



Australian Government
Department of Health
Therapeutic Goods Administration

Evidence guidelines

Guidelines on the evidence required to support indications for listed complementary medicines

Version 2.1, July 2014

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 <<https://www.tga.gov.au>>.

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Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Therapeutic Goods Administration, Office of Complementary Medicines	October 2001
V1.1	Change of format	Therapeutic Goods Administration, Office of Complementary Medicines	April 2011
V2.0	Revision	Therapeutic Goods Administration, Office of Complementary Medicines	March 2014
V2.1	Row 1, Table 6, page 41 correction of BMI range to state 25-30kg/m ²	Therapeutic Goods Administration, Office of Complementary Medicines	July 2014

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Guidelines on the evidence required to support indications for listed complementary medicines

Who are these guidelines for?

These guidelines provide information for sponsors and applicants:

- on the type of evidence that is required to support indications for listed complementary medicines; and
- to help you understand your regulatory obligations in relation to holding evidence to support indications for your medicine.

How are complementary medicines regulated in Australia?

Therapeutic goods that are imported or manufactured for supply in Australia are required to be included in the Australian Register of Therapeutic Goods (ARTG) by the *Therapeutic Goods Act 1989* (the Act) unless they are specifically exempted by the Therapeutic Goods Regulations 1990 (the Regulations).

Within the regulatory framework, complementary medicines are either listed or registered in the ARTG based on their ingredients and the indications made for the medicine. While some complementary medicines are registered, most are listed.

Listed medicines are considered 'low risk' medicines. The listing process allows for rapid market access for listed complementary medicines. Unlike registered medicines, the TGA does not evaluate listed medicines prior to inclusion in the ARTG.

Refer to the [Australian regulatory guidelines for complementary medicines \(ARGCM\)](#) for more information on the regulation of complementary medicines in Australia.

What are your regulatory obligations when you list a medicine on the ARTG?

Before you list a medicine in the ARTG, you must ensure that the medicine complies with all applicable regulatory requirements. When you apply to list your medicine via the online application portal¹, you, as the sponsor of the medicine, must certify that the medicine meets the regulatory requirements of:

- Section 26A(2)(a)–(k) of the Act; and
- subsection 26A(3) of the Act if your medicine is manufactured outside Australia.

The range of regulatory requirements includes that:

- your medicine only contains ingredients permitted for listed medicines
- you hold evidence to support any indications and claims made about your medicine; and
- the presentation of your medicine is not unacceptable.

¹ Refer to the [Listed medicines application and submission user guide](#) for information on the application and submission process

In relation to evidence for your medicine, Section 26A of the Act provides that you must:

- hold evidence to support your indications at the time the medicine was included in the ARTG
- retain that evidence at all times while the medicine remains listed; and
- provide that evidence to the TGA if requested to do so.

There are offences for making false statements in, or in connection with, a certification of any matter under subsection 26A(2) of the Act.

When will the TGA look at the evidence you hold for your medicine?

After listing in the ARTG, a proportion of listed complementary medicines are reviewed for compliance with the regulatory requirements. Your medicine may be selected for compliance review at any time after it is listed in the ARTG. For further information see [Listed complementary medicine compliance reviews](#).

Briefly, a compliance review of a listed complementary medicine involves:

- assessing information about the product against the relevant legislative requirements, including, where relevant, the certifications given by the sponsor at the time the product was listed; and
- taking appropriate actions when a breach of the legislative requirements is identified.

If your medicine is selected for a compliance review, you will be required to provide necessary information to the TGA. Evidence provided to the TGA for an 'evidence-based listing compliance review' must be sufficient to address all relevant regulatory requirements.

The TGA may take regulatory action (including cancellation of the listing in accordance with section 30 of the Act), if it is found that any of the certifications (among other things) made at the time of listing were incorrect.

What are the types of evidence for listed medicines?

Evidence used to support indications for listed medicines is usually sourced from the available open literature, rather than from clinical trials specifically conducted with a particular medicine².

Depending on the proposed indication, the evidence will be sourced from scientific literature or based on a history of traditional use.

What information do these guidelines contain?

The document is comprised of two parts:

Part A provides guidance on:

- the types of indications and evidence sources

² If you wish to conduct clinical trials on your medicine - information is available from the [National Health and Medical Research Council \(NHMRC\) website](#).

- how to assess the relevance, quality and balance of scientific evidence
- how to assess the credibility and relevance of evidence of traditional use; and
- how to obtain, record and present the evidence that supports your indication/s.

