 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. For listed medicines, ingredients of herbal origin must meet the definition of a herbal substance included in the Regulations—refer to [‘Ingredients permitted for use in listed medicines’](#).

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 4 and 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:

4. mother tinctures
 - 4A. homoeopathic preparations that:
 - (a) consist of, or contain a dilution of, mother tincture that:
 - i) is a 1,000 fold dilution, or a lesser dilution, of that mother tincture; and
 - ii) is not required to be sterile; and
 - iii) is not included in a Schedule to the Poisons Standard or Appendix C of the Poisons Standard otherwise than because of a component that is more than a 1,000 fold dilution of a mother tincture; and
 - (b) do not consist of, or contain as a component, a preparation of a herb specified in Part 4 of this Schedule as a 1,000 fold dilution, or a lesser dilution, of a mother tincture.
5. homoeopathic preparations (where each dilution is more dilute than a one thousand fold dilution of a mother tincture), each of which:
 - (a) is not required to be sterile; and
 - (b) according to the indications proposed by the sponsor of the preparation, is 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

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](#); or
- Part 4 of Schedule 4 to the Regulations

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.

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 for medicinal products as current and in force (currently TGO 69), and any other applicable [official standards](#).

[TGO 69](#) Part 3 includes some special requirements for homoeopathic preparations:

3(15) Homoeopathic preparations

Where all the active ingredients in the goods are homoeopathic preparations then:

- (a) the label on the container and the label on the outside of the primary pack if any, must include, in addition to the relevant requirements in subclauses 3(2) and 3(3), a statement indicating that the active ingredients in the goods are homoeopathic preparations, such as, 'homoeopathic product' or 'homoeopathic preparation'; and
- (b) where the indications for use are of a kind permitted to be advertised only to persons described in subregulations 4(1) and 4(2) of the Regulations, the label on the container and the label on the outside of the primary pack if any, must include a statement that the therapeutic indications have not been approved, such as 'Homoeopathic product without approved therapeutic indications'.

3(16) Formulations containing both homoeopathic and non-homoeopathic ingredients

Where goods contain active ingredients that are homoeopathic preparations and other active ingredients that are not homoeopathic preparations -

- (a) the label on the container and the label on the outside of the primary pack, if any, must include, in addition to the relevant requirements in subclauses 3(2) and 3(3), a statement that the goods include ingredients that are homoeopathic preparations, such as 'Contains homoeopathic ingredients'; and
- (b) where the indications for use are of a kind permitted to be advertised only to persons described in subregulations 4(1) and 4(2) of the Regulations, the label on the container and the label on the outside of the primary pack, if any, must include a statement that the therapeutic indications of the homoeopathic ingredients have not been approved, such as, 'Contains homoeopathic ingredients without approved therapeutic indications'.

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 TGO 69, the label on the container and on the primary pack must include a statement to indicate that the medicine contains homoeopathic ingredients with indications that have not been 'approved' by the TGA.

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](#); [TGO No. 69—General requirements for labels for medicines](#); 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: [TGO 69](#), [TGO 78](#) and [Required Advisory Statements for Medicine Labels](#) (RASML).

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. In general, indications in relation to spiritual or emotional states (apart from those that state or imply depression or other mental illness) are not considered 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@TGA.gov.au for such enquiries.

Proprietary ingredients in complementary medicines

The term 'proprietary ingredient' means a formulation about which some information is not in the public domain. Proprietary ingredients are included on the ARTG 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](#). Sponsors may select proprietary ingredients included on the ARTG for use in their 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.

In general, active pre-mix proprietary ingredients can contain only one active ingredient (with the exception of vitamin and mineral pre-mixes) to be included in listed medicines via the electronic application and submission portal. Note this restriction is not applicable to registered medicines.

For any proprietary ingredient to be eligible for inclusion in a listed complementary medicine, all ingredients (except flavours and fragrances—see below) included in the proprietary ingredient's formulation must be permitted for use in listed medicines. The colourings contained in proprietary ingredients used in oral 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 (and the proprietary ingredient is not a flavour or fragrance) 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.

Proprietary ingredient commercially confidential information

Certain information supplied in relation to the inclusion of proprietary ingredients on the ARTG is treated as commercially confidential information. Refer to the [Guide to the completion of a notification of a new proprietary ingredient form](#) for the information required to be submitted in the notification form and the information considered to be commercially confidential.

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 TGO 69, including the declaration of excipient ingredients that must be declared on the medicine label.

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 Part 3 of Schedule 4 to [the Regulations](#) 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](#)
- [Australian Customs and Border Protection Service](#)
- [Department of Agriculture](#)



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.

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 Order No. 69—General requirements for labels for medicines](#) (TGO 69) (as amended)
- Part 5-1 (Advertising and generic information) of the [Therapeutic Goods Act 1989](#)
- The [Therapeutic Goods Advertising Code](#)
- The [Therapeutic Goods Regulations 1990](#)
- The [Required Advisory Statements for Medicine Labels](#) (RASML)
- 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 TGO 69 (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.

Approvals for restricted representations must be gazetted in the [Government Notices Gazette](#) in order to take effect.

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 under [TGO 69](#).

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 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 through 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 indications²; 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 indications³; or

² Note that if the change is to an indication (which technically would make the medicine ‘separate and distinct’), but the change only reduces the class of persons for whom the goods are suitable, a variation to the existing medicine under section 9D(2) of the Act may be possible—see [Variations to complementary medicines permitted under section 9D of the Act](#).

³ *Ibid*

- (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](#).

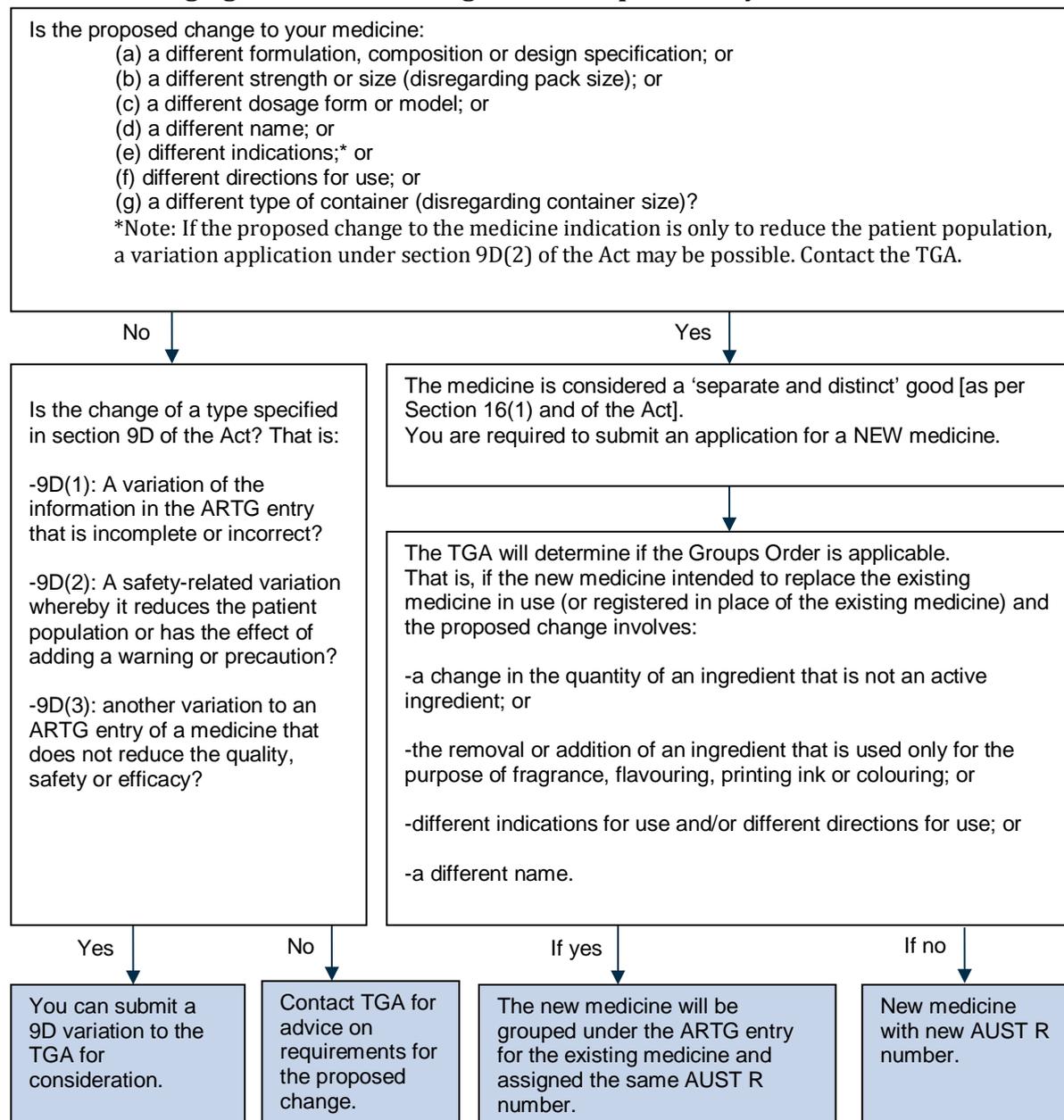
There is a provision in the application and submission portal to request the same change to be made across a number of currently listed medicines. Each medicine change will incur any applicable fees.