Part B provides additional technical guidance:

- to help you assess the relevance, quality, outcomes and overall balance of currently available scientific evidence; and
- on the evidence required for indications relating to weight loss, biomarkers and nutritional supplementation.

Evidence package checklists are available on the TGA website to help you assess, record and present the available evidence for the indication/s for your medicine. Appendix 1 provides assistance for completing the checklists.

TGA disclaimers

- This document is a guide only. It is the responsibility of each sponsor to understand and comply with the regulatory requirements contained in the Act and supporting regulations. You are encouraged to seek your own professional advice to find out how therapeutic goods legislation and other applicable laws apply to you.
- Indications used in these guidelines have been provided as examples only. These indications do not relate to actual medicines and whether there is evidence to support the indications has not been assessed by the TGA.
- These guidelines reflect the TGA's approach to assessing evidence to support indications for listed complementary medicines during compliance reviews. However, there may be specific circumstances that justify a departure from the evidence guidelines and in this situation the TGA will consider the merits of each case against the regulatory requirements.
- This document will evolve over time and updates and clarifications will be included as required.



Part A: Evidence to support indications for listed complementary medicines

Indications for listed medicines

What is an indication?

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*'.

The indication of a medicine is its claimed purpose or health benefit, for example: 'relieves coughs'.

What is not an indication?

Statements or claims which do not convey a specific therapeutic use such as references to the properties of the product or the packaging are not considered to be therapeutic indications. Some examples are:

- 'contains 25% more'
- 'new formula'; and
- 'high in vitamin C'.

Indications must be included in the ARTG entry for a medicine, whereas other claims not related to therapeutic use are not required to be in the ARTG. However, sponsors must hold evidence to support both indications and other claims for their medicine.

Any statement you make in relation to the medicine, such as marketing claims, must be truthful, factual and not misleading. Refer to the [Therapeutic Goods Advertising Code \(TGAC\)](#) for details of advertising requirements.

What indications are suitable for use in listed medicines?

Consistent with their low risk, listed complementary medicines may only carry appropriate indications that will not lead to their unsafe or inappropriate use.

When listing a medicine, you must certify³ that the medicine is eligible for listing. To be eligible for listing (pursuant to Schedule 4 of the *Therapeutic Goods Regulations 1990*), the indications for the goods must not refer to the treatment of specified types of diseases, conditions, ailments or defects⁴.

In addition, to be included on the label, an indication must not refer to a serious form of those diseases, conditions, ailments or defects without prior approval by the TGA⁵. Serious forms include conditions which are generally accepted not to be diagnosed, treated or managed safely without the assistance of a qualified healthcare practitioner.

In general, an indication suitable for use in listed medicines:

³ Section 26A(2)(a) *Therapeutic Goods Act 1989*

⁴ The diseases, conditions, ailments or defects are listed in Appendix 6 of the *Therapeutic Goods Advertising Code 2007*.

⁵ Part 5(2) of the *Therapeutic Goods Advertising Code 2007*.

- will describe a specific therapeutic use
- may refer to health maintenance and/or health enhancement
- may not refer to the treatment or cure of a disease, ailment, defect or injury; and
- may not refer to a serious form of a disease, ailment, defect or injury.



Indications not suitable for listed medicines

In general, indications that refer (explicitly or implied) to the treatment, or cure of diseases, conditions, ailments or defects are **NOT** suitable for use in listed medicines.

In specific circumstances, the TGA may allow indications for listed medicines to refer to serious forms of conditions (referred to as [restricted representations](#)) where it is considered in the public interest to do so. This can occur upon [application by the sponsor for approval to use a restricted representation](#) under s 42DK(1) of the Act.

Should a sponsor wish to make a high-level indication for their medicine, then the product is required to be registered and must undergo full pre-market evaluation by the TGA for quality, safety and efficacy.

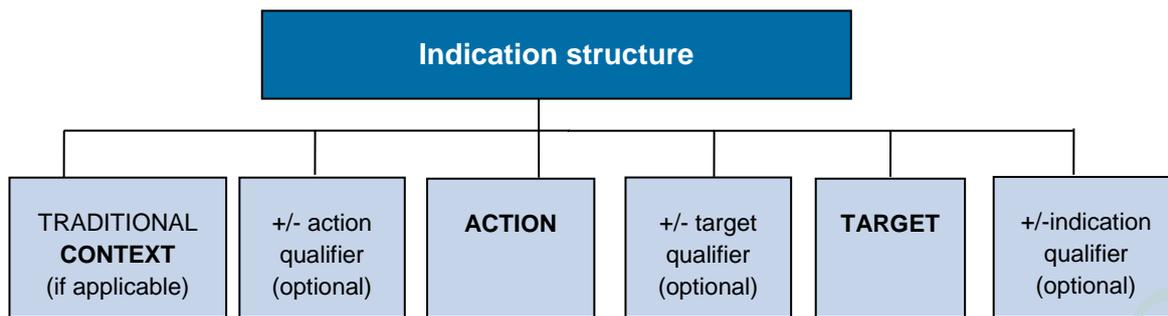
What does an indication look like?