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**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 tables 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:

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](#).

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 Assistant 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](#) or relevant [Therapeutic Goods Listing Notices](#) made under subsection 9A(5) of the [Therapeutic Goods Act 1989](#) (the Act).



The TGA is developing a list of permitted ingredients under section 26BB of the Act.

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 and excipient) [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. To be consistent with their low risk status, regulatory limits/requirements may be placed on the use of certain ingredients in listed medicines.

Schedule 4 to the Regulations and [Therapeutic Goods Listing Notices](#) provide the types of ingredients that are eligible for inclusion in medicines listed on the ARTG.

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](#)).

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.

1. Select 'Public TGA Information' from the left hand menu.
2. From the dropdown menu select 'Ingredients'.
3. Enter the ingredient name or synonym you are looking for in the 'search field' and ensure that in 'all fields' is selected. Click 'Go'.
4. 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).
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 Schedule 4 of the Regulations that may be in place for the ingredient. It is important to note that an application to list a new medicine will not pass electronic validation if ingredient restrictions are not met.

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.

Vitamins and minerals permitted for use in listed medicines

Schedule 4, Parts 1, 2 and 3 of the Regulations and [Therapeutic Goods Listing Notices](#) provide the vitamins and minerals and their salts that are eligible for inclusion in listed medicines on the ARTG.

Note certain substances at particular doses are subject to a schedule of the [Poisons Standard](#), for example: vitamin B6 above a certain dose is scheduled and therefore no longer listable.

Herbal Ingredients permitted for use in listed medicines

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. Meeting the definition of a herbal substance, as provided in Regulation 2 of the Regulations, is an important step for supporting the safety of the substance:

herbal substance means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

- (a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and
- (b) that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form.

The definition describes the types of herbal substances that are eligible to be included in listed medicines without further evaluation by the TGA.

Herbal ingredients differ from pharmaceutical ingredients in that they may be complex multi-component substances. Significant changes in the chemical composition of herbal substances, as a result of natural variation or selective breeding/modification, may affect the safety of the originally approved material. Some manufacturing processes result in materials that do not meet the current definition of an herbal substance. These materials cannot be assumed to have the same safety profile of the herbal ingredient on which their safety was based. Ingredients that do not meet the definition are regarded as new substances and, as such, are not eligible for inclusion in listed medicines, unless they are evaluated and their safety demonstrated.

An isolated substance derived from a plant, or synthesised to mimic a naturally occurring plant constituent would not be permitted in listed medicines as a 'herbal ingredient'. However, the isolated plant constituent may be eligible for use as a new substance if evaluated and approved by the TGA for use in listed medicines.

Sponsors and potential applicants should be aware that some herbal ingredients have additional restrictions placed on them (for example: dosage, route of administration) in order to be considered suitable for use in listed medicines.

Additional guidance on [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](#)

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, applicant/sponsors 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.

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.



The 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/sponsor and a certification by the applicant/sponsor 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 to the Regulations and [listing notices](#) made under subsection 9A(5) of the Act provides the types of preparations that can be included in listed medicines on the ARTG and the conditions that must be met for them to be eligible for listing, for example: the preparation must not be required to be sterile; 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/sponsor 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 medicine 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 reports⁴.

- 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](#).

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

⁴ The timing of and the type of adverse reactions to be reported are outlined in [Australian pharmacovigilance requirements and recommendations for medicine sponsors](#).

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 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.

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@tga.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@tga.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: New complementary medicine substance evaluation

This guidance is for applicants proposing new substances for use as an ingredient in listed medicines. You can submit an application for evaluation for suitability for use in listed medicines for:

- a new complementary medicine substance not currently a permitted ingredient; or
- a proposed new role or a change to a regulatory requirement of use for a permitted ingredient, for example: a proposal for an ingredient permitted for use as an excipient to be used as an active ingredient; or change to the permitted level of use; or change the permitted route of administration.

A request for evaluation of a new complementary medicine substance is considered under Regulation 16GA of the Therapeutic Goods Regulations 1990 (the Regulations). There is an associated [fee](#).



The primary reason for the evaluation of a substance is to determine whether it is of appropriate quality and safety to be permitted for use as an ingredient in listed complementary medicines.

Once permitted for use in listed medicines, an ingredient may be used in a listed medicine by any sponsor.

Route of evaluation for complementary medicines

Legislative provisions determine the 'route of evaluation' for an application. This in turn determines data requirements, fees and the timelines. Schedule 10 of the Regulations prescribes which office within the TGA conducts the evaluation of specific therapeutic goods.

Part 2 of Schedule 10 states that complementary medicines that do not contain substances in Schedule 4, 8 and 9 of the Poisons Standard are evaluated by the Office of Complementary Medicines (now named Complementary Medicines Branch).

If you are of the view that your application has been incorrectly referred to a particular TGA office 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

- where the substance is of herbal origin, it is not subject to a restriction or included in Division 1 of Part 4 Schedule 4 to the Regulations (plant material from which herbal substances in listable goods must not be derived)
- 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, route of administration) must be placed on the use of such an ingredient in listed 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 phases for a new complementary medicine substance

Your application for evaluation of a new complementary medicine substance for use in listed 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:** Delegate determination
- **Phase 6:** Finalisation



There is currently no statutory time frame for the evaluation of complementary medicine substances. The complexity of the substance, the adequacy and the quality of the data submitted in the application will all influence the length of time required for evaluation.

Phase 1: Pre-submission meeting

We recommend you arrange a meeting with us prior to submitting an application for evaluation of a complementary medicine substance. You should contact us to arrange meeting details. There is no fee associated with a pre-submission meeting—refer to [Pre-submission meetings with the TGA](#).

The purpose of the meeting is to ensure that you are aware of the legislative requirements for ingredients used in listed 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 new complementary medicine substance form](#), the dossier and the evaluation fee. Fees are subject to change, and you should refer to [Summary of fees and charges](#) available on our website.

You are expected to self-determine the appropriate evaluation fee for your application, which is based on the total page count of safety data. Administrative and quality data are excluded from the page count. The following types of safety data are included in the calculation of evaluation fees:

- biological activity/pharmacodynamics
- pharmacokinetics
- animal studies
- bioavailability/bioequivalence studies
- human data (including clinical study reports)
- published papers and reviews
- meta-analysis reports
- literature search strategy and results
- expert overviews/summaries/reports
- case reports and adverse reaction reports.



All data should be submitted at the time you lodge your application. It is important that relevant data are not omitted from your application in order to reduce the evaluation fee, as this may jeopardise the acceptance of your application or cause unnecessary delays in evaluation.

We 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

The screening of the application consists of two parts: an administrative screen and a technical screen.

The administrative screen confirms that all fields on the application form have been completed and an evaluation fee has been paid. If these basic requirements are not met, we will consider that the application is ineffective.

The technical screen determines whether data requirements have been addressed and whether the fee paid is appropriate. If you have paid more than the required evaluation fee, a refund will be organised by the TGA. Where less than the required fee has been paid, you will be required to make up the shortfall before the application can proceed.

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.

Application accepted for evaluation

Applications that are accepted in the screening phase progress to the evaluation phase. You will receive a letter advising that the application has been accepted for evaluation and providing you with the details of a TGA contact person for the application.

Application not accepted for evaluation

An application will not proceed to evaluation if:

- the substance is not eligible for use in listed medicines (see [Substances eligible for evaluation for use in listed complementary medicines](#))
- any portion of the evaluation fee remains outstanding (an application will be considered lapsed if the outstanding fee is not received within 28 calendar days from date of invoice)
- 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; or
 - no certified English translation of foreign language documents
- there is gross deficiency or insufficiency of information; and/or
- appropriate justification is not 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.

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.

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.

Quality and safety are the main parameters considered when evaluating a substance for suitability for use as an ingredient in listed medicines.

Quality aspects (for example: chemical identity, manufacturing process, process controls and stability) are evaluated for the purpose of characterising (identifying the physical and chemical properties of) the substance. 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 an approved new complementary medicine substance is included in a new listed medicine, 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. 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.

Clarification of information

At any time during the evaluation process you may be asked for further information to clarify issues or address deficiencies in the application. You will receive a written letter outlining the deficiencies and the additional information and/or clarification that is required. The evaluation of the application will not proceed until identified issues are addressed. After addressing any issues identified, the evaluation report with the evaluators' recommendations will be finalised.

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 Medicine Scheduling or the Advisory Committee on Safety of Medicines. You will be informed that the 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: Determination

In making a determination on the application, the TGA takes into consideration the evaluation report recommendations, any advice from advisory committee/s as well as any response from the applicant. If the application is unsuccessful, you will be advised in writing as soon as practicable and provided the reasons why it was not successful.



There are no provisions in the Act to appeal a negative determination on a new substance evaluation, however, if you are not satisfied with an outcome, you can arrange a meeting with the TGA to discuss your options.