An indication must describe the specific therapeutic use(s) of the goods. An indication is made up of the components listed in Table 1.

Table 1: Components of an indication

Component	Explanation	Examples
Context of traditional use (where applicable)	For traditional indications , the indication must include a statement providing the 'context of traditional use, which is the traditional paradigm. A statement of 'traditional context' is not required for scientific indications .	'Traditionally used in Western herbal medicine...' 'Traditionally used in Chinese herbal medicine...'
Action	The action or effect.	Reduces; prevents; improves; maintains; stimulates
Target	The target may be a biological factor or process, a health state or a clinical condition. Targets may be non-specific or specific.	Non-specific targets: 'general health and wellbeing'; 'growth and development' Specific targets: headache; fever; joint pain
Additional qualifying terms (optional)	Additional qualifying terms may be included to provide information relating to the action, the target or the indication context (of therapeutic use).	Action qualifiers: helps; assists Target qualifiers: mild; healthy Indication qualifier: 'in postmenopausal women'

The structure of an indication is provided in Diagram 1.

Diagram 1: Indication structure

Examples of indication structure

'Traditionally used in Western herbal medicine (context) to help (action qualifier) reduce (action) mild (target qualifier) nausea (target) in pregnant women (indication qualifier)'.

'For the temporary (action qualifier) relief (action) of mild (target qualifier) headache (target)'.



An indication that does not clearly specify the tradition it belongs to is, by default, scientific and is required to be supported by scientific evidence.

What are the different types of indications?

Indications for listed medicines are either [traditional](#) or [scientific](#), based on the type of evidence supporting the indication.

Traditional and scientific indications are further classified into ['non-specific' or 'specific'](#) sub-types depending on the how the indication is phrased.

What are traditional indications?

Traditional indications belong to a recognised paradigm outside modern conventional medicine. Traditional medicine is an integral part of many cultures and includes a diverse range of health practices, approaches, knowledge sets and belief systems relating to medicines. Examples of traditional medicines include:

- Traditional Chinese Medicine (TCM)
- Aboriginal and Torres Strait Islander healing practices
- Ayurvedic medicine
- Western herbal medicine
- Homoeopathic medicine
- Aromatherapy; and
- other indigenous medicines.

Traditional indications must indicate that the health benefit is based on long-term use and experience in a specific traditional paradigm. As traditional indications are not based on scientific evidence, they cannot imply efficacy in a clinical setting.

Examples of traditional indications:

'Traditionally used in Chinese medicine to 'resolve phlegm' to relieve cough'.

'Traditionally used in Western herbal medicine to relieve nasal congestion'.

'Traditionally used in Homoeopathic medicine to improve appetite'.

'Traditionally used in Ayurvedic medicine to support healthy immune function'.

What if your traditional medicine includes multiple ingredients?

For medicines that have multiple active ingredients from the same traditional paradigm, indications can be linked to individual ingredients or relate to the entire medicine (if the indications for each ingredient are traditionally used for the same health benefit).

Example of a traditional indication for multiple ingredients from the same paradigm:

'The ingredients in this medicine are traditionally used in Western herbal medicine to maintain a healthy liver function'.

What if your medicine includes multiple ingredients from different traditional paradigms ('multiple traditional paradigm medicine')?

If all the active ingredients from the different traditional paradigms are traditionally used for the same health benefit, the indication/s can be applied to the whole medicine. Alternatively, an indication can be provided for each individual ingredient.

Example of a traditional indication for a 'multiple traditional paradigm medicine':

'Ingredients in this medicine have traditionally been used in Ayurvedic and Chinese medicine for relieving common cold symptoms'.

Example of individual indications for different ingredients in a 'multiple traditional paradigm medicine':

'Trichosanthis kirilowii (tian hua fen) is traditionally used in Chinese medicine to 'clear and drain lung heat' to help relieve chest congestion' and

'Ocimum tenuiflorum is traditionally used in Ayurvedic medicine to help remove excess 'kapha' (mucus) from the lungs and nasal passages'.

What are scientific indications?