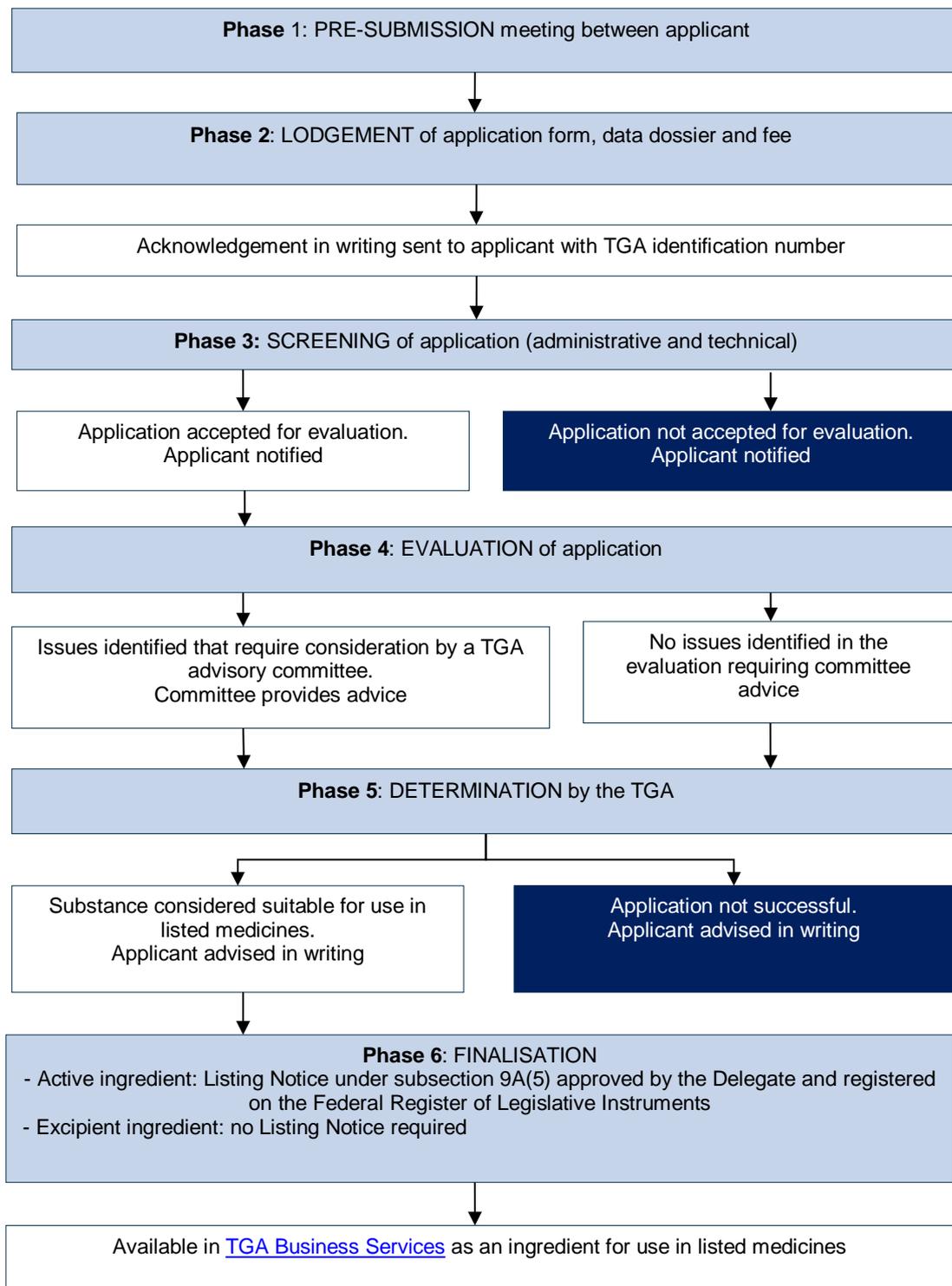
Phase 6: Finalisation

If an active ingredient is evaluated as suitable for use in listed medicines, the delegate for the Minister makes a Therapeutic Goods (Listing) Notice under subsection 9A(5) of the Act. This results in the approved active ingredient being included in [TGA Business Services](#) and made available for use in listed medicines.

New approved excipient ingredients are made available for use without the requirement for publication of a Listing Notice.

[Listing notices](#) can be viewed on our website.

Chart C1 illustrates the application stages for the evaluation of a new complementary substance.

Chart C1: Evaluation process for a new complementary medicine substance

Information required for an application for evaluation of a new complementary medicine substance

Table C1 outlines the type information required in an application for evaluation of a new complementary substance to be used in listed medicines.

Table C1: Identification of data that is not in the public domain and may be commercially confidential—where required

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
Quality information	
Definition	Description of the substance State if the substance is derived from or contains genetically modified substances.
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

Required information	
	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
Container closure system	Storage conditions, for example: 'protect from light'
Stability	Stability data throughout storage period (with trend analysis)
Safety information	
Literature search	Search strategy and results with justification for inclusion/exclusion of data

Required information	
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
Ingredients 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 new 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 new 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 an evaluation of a new complementary medicine substance](#).

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](#).

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 complementary 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

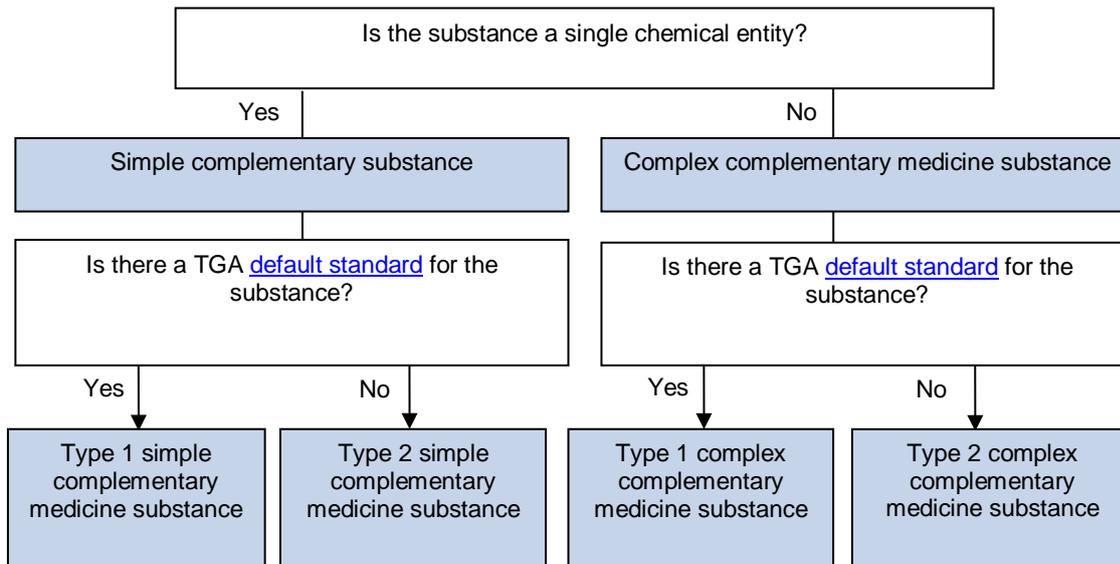
A simple complementary medicine substance is a single chemical entity that can be readily characterised, for example: ubiquinol-10 or calcium carbonate.

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 new complementary medicine substance

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'.

The 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 and 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 complementary medicine substance

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 complementary medicine substance

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:

$$\text{Limit} = \frac{\text{ADI} \times \text{M}}{\text{MDD} \times 100}$$

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= 60kg

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

$$\text{Limit} = \frac{\text{ADI} \times \text{M}}{\text{MDD} \times 100} = \frac{0.0036 \text{ mg/kg} \times 60 \text{ kg}}{0.0006 \text{ kg} \times 100} = 3.6 \text{ mg/kg}$$

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:

$$\text{Limit} = \frac{\text{ADI} \times \text{M} \times \text{E}}{\text{MDD} \times 100}$$

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 complementary medicine substance

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 scientific guideline: [Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products CPMP/QWP/122/02, rev 1 corr.](#)

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 new complementary medicine substance for use in listed medicines

The safety of a substance for use in listed 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 substances permitted for use in listed 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 search and evaluation](#). 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 systems
- 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 C2](#)) 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.

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*, kawa, *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 C3](#).

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.

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](#).

Table C2: 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 <i>et al.</i> 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 bwt, heart rate, systolic & diastolic bp, ALT, glucose, creatinine. Adverse reaction reports: cephalgia (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.

Table C3: Example format – Summary of adverse events

Report reference and date reported	Patient details	Product details	Treatment details	Other medicines	Adverse reaction	Comments (for example, outcome; laboratory results)	Causality
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 VLDL: very-low-density lipoprotein

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](#).



Note: 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.

How a new registered complementary medicine is evaluated

A request for a new registered complementary medicine substance is made under Section 23 of the [Therapeutic Goods Act 1989](#) (the Act). There are associated [application and evaluation fees](#).

In determining if a medicine can be approved for registration, consideration is given to:

- whether the quality, safety and efficacy of the medicine for the purposes for which it is to be used have been satisfactorily established
- the presentation of the medicine is acceptable; and the medicine complies with all applicable legislative requirements (under section 25 of the Act).



There is currently no statutory time frame for the evaluation of a new registered complementary medicine. The complexity of the medicine and its ingredients, as well as the completeness and the quality of the data submitted in the dossier will influence the length of time required for evaluation.

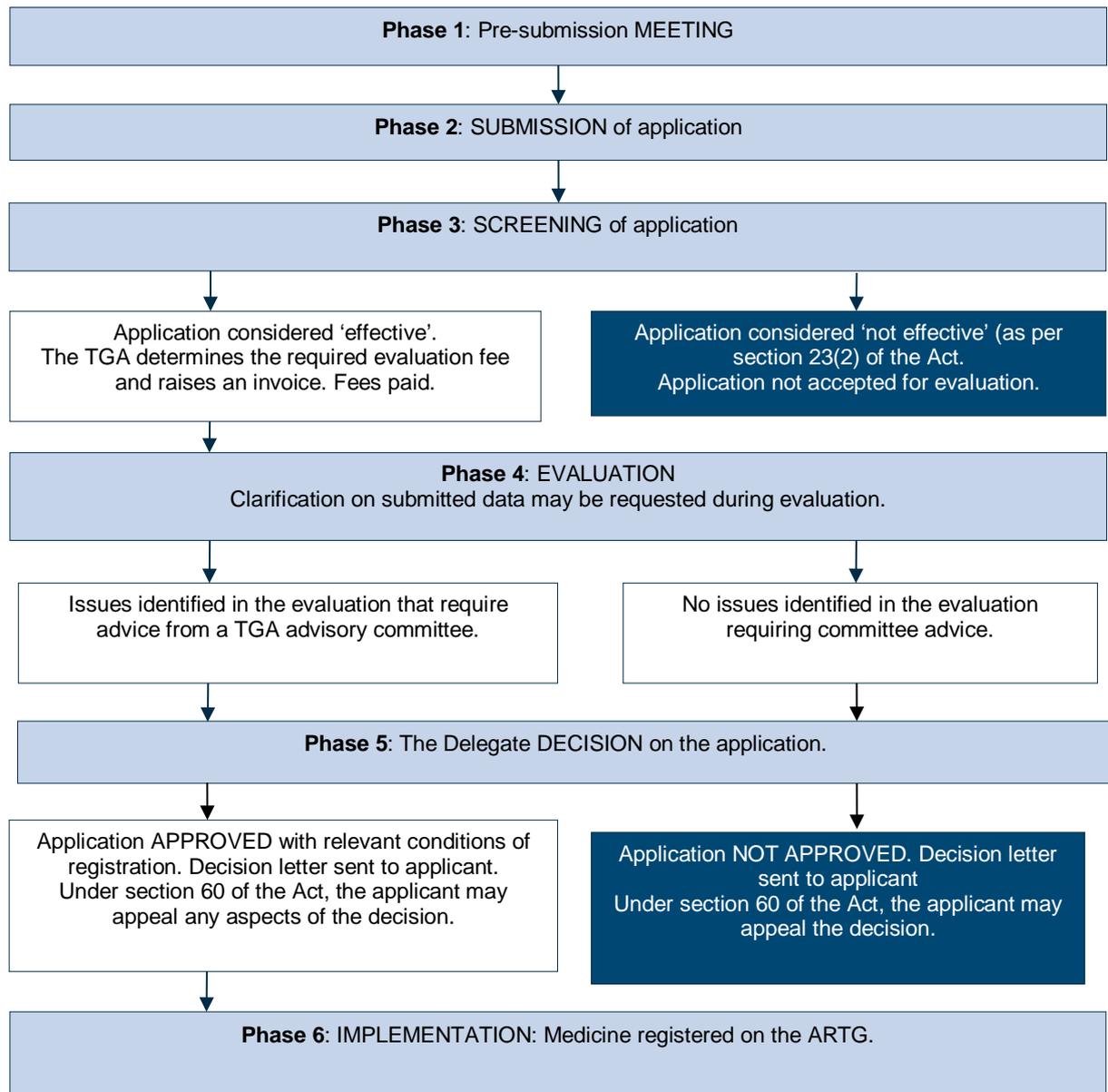
Application phases for a new registered complementary medicine

The application phases for a new registered complementary medicine are as follows:

- **Phase 1:** Pre-submission meeting (recommended)
- **Phase 2:** Submission of application and payment of application fee
- **Phase 3:** Screening of application, determination and receipt of evaluation fee
- **Phase 4:** Evaluation
- **Phase 5:** Decision
- **Phase 6:** Implementation

Note that you may choose to withdraw your application at any phase.

Chart D1 illustrates the application phases for a new registered complementary medicine.

Chart D1: New registered complementary medicine application process flow chart

Phase 1: Pre-submission meeting

It is recommended that you arrange a meeting prior to submitting your application for a new registered complementary medicine. The intention of the meeting is to assist you to submit a high quality, complete dossier. Discussion will focus on the structure of your proposed application, the identification of critical issues and the suitability of your proposed approach. It should be noted that no assessment or evaluation of data will be undertaken as part of a pre-submission meeting.

You should contact the TGA to arrange a meeting - there is no fee associated with a pre-submission meeting. For more information on the conduct of meetings—refer to [Pre-submission meetings with TGA](#).

Phase 2: Submission of application and payment of application fee

Your application for a registration of a complementary medicine has to be submitted electronically via the TGA Business Services portal. You require a user name and password to

[access TGA Business Services](#), which is obtained by submitting an 'Organisation Details Form' followed by an '[TGA Business Services Access Request Form](#)'.

Your application must be accompanied by an 'application fee' (non refundable) and the dossier. Information on [current fees](#) can be found on the TGA website.

The TGA will acknowledge receipt of your application.

Phase 3: Screening of application, determination and receipt of evaluation fee

The screening of your application consists of an administrative and a technical screen.

In general, screening aims to identify firstly, whether your application is considered 'not effective' as determined under 23 (2) of the Act:

- 23 (2) An application is not effective unless:
- (a) the prescribed application fee has been paid; and
 - (b) the applicant has delivered to the office to which the application was made such information, in a form approved, in writing, by the Secretary, as will allow the determination of the application; and
 - (ba) if the application is for the registration of restricted medicine - the application is accompanied by product information, in relation to the medicine, that is in the form approved under section 7D in relation to the medicine; and
 - (c) if the Secretary so requires—the applicant has delivered to the office to which the application was made a reasonable number of samples of the goods.

The screening phase determines that:

- all required fields on your application form have been completed
- you have paid the 'application fee'
- your dossier provides sufficient information
- the route of evaluation for the application is appropriate.

If your application is considered 'not effective' (and therefore not suitable for evaluation as a new registered complementary medicine) you will be informed of the reasons for this decision.



A decision that an application is 'not effective' is not included in the appeal provisions under subsection 60(1) of the Act. Therefore you do not have a right of review under section 60 of the Act, but you do have a right to apply to the Federal Court on questions of law.

If your application is considered 'effective' (and therefore, acceptable for evaluation) the TGA determines the 'evaluation fee' payable. The 'evaluation fee' is in addition to the 'application fee' and is based on the number of pages of clinical and nonclinical data submitted (administrative and quality data are excluded from the page count). The following types of safety data count towards the calculation of evaluation fees:

- biological activity/pharmacodynamics
- pharmacokinetics
- animal/toxicological studies
- bioavailability/bioequivalence study
- human data

- published papers and reviews
- meta-analysis reports
- literature search strategy and results
- expert overviews/summaries/reports
- case reports and adverse reaction reports.



You should submit all relevant data at the time the application is lodged. The omission of such data may jeopardise the success of your application.

In some cases, where an application is found to be suitable for evaluation, the screening may identify minor errors or omissions that can be readily addressed. In this circumstance, you will be advised that the application has been accepted for evaluation, and be given the opportunity to address these minor errors or omissions.

You will be notified in writing regarding the acceptance of your application for evaluation and the applicable evaluation fee. The evaluation process will not commence until you have paid the evaluation fee in full. Your application will lapse if evaluation fees are not paid within two months of becoming payable. In this case, you will be notified that your application has lapsed and advised that, should you wish to continue, a new application will be required.

Phase 4: Evaluation

In the evaluation stage, the quality, safety and efficacy of the proposed new registered medicine are critically assessed and an evaluation report is produced.

Quality

The data are evaluated to determine the quality of the medicine, including the identity, impurities and stability of all ingredients. The assessment also takes into account information about the manufacturing processes and the compliance with good manufacturing practice (GMP). Quality-control measures are assessed to determine if the medicine will be produced to a consistent quality. Stability data for the medicine are evaluated to confirm that the medicine is of appropriate quality over its proposed shelf-life.

Safety

History of use, biological activity, toxicology, clinical trials and reports of adverse reactions are assessed to determine the safety of the medicine.

Efficacy

The assessment of the efficacy data includes a detailed evaluation of the proposed indication(s) and any claims that you intend to make for the medicine to determine whether the data supplied adequately support the requested indication(s)/claim(s).

Where the evidence is considered not likely to support the proposed indication, you will be advised in writing and asked whether you wish to amend the indications in line with the available evidence.

Medicine presentation, consumer medicine information and product information

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

When provided, [Product Information and Consumer Medicine Information](#) are also assessed.

During evaluation, the evaluator will identify any matters that require clarification or information, and where necessary a consolidated set of questions will be prepared by the TGA delegate and sent to you (under Section 31 of the Act).

Possible consideration by a TGA advisory committee

In some circumstances the Delegate for the Secretary of the Department of Health (the Delegate) may seek advice from a [TGA advisory committee](#) in relation to an application. In this situation, you will be informed that the committee's advice is being sought and you may choose to provide comment for the committee's consideration. Subsequently you will be informed of any relevant advice given by the committee.

Phase 5: Decision

In making a decision on the application, the Delegate will take into consideration the evaluation report, any advice given by the advisory committee and any subsequent comment provided by you. The decision to register the medicine may be a complex one and is based on the need for the medicine and its benefit-to-risk ratio.

You will be advised in writing of the Delegate's decision. If the decision is to reject the application, the letter will provide the reasons for the decision. If the decision is to approve the application, the [standard and specific conditions of registration will be provided](#).

If you do not agree with the decision of the Delegate, you have the right to appeal under Section 60 of the Act.

Phase 6: Implementation

The decision letter will include a request for the future sponsor of the medicine to provide assurance that all details of the medicine are correct prior to the medicine being entered on the ARTG. After being entered, a registration certificate will be available online for printing by the sponsor. The registration of therapeutic goods begins on the day specified in the certificate of registration and remains valid until suspended or cancelled. Annual renewal charges will apply while the medicine remains registered on the ARTG.

Information required in an application for a new registered medicine

General application format

An application for a new registered complementary medicine must include a comprehensive dossier of relevant safety, quality and efficacy data.

It is preferred that the data is presented in an electronic format that is able to be electronically searched and copied. If provided in hard copy two complete sets must be provided. The dossier must be sequentially numbered (either the whole dossier or within each module/part).

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.

It is recommended that the data is presented in a manner consistent with the European Medicines Agency (EMA) - [Common technical document](#) (CTD). Although the CTD format is not a mandatory requirement for a new registered complementary medicine application, presentation in this manner will expedite evaluation. The CTD is divided into five modules and is an internationally agreed set of specifications for a submission dossier:

Module 1: Administrative information and prescribing information for Australia

Module 2: Summaries of quality, safety and clinical data

Module 3: Quality

Module 4: Nonclinical data

Module 5: Clinical data

For some complementary medicine registration applications, some parts of the CTD are not relevant. Where data are not available for a particular CTD heading, a scientific justification as to why this data are omitted must be provided. It is valuable for these issues to be discussed with the TGA at the pre-submission meeting.

If you choose not to present the dossier in CTD format, the following guidance outlines the type of information required in an application for a new registered complementary medicine. As above, justifications as to why any data are omitted must be provided and discussed with the TGA at the pre-submission meeting. The information required is summarised in Tables D1 to D5.

Table D1: Administrative information for a new registered complementary medicine application (consistent with CTD Module 1)

Administrative information (consistent with CTD Module 1)	
Application form	Form submitted via the TGA Business Services portal
Application covering letter	Outlining purpose of application and a summary of dossier contents
Table of contents	Provided for the complete dossier or for each individual part/module
Identification of information that is not in the public domain and may be commercially confidential	Where required
Proposal for a new ingredient name	Where an ingredient does not have an approved Australian name
Literature search	Search strategy, results with justification for inclusion/exclusion of data

Administrative information (consistent with CTD Module 1)	
Labelling and packaging	Drafts provided of all proposed medicine labels and other packaging including closing device, where applicable
Australian Product & Consumer Information	Required for medicines that contain a substance in Schedule 3 of the Poisons Standard
Expert information	Details and declaration of any association with applicant or sponsor
Good manufacturing practice	A list of manufacturers with evidence of acceptable GMP
Genetically modified organisms	Notified to the TGA
Ingredients of human or animal origin	Evidence of the material used as per Guidance 10: Adventitious agent safety of medicines
International regulatory status	Where relevant, country, regulatory status, length of time and volume of supply
Pre-submission meetings	A summary of any pre-submission meeting undertaken with the TGA
Other information where available	For example: patent certificates, summary of biopharmaceutical studies or information relating to pharmacovigilance

Table D2: Overview and summaries of quality, safety and efficacy data for a new registered complementary medicine application

Overview and summaries of quality, safety and efficacy data (consistent with CTD module 2)	
Medicine details	
Name	Proposed name of medicine
Dosage	Dosage form, range, frequency and duration of use and pack sizes
Composition	Medicine formulation
Route of administration	For example: oral, topical
Container type	For example: PET bottle with child-resistant closure or blister pack in carton

Overview and summaries of quality, safety and efficacy data (consistent with CTD module 2)	
Proposed therapeutic use	Proposed indications and target population
History of use	Human exposure data, dietary, traditional and commercial use in Australia and internationally
Expert summaries	
Summary of quality information	
Summary of safety information	
Summary of efficacy information	
Risk-benefit assessment	

Table D3: Quality information for a new registered complementary medicine application

Quality information (consistent with CTD Module 3)	
Information on quality for each active ingredient of the medicine	
Nomenclature	Using Australian approved name format
Structural formula	Structural formula of the ingredient and/or components e.g. herbal components
General properties	Physiochemical and other relevant properties
Manufacturing details	List of manufacturers
	Description of manufacturing process and process controls
	Control of materials
	Control of critical steps and intermediates
	Process validation and/or evaluation
	Manufacturing process development
Characterisation	Elucidation of structure and other characteristics of ingredient and/or components e.g. herbal components
	Impurities

Quality information (consistent with CTD Module 3)	
Control of substances— specifications of raw materials	Specifications providing set of tests and limits
	Analytical procedures and validation
	Batch certificate of analysis
	Justification of specifications
Reference standard	Reference standards or materials
Stability of active ingredients	Stability summary and conclusions
	Stability data
Information on quality for the medicine (finished product)	
Description and composition	Name, Dosage form, including any special characteristics, for example: modified release
Medicine development	Formulation of the medicine—table of the active and excipient ingredients and their purpose in the formulation
	Formulation development 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
	Physiochemical and biological properties
	Manufacturing process development
	Container closure system
	Microbiological attributes
	Compatibility
Manufacture of the medicine	Manufacturer information
	Batch formula
	Description of manufacturing process and process controls
	Control of critical steps and intermediates

Quality information (consistent with CTD Module 3)	
	Process validation and/or evaluation
Control of excipient/s	Specifications
	Analytical procedures
	Validation of analytical procedures
	Justification of specifications
	Excipients of human or animal origin
	Novel excipients
Control of finished product	Specifications
	Analytical procedures
	Validation of analytical procedures
	Batch analysis
	Characterisation of impurities and requirements for non-pharmacopoeial products
	Justification of specifications
Reference standards or materials	
Container closure system	
Finished product stability	Stability summary and conclusion
	Stability data

Table D4: Nonclinical data for a new registered complementary medicine application

Nonclinical data (addressing safety* and efficacy*)(consistent with CTD Module 4)	
Pharmacology	Primary pharmacodynamics: <i>in vitro</i> and <i>in vivo</i>
	Secondary pharmacodynamics: <i>in vitro</i> and <i>in vivo</i>
	Safety pharmacology
	Pharmacodynamic drug interactions

Nonclinical data (addressing safety* and efficacy*)(consistent with CTD Module 4)	
Pharmacokinetics	Analytical methods and validation reports
	Absorption
	Distribution
	Metabolism
	Excretion
	Pharmacokinetic drug interactions (nonclinical)
	Other pharmacokinetic studies
Toxicology	Single dose toxicity
	Repeat dose toxicity
	Genotoxicity: <i>in vitro</i> and <i>in vivo</i>
	Carcinogenicity: long term studies and short or medium term studies
	Reproductive, developmental toxicity: fertility and early embryonic development, prenatal and postnatal development, studies in offspring
	Local tolerance
	Other toxicity studies: antigenicity, immunotoxicity, mechanistic studies, dependence, metabolites, impurities

Table D5: Clinical data for a new registered complementary medicine application

Clinical data (addressing safety and efficacy) (consistent with CTD Module 5)	
Pharmacology studies	Pharmacokinetics
	Pharmacodynamics
Efficacy studies	Controlled and uncontrolled efficacy clinical trials
	Efficacy-related PI/CMI comments (where applicable)
Safety studies	Controlled and uncontrolled safety clinical trials
	Safety-related PI/CMI comments (where applicable)

Clinical data (addressing safety and efficacy) (consistent with CTD Module 5)	
	Post-marketing data

Administrative information

Application form

Your application for a new registered complementary medicine has to be submitted via the TGA Business Services portal. To access to the application portal refer to [TGA Business Services Access Forms](#).

Application covering letter

Your covering letter should accompany the application and provide:

- the purpose of the submission
- the medicine name, active ingredient name(s), dosage forms, strength
- scheduling details from the [Poisons Standard](#), where relevant
- the proposed therapeutic indications
- the number of volumes and a total page count for each module/section of the dossier
- the proposed sponsor of the medicine if approved for registration on the ARTG.

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.

Treatment of information provided to the TGA

Information provided to the TGA, whether as part of an application or otherwise, may be commercially confidential. Such information will be treated appropriately by the TGA. Information about this treatment can be found 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](#)
- for information requested under the Freedom of Information refer to: [TGA Approach to disclosure of commercially confidential information](#).

Proposal for a new ingredient name

All the components of the proposed medicine should be identified using Australian approved terminology. The [TGA approved terminology for medicines](#) publication provides approved terminology for substances, containers, dosage forms, routes of administration and units of measurement.

Where the proposed new registered complementary medicine includes an ingredient that does not have an approved name, a proposal for a new name is required to be submitted with the application. The various [forms for this purpose](#) are available on the TGA's website.

Literature search

In addition to providing the literature search strategy—refer to: [Literature search and evaluation](#)), the reasons for the inclusion or non-inclusion of any material should be provided.

Labelling and packaging

You must include final or drafts of all medicine labelling in the application. Artwork ready for printing or examples of the printed labels are preferred. If only the draft label text is submitted, the size, colour and positioning of the text on the label should be made clear. This information is necessary to assess compliance with the various legislative requirements. Where draft labelling is submitted, this may be satisfactory for the medicine to be approved for registration on the ARTG. However, in this circumstance, it is usually a condition of registration that the final labels are provided to the TGA for approval before the medicine can be supplied in Australia.

Where the pack sizes differ but the label is to remain the same (and you give an assurance to that effect) only one set of labels is required in the application. An assurance that the text size is also identical must also be included. If the text size is different for pack sizes, or if the presentation of the information is different, the label for the additional pack size must be submitted.

Labelling must comply with the legislation and with the current version of [Therapeutic Goods Order No 69 – General requirements for labelling of medicines](#) (TGO 69).

Australian product and consumer information

There are legal requirements for certain medicines to provide a Product information (PI) document and a Consumer Medicine Information (CMI) document:

- A PI is required for restricted medicines. The [Restricted Medicine Specification 2011](#) lists the following medicines or classes of medicine as 'restricted medicines':
 - medicines that are subject to Schedule 3 of the Poisons Standard
 - medicines contained in a therapeutic good mentioned in Part 1 of Schedule 10 to the Regulations other than in items 1(b) and 14.

The PI contains technical information intended for healthcare practitioners and must not include promotional material. Refer to [Product information](#) on our website for more information required in a PI.

- A CMI is required (under Regulation 9A of the Regulations) for:
 - medicines subject to Schedule 3 of the Poisons Standard
 - therapeutic goods included in Part 1 of Schedule 10 to the Regulations.

The CMI contains general information about the medicine, written in plain English, intended for the consumer and cannot include promotional material. The CMI must be consistent with the PI and comply with the requirements specified in Schedule 13 of the Regulations, although the information does not have to be set out in the order in which it set out in the Schedule.

While not a mandatory requirement for medicines other than those identified above, a sponsor may choose to include a PI or CMI document for their new registered complementary medicine

in order to provide as much information as possible about their medicine. In these instances, the requirements for the documents are the same as outlined above.

All package inserts for registered medicines are considered part of product labelling (refer to the definition of 'Label' in the Act) and require approval by the TGA.

Expert information

The author of an Expert Report (see [Expert summaries](#)) should be a person with appropriate qualifications and experience relevant to the subject matter, for example; the expert used in an application for a mineral or vitamin supplement should be someone with expertise in nutritional epidemiology.

The expert's curriculum vitae should be included in the 'Administrative' part of the application. The expert should also provide a statement declaring the extent, if any, of their professional or other involvement with the dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Module 1.4 of the CTD document modified for Australia [CTD Module 1 – Administrative information and prescribing information for Australia](#) contains a pro-forma for supplying information about the expert.

Good manufacturing practice

List the manufacturer/s with evidence of acceptable GMP- for manufacturers in Australia, this would be the TGA licence number, for overseas manufacturers this would be: a copy of the Office of Manufacturing and Quality preclearance letter.

Genetically modified organisms

You should advise the TGA if the proposed new registered complementary medicine includes a substance that is, or is obtained from, a genetically modified organism—refer to [genetically modified organisms in complementary medicines](#).

If the medicine is approved, the TGA is obliged to notify the [Office of the Gene Technology Regulator](#).

Ingredients of human or animal origin

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](#).

International regulatory status

If the same or a nearly identical product is supplied in other countries, the country, approval date (or date and length of time of supply) and the regulatory status (for example: dietary supplement) should be provided, where it is reasonable to expect that the applicant has access to that information. Provision of documentation detailing the annual sales volume and estimates of the size of the exposure population is not mandatory, but this is considered to be supporting data and will assist the assessment of the application. If an application for the product has been made to a regulatory authority in any other country, this should be stated, as well as the outcome of that application, that is: approval or rejection.

Pre-submission meetings

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

Other information

Where available, provide:

- patent certificates (see subsection 25(4) and section 26 B of the Act)
- summary of Biopharmaceutic Studies (using the [Summary of a bioavailability or bioequivalence study form](#))
- information relating to pharmacovigilance.

Overview and summaries of quality, safety and efficacy data in an application for a new registered complementary medicine

Name

Provide the proposed name of the medicine.

Dosage of medicine

State the dosage form, dosage range, frequency and duration of use and the pack size/s.

Composition of the medicine

List the ingredients in the medicine formulation.

Route of administration for the medicine

Provide the proposed route of administration, for example: oral, topical.

Container type for medicine

Describe the container type/s, for example: 'PET bottle with child-resistant closure' or 'Blister pack in carton'.

Proposed therapeutic use of medicine

Provide the proposed therapeutic indications and state the target population.

History of use of medicine

Provide a summary of human exposure data, dietary, traditional and commercial use in Australia and internationally.

Details of the number of people estimated to have been exposed to the medicine since the start of supply should be provided and categorised, as appropriate, by indication, dosage and route of administration, treatment duration and geographical location.

Traditional use

Where evidence of traditional use is provided in the dossier, it must be demonstrated that the proposed medicine is consistent with the traditional preparation and the traditional use (including dose, route of administration and duration of use).

Traditional use cannot fully establish the safety and efficacy of a proposed new registered complementary medicine. However, traditional, long-term and safe therapeutic use may be taken into account in evaluating the safety of a medicine.

Expert summaries

You should include expert reports, cross-referenced by page number or hyperlinked to the submission, providing separate critical appraisals of the quality and manufacturing, nonclinical and clinical efficacy and safety of the medicine.

Guidance on the content and format of Expert Reports may be found in Module 2 of the [CTD](#).

Summary of quality information

Provide a critical scientific summary explaining how the quality of the medicine has been established.

Summary of safety information

Provide a critical scientific summary explaining how the safety of the medicine has been established. In establishing the safety profile of the medicine, the nonclinical and clinical data should be summarised and discussed. Adverse events (both serious and non-serious) should be discussed noting any causal relationships. The summary of information should demonstrate that the total amount of the active ingredient from the medicine and from the food supply of the target population has been considered.

Summary of efficacy information

Provide a critical scientific summary explaining how the efficacy of the medicine has been established. The overview of the clinical data should discuss both positive and negative outcomes and should explain how the data support the proposed indications and claims. Where more than one indication is proposed, each indication should be separately justified.

Risk-benefit assessment

Provide a critical scientific summary analysing the risk/ benefit of the medicine.

Information on quality required for an application for a new registered complementary medicine

You should 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](#). While presentation of data in the CTD format is not mandatory, 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.

Information on quality for active ingredient/s

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 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 complementary 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/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.](#)

Information on quality for the medicine/ finished product

Description and composition of the medicine

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.

Medicine development

Formulation details for the medicine

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%

Excipient type	Range
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.

Manufacture of the medicine

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 for overseas manufacturers](#)
- [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.

Validation of analytical procedures

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.

Validation of analytical procedures

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.

Characterisation of impurities and requirements for non-pharmacopoeial products

Solvent residues

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 VIII L – Residual Solvents.

Impurity requirements for 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 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.

Information on safety and efficacy required 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. The [ARGOM Appendix 1: Guidelines on efficacy and safety aspects of OTC applications](#) provide guidance for applicants choosing to submit a literature-based submission.

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) (Tables 4 and 5 above).

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 medication/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.

Postmarketing data

The application should include all relevant postmarket 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 postmarketing data.

ARGCM additional guidance material

1. Compositional guidelines for complementary medicine substances

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 and is open for a six week stakeholder consultation. After reviewing the stakeholders' submissions, we will publish our response and all non-confidential submissions on our website. The compositional guideline will be amended if required and then published 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 for wider consultation.

Guidance for developing 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](#).

2. 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 Pharmacopoeia – 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 B '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.

Quantified by input

[Guidance on the use of the term 'quantified by input' for listed complementary medicines](#)

describes the criteria under which a manufacturer is not required to assay an ingredient in a listed medicine. It also details the wording that should be used on a certificate of analysis, where an actual ingredient has been 'quantified by input'.

3. Guidance on use of the term ‘quantified by input’ for listed complementary medicines

This guidance document describes the criteria under which a manufacturer of a listed complementary medicine would not be required to assay an ingredient in a finished product. The document 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 document 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](#)), be identified in either Schedule 4 to the Therapeutic Goods Regulations 1990 (the Regulations) or in a [Listing Notice](#)
- 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 Poisons Standard, Schedule 4 of the Regulations, a condition of listing (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 Schedule 4, Part 4,

Division 2 of the Regulations), 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 the CMB.

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 Schedule 4 to the Regulations 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.

4. Literature search and evaluation

All applications for new substance evaluation and for new registered complementary medicines should include an outline of the search strategy used to obtain the data to support the application. We will evaluate the adequacy of the search strategy submitted and may identify important papers that have not been supplied which the applicant may be requested to provide. Requests for such additional information may attract additional evaluation fees. Applicants may justify why particular papers identified in this way are not pertinent to the evaluation.

Ideally, the studies relied on by an applicant to support safety/efficacy should be largely consistent with the surrounding body of evidence. Wide variation in outcomes of studies, and inconsistent or conflicting results of studies, will raise questions about the adequacy of an applicant's substantiation. Where there are inconsistencies in the evidence, it is important to examine if there is a plausible explanation for them, for example: study methodology. If several studies of different quality have been considered, greater weight should be given to the higher quality work. A summary of the types of data used to assess the safety of a complementary medicine substance and the objectives of those data are shown in Table 1.

Table 1: Data to be provided in support of an application for a new complementary medicine substance or a new registered complementary medicine

Data	Objective
Chemical characterisation and constituents.	To establish chemical composition, constituents, analysis.
History, mode and patterns of previous human use (ethnobotany, including cultivation, preparation, potential for substitution and contamination).	To determine the conditions, if any, under which the substance has been used by humans in the past.
Biological activity including: pharmacokinetics, pharmacology, metabolism and bioavailability.	To describe the role of the substance/active ingredient in human metabolism.
Toxicology (toxicity, carcinogenicity, mutagenicity, teratogenicity, reproductive toxicology, safety in pregnancy and lactation).	To describe what is known about and, where possible, quantify potential risk associated with the use of the substance/medicine.
Clinical trials.	To report the results of use of the substance/medicine by humans under clinical trial conditions to identify risks from the experience of use in humans.
Adverse reactions (safety, risk, adverse events, interactions, contraindications, poisoning and overdose).	To determine the nature, severity and frequency of adverse reactions where there has been a history of use of the substance/medicine.

Papers per se do not provide the evidence in support of an application. The applicant needs to show that:

- the literature has been methodically scrutinised and the methodology is clearly explained
- the range of published evidence selected for submission is justified in the application dossier
- issues raised in the literature with a bearing on the application have been resolved.

There is no single search strategy that can be applied in all cases. It is important that, whatever the methodology used, it is clearly explained and justified in the application.

Conducting the search

Searching for the published information literature search is divided into three components to cover all of the data requirements detailed in [Table 1](#).

Chemical identification and constituents

- As many descriptors as possible for the substance should be identified and used in the literature search. This should include generic and trade names, traditional names, botanical terminology and Chemical Abstracts Service (CAS) registry numbers.
- In the case of botanicals, or substances where there may be multiple constituents, terms for the constituents should also be searched; for example, in the case of *Zingiber officinale*, terms such as zingiber, ginger, zingerols, zingiberenes should be searched.
- Where different terms are used, there should be clear evidence of identity; for example, shosaikoto (Japanese) is xiao chai hu tang (Chinese Pin Yin), and both are also called 'Minor bupleurum decoction' in the Chinese literature. Similarly, there should be evidence of chemical identity; for example, CAS registry numbers should be consistent across different records.

Literature on traditional use

Provide search results from both databases and print sources. Examples of sources for such literature include:

- pharmacopoeias, which may be national or international
- current and/or classical references in the specific field under review; for example, 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 a summary of the references retrieved, ideally in a table format.

Scientific literature

The minimum requirement for a search of the scientific literature is a systematic, robust and reproducible search of either Medline or EMBASE, together with TOXNET.

If relevant, a search of Food Science and Technology Abstracts must also be conducted.

A comprehensive search would normally include multiple and significant biomedical, pharmaceutical, food science, botanical, toxicological and alternative medicine databases.

Other major databases of relevant peer-reviewed literature are BIOSIS (Biological Abstracts), CHEMICAL ABSTRACTS, NAPRALERT, AMED (Allied and Complementary Medicine), CAB

ABSTRACTS, and SCISEARCH (Science Citation Index). These databases are available by subscription.

Depending on the nature of the application, specialist sources may have to be used. For example, if a product is of marine origin, the literature search may include databases of aquatic literature and pertinent standard references in marine science.

Terms identified in the chemical and constituent search should be a starting point for systematic searching. These should be combined appropriately with terms covering all the concepts detailed in the data requirement table.

If additional references are known or identified outside of the systematic search, these may be included, together with a brief explanation of how they were located.

Searches should not be limited to English, as many sources are in the language of country of use.

Recording the search strategy

When submitting an application, provide a summary report on the literature search including:

- a detailed description of the methodology, including the complete and unedited strategy used for any database searches For details of how to record a search see: [Systematic Reviews: CRDs guidance for undertaking systematic reviews in health care. Appendix 3, Documenting the search process.](#) York, UK; Centre for Reviews and Dissemination, January 2009. Sighted 7th Nov. 2011.
- a justification for the approach taken
- For the systematic search component, a full list of references retrieved, together with selection criteria for inclusion in or exclusion from the submission. Note there should be no discrepancy between the sets retrieved for the systematic search and the number of references reviewed.
- For the evidence of traditional use, a completed table of references with full bibliographic citations.

Compiling the evidence

The value of references to the application depends on their integrity, authority and scientific validity.

Full copies of selected papers and monographs in English must be submitted. Abstracts of papers are rarely suitable for use for evaluation. Where there are papers in other languages, certified translations should be provided.

Copies of secondary evidence, for example: from websites, are only supporting evidence if they reference the primary literature. It is expected that the primary references will be sourced and supplied in full.

5. Changes tables for registered complementary medicines

The [Changes tables](#) list [changes to a registered complementary medicine](#) that:

- can be requested under section 9D of the [Therapeutic Goods Act 1989](#) (the Act); or
- would result in a 'separate and distinct' good and therefore require an application to be made under section 23 of the Act; or
- do not require an application.

The required application type, required documentation and the types of assurances required for the changes are provided in the 'Changes tables'.

The codes used in the 'Changes tables' are provided in the 'Codes tables'.



Note: If you cannot find the change proposed for your medicine in the Changes tables, you should contact the TGA. The absence of the proposed change does not imply that you may proceed with the change without notifying the TGA.

Codes tables

The three codes tables below provide the meaning of the codes used in the [Changes tables](#)

Codes for APPLICATION TYPE	
Code	Meaning
AF	Application - Processing fee and evaluation fee is payable
AN	Application - Only a processing fee is payable
O	No application required. Changes with status 'O' have been included for completeness
NEW	Application for a new registration required
ASK	Contact the TGA

Codes for the types of DOCUMENTATION required in support of the application

Code	Meaning
E	Evidence to support the change where an ARTG entry is to be corrected
L	A copy of the current label plus a draft copy of the new label, with the relevant changes highlighted, have been supplied. If the medicine has a package insert, CMI and/or a PI, these documents (current and draft) should also be supplied when the change impacts on them
PI	A copy of the current Product Information (PI) of the product plus a draft copy of the new PI, with the relevant changes highlighted, have been supplied
P	The SUSMP schedule (or 'N' for unscheduled goods) for the new pack size is stated in the application form

Codes for the types of ASSURANCES required in support of the application

Code	Meaning
1	These fields are intentionally blank in order that the code numbering aligns with 'Guidelines on changes to OTC medicines'.
2	
3	
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 (quality) data or other product details 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 that 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 <i>Standard for the Uniform Scheduling of Medicines and Poisons</i> or <i>Required Advisory Statements for Medicine Labels</i> .
9	The nominated manufacturer is licensed to manufacture products of this type.

Codes for the types of ASSURANCES required in support of the application	
10	The container type (as defined in TGA Approved Terminology for Drugs) 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: a) neither the existing nor the new material is a modified starch b) the changeover has been validated c) at least 6 months stability data have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 months data at a temperature at least 10°C higher than the maximum recommended storage temperature d) stability testing will continue for the full term of the product's shelf life, any batches not meeting specifications will be withdrawn from the market immediately, and the CMB will be notified immediately.
13	a) The changeover has been validated and the sponsor is satisfied that the change will not adversely affect the stability of the product b) Stability testing will continue for the full term of the product's shelf life and the TGA will be advised immediately of any batches not meeting specifications.
14	No new text or graphics have been introduced.
15	The change of material is one of the following: a) polystyrene to PVC, polyethylene, polypropylene or glass b) PVC to polyethylene, polypropylene or glass c) polyethylene to glass or polypropylene of density ≥ 0.89 d) from one density of polyethylene to a higher density; or e) any change between glass, polyethylene of density ≥ 0.95 , and polypropylene of density ≥ 0.89 .
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.

Codes for the types of ASSURANCES required in support of the application	
18	The change to the plastic component is one of the following: a) PVC to PVC/PVDC or to PVC/PCTFE b) PVC/PVDC to PVC/PCTFE; or c) 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).
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.

Changes tables

Refer to the [Codes tables](#) for explanation of the codes used in the Changes tables.

Label changes

Code	Label changes	Status	Assurances / Documentation	Applicable section of the Act
	Proprietary name (may meet the criteria of the Groups order)	NEW	-	23
	New therapeutic indications (may meet the criteria of the Groups order)	NEW	-	23
LIW	Therapeutic indications or directions for use – change of wording without altering meaning	AF	4, L	9D(3)
LIS	Therapeutic indications – removal of subset of indications from label	AN	5, L	9D(2)
LIR	Therapeutic indications – addition of registered indications to label	AF	5, L	9D(3)
LDU	Change in directions for use- that only reduces patient population	AF	L	9D(2)

Code	Label changes	Status	Assurances / Documentation	Applicable section of the Act
	Change in directions for use – other than LIW or LDU – (may meet the criteria of the Groups order)	NEW	-	23
PSC	Recommended storage conditions – more restrictive	AN	5, L	9D(3)
PST	Recommended storage conditions – less restrictive	AF	5, L	9D(3)
LSR	Addition of more restrictive safety-related statements	AN	5, L	9D(2)
LSF	Changes on label (signal headings, warning statements) in compliance with new SUSMP requirements, where there is a change in scheduling	AF	5, L	9D(2)/9D(3)
LSU	Changes on label (signal headings, warning statements) in compliance with new the SUSMP requirements, other than LSF	AN	5, 8, L	9D(2)/9D(3)
LLO	Changes to bring a label into compliance with the Labelling Order – other than changes to the proprietary name, indications or directions for use	AN	5, 7, L	9D(2)/9D(3)
LLR	Addition of a required representation to a label (Part 2 of Schedule 2 to the Regulations)	AN	5, 7, L	9D(2)
LCF	Colour, font, type size only (no change in label copy)	AN	5, L	9D(3)
LGR	Introduction/removal of new graphics/icons (other than as specified in change SSP or KSP)	AF	5, L	9D(3)
LFO	Reformatting of pre-existing text (i.e. moving of blocks of text and not rewording – see LIW, LRT)	AN	5, L	9D(3)
LRT	Rewording of pre-existing text without altering meaning (other than indications or directions for use – see LIW or LDU)	AF	L	9D(3)

Code	Label changes	Status	Assurances / Documentation	Applicable section of the Act
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)	AF	L	9D(3)
LOC	Other changes	ASK	-	-

Sponsor changes

Code	Sponsor changes	Status	Assurances / Documentation	Applicable section of the Act
SSP	Sponsor name/logo/ sponsor address (same sponsor of goods) and/or change to manufacturer/supplier details on label	AN	5, L	9D(3)

Product detail changes

Code	Product detail changes	Status	Assurances / Documentation	Applicable section of the Act
PSZ	Pack size – other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) (see also KBT, KGL, KBL and KOT)	AN	5, 6, 10, L, P	9D(3)
PLS	Pack size – liquids/semi-solids	AN	5, 6, 10, 13, L, P	9D(3)
PMZ	Pack size – metered dose aerosols	AF	-	9D(3)
	Dosage form	NEW	-	23
PVI	Visual identification (note that novelty shapes, e.g. animal-shaped tablets, are not acceptable)	AN	5, 13, 19	9D(3)
PSL	Shelf life – increase (other than in change PSP)	AF	-	9D(3)
PSR	Shelf life – decrease	AN	5	9D(3)

Code	Product detail changes	Status	Assurances / Documentation	Applicable section of the Act
PSP	Shelf life – increase (in accordance with an approved stability testing protocol for that product)	AN	5, 11, 20	9D(3)
PPR	Approval of a stability testing protocol for a specific product	AF	-	9D(3)
PSC	Recommended storage conditions – more restrictive	AN	5, L	9D(3)
PST	Recommended storage conditions – less restrictive	AF	5, L	9D(3)
PMI	Sterility status/technique	AF	-	9D(3)

Formulation detail changes –active ingredient

Code	Formulation detail changes – active ingredient	Status	Assurances/ Documentation	Applicable section of the Act
	Addition or deletion of an active ingredient (including those in a proprietary ingredient)	NEW	-	23
AOV	Overage-decrease	AN	5	9D(3)
AOA	Overage-increase	AF	-	9D(3)

Formulation detail changes –excipient ingredient

Code	Formulation detail changes- excipient ingredients	Status	Assurances/ Documentation	Applicable section of the Act
	Addition, deletion or change in amount of an excipient ingredient (including, but not limited to a: fragrance, flavour, printing ink or colouring agent). This also applies to excipients in proprietary ingredients. (May meet the criteria of the Groups order)	NEW	-	23
EST	Type of starch	ASK	-	-

Quality control changes – finished product specifications changes

Code	Finished product specification change	Status	Assurances/ Documentation	Applicable section of the Act
QFX	Specification ranges – more restrictive	O	-	9D(3)
QFE	Specification ranges – less restrictive	AF	-	9D(3)
QFT	Addition of an extra test	O	-	9D(3)
QFU	Deletion of an existing test	AF	-	9D(3)
QFA	Analytical method – to comply with amendments to a default standard or a ministerial standard	ASK	-	-
QFB	Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)	ASK	-	-
QFC	Analytical method – other than as specified above in change QFB	AF	-	9D(3)
QFS	Expiry specification ranges following changes to a default standard or a ministerial standard	O	-	-

Quality control changes – starting material specifications changes

Code	Starting material specification change	Status	Assurances/ Documentation	Applicable section of the Act
QSX	Range – more restrictive	O	-	-
QSE	Range – less restrictive	AF	-	9D(3)
QST	Addition of an extra test	O	-	-
QSU	Deletion of an existing test	AF	-	9D(3)
QSA	Analytical method – to comply with amendments to a default standard or a ministerial standard	O	-	-

Code	Starting material specification change	Status	Assurances/ Documentation	Applicable section of the Act
QSB	Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)	ASK	-	-
QSC	Analytical method – other than as specified above in change QSB	AF	-	9D(3)
QSM	Manufacturer of starting material (specifications unchanged)	0	-	-
QSS	Supplier of starting material	0	-	-

Packaging changes

Code	Packaging change	Status	Assurances/ Documentation	Applicable section of the Act
	Container type	NEW	-	-
KBT	Container material – if the container is a bottle, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 15	AN	5, 10, 13, 15 & 16	9D(3)
KGL	Container material – clear to coloured glass	0	-	9D(3)
KBL	Container material – if the container is a blister pack, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 18	AN	5, 10, 13 & 18	9D(3)
KOT	Container material – other than in changes KBT, KGL or KBL	AF	-	9D(3)
KCL	Closure	AN	5, 13	9D(3)

Code	Packaging change	Status	Assurances/ Documentation	Applicable section of the Act
KSL	Tamper-resistant seal – addition (including label notice to alert consumers to presence of seal)	0	-	-
KSX	Tamper-resistant seal – removal (including removal of label notice re seal)	0	-	-
KWA	Inert wadding material – addition, substitution or removal where stability is not affected by the action	0	-	-
KDA	Desiccant – inclusion in container	AF	-	9D(3)
KDX	Desiccant – removal from container	AF	-	9D(3)
KPP	Specifications of primary pack (other than labelling)	0	-	-
KSP	Introduction of a measuring device (e.g. spoon, cylinder) or applicator (e.g. finger cot); this change can include graphical representation of the device on the label (copy of current and proposed label must be supplied if label is changed)	ASK	-	-
KMD	Changes to existing measuring device (e.g. spoon, cylinder) or applicator supplied with the goods, or removal of a measuring device or applicator, where other means of accurately measuring or applying the dose are readily available	ASK	-	-

Code	Packaging change	Status	Assurances/ Documentation	Applicable section of the Act
KPA	Introduction of a primary pack (no new text or graphics)	AN	5, 14	9D(3)
KPI	Introduction of a package insert	AF	L	9D(3)
KRI	Removal of a package insert	AF	L	9D(3)
	Changes to package insert text (see Label Change section)		L	-
KPX	Removal of a primary pack	AN	5, 17	9D(3)
KRP	Introduction of a refill pack	AF	-	9D(3)
KRR	Removal of refill pack	AN	-	9D(3)
MDA	Changes in pump or pump components of meter-dose aerosol (e.g. valve material)	AF	-	9D(3)

Manufacturing changes – finished product changes

Code	Manufacturing change	Status	Assurances/ Documentation	Applicable section of the Act
MMA	Addition or deletion of TGA-licensed Australian manufacturer (includes site of manufacture)	AN	5, 9	9D(3)
MSA	Addition or deletion of steps of manufacture of a TGA licensed manufacturer	AN	5, 9	9D(3)
MOS	Addition or deletion of an international manufacturer (includes site of manufacture)	AN	5, 9	9D(3)
MSO	Addition or deletion of steps of manufacture of an international manufacturer	AN	5, 9	9D(3)

Code	Manufacturing change	Status	Assurances/ Documentation	Applicable section of the Act
MPR	Manufacturing process (other than MBS)	AN	13	9D(3)
MBS	Batch size for pressurised inhalation (nasal and oral respiratory) products	AF	-	9D(3)
MUP	GMP clearance NUMBER update	ASK	-	

Consumer Medicine Information (CMI)

Code	CMI change	Status	Assurances/ Documentation	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 Regulations and is not to be included as a package insert*	0	-	-
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**	0	-	-

* Change KPI applies where the CMI is to be included as a package insert.

** Refer to the Label Change section for guidance on changes to a CMI where the CMI is to be supplied directly with the medicine (a CMI is treated as part of the label when it is on or attached to the goods; or on or attached to a container or primary pack in which the goods are supplied; or supplied with such a container or pack).

Product Information (PI) changes table

Code	Change	Status	Assurances / Documentation	Applicable section of the Act
DPI	Introduction of a PI for an existing product	AF	-	9D(3)
DRS	Addition of more restrictive safety-related statements	AN	5, PI	9D(2)
DOT	Changes other than the addition of more restrictive safety-related statements	AF	-	9D(3)

Other changes table

Code	Change	Status	Assurances / Documentation	Applicable section of the Act
CTA	Correction of ARTG record in accordance with section 9D(1) of the Act	AN	E, 5, 21	9D(1)
OTH	Other changes	ASK	-	-

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Reference/Publication #