Scientific indications belong to conventional modern medicine and are supported by scientific literature, such as clinical studies or systematic reviews (refer to ['Do you have scientific evidence?'](#)).

Examples of scientific indications:

'Helps relieve common cold symptoms.'

'Helps maintain blood circulation to the peripheral areas of the body.'

'Assists in the management of mild acne pimples.'

'Helps support a healthy immune system.'

What if your medicine has a combination of traditional and scientific indications ('cross evidence base medicine')?

A medicine with a combination of scientific and traditional indications (a 'cross evidence base' medicine) requires scientific evidence to support the scientific indications and evidence of traditional use to support the traditional indications.

Example of indications for a medicine that has cross paradigm indications:

A medicine that contains *Panax ginseng*, *Bacopa monnieri* and folic acid may have the following indications (if supported by appropriate evidence):

'This medicine has been formulated from traditional and non-traditional ingredients, to help support a healthy memory, specifically:

Panax ginseng is traditionally used in Chinese medicine to tonify qi (vital energy) and support memory in times of fatigue.

Bacopa monnieri is traditionally used in Ayurvedic medicine to improve memory.

Folic acid helps support cognitive function'.

What are the indication sub-types (specific or non-specific)?

Traditional or scientific indications can be further classified into two sub-types:

Sub-type 1: Non-specific (general indications)

Non-specific indications refer to general health and wellbeing, such as:

- health maintenance
- relief of symptoms not related to a named condition; and
- general vitamin, mineral or nutritional supplementation.

Sub-type 2: Specific indications

Specific indications refer to health benefits beyond general health and wellbeing, such as:

- health enhancement
- reduction of risk or frequency of a named condition or symptoms
- management or relief of symptoms linked to a named condition; and
- nutritional supplementation claims linked to a specific therapeutic benefit.

Whether using traditional or scientific indications, the specificity of your indication determines the level of evidence required to support your indication (refer to ['What level of indication does your traditional evidence support?'](#) and ['What level of indication does your scientific evidence support?'](#))

Tables 2a and 2b provide examples of specific and non-specific indication sub-types.

Table 2a: Non-specific indications for listed medicines

Non-specific indications (scientific or traditional)		
Health benefit	Definition of health benefit	Example of an indication
Health maintenance	Normal physiological effects of substances in growth, development and normal functions of the body.	<i>'Helps maintain general health and wellbeing'</i> <i>'Traditionally used in Ayurvedic medicine to support a healthy digestion function'.</i>
Relief of general symptoms	Symptoms not related to a named condition	<i>'Helps soothe dry skin'</i> <i>'Traditionally used in homoeopathic medicine to relieve muscle aches and pains'.</i>
General nutritional supplementation (scientific indications only)	Supplementation with vitamins, minerals or other essential nutrients (for example: a source of calcium) that imply a general health benefit such as the maintenance of good health. Note: to make a supplementation claim for a named vitamin or mineral, the product must provide at least 25% of the recommended dietary intake (RDI) for that vitamin or mineral.	<i>'Provides vitamins and minerals to help support the body's nutritional needs'</i> <i>'Provides vitamin A to help maintain healthy hair and skin'.</i>

Table 2b: Specific Indications for listed medicines

Specific indications (may be scientific or traditional)		
Health benefit	Definition of health benefit	Example of an indication
Health enhancement	Specific beneficial effects of nutrients and other substances on the physiological and psychological state of the body above and beyond normal growth, development and functions of the body.	<i>'Helps increase blood circulation to the peripheral areas of the body (hands and feet).'</i> <i>'Traditionally used in Chinese medicine to stimulate digestion'.</i>

Specific indications (may be scientific or traditional)		
Reduce risk or frequency of a named condition, symptoms or discrete event	Reduce the risk of a specified, non-serious illness, condition, disease or disorder.	<i>'Helps reduce the risk/ occurrence of indigestion'. 'Traditionally used in Chinese medicine to reduce the occurrence of common colds.'</i>
Management or relief of symptoms linked to a named symptom/disease/disorder condition.	Reduces the frequency, duration and/or severity of a symptom or cluster of symptoms associated with a named illness.	<i>'Helps relieve mild dermatitis itchy red skin'. 'Traditionally used in Western herbal medicine to reduce common cold symptoms'.</i>
	Improved quality of life without resolution of the underlying non-serious illness, condition, disease or disorder.	<i>'Assists in management of mild/moderate indigestion abdominal bloating'. 'Traditionally used in Western herbal medicine to relieve arthritic joint pain'.</i>
Supplementation indications linked to a specific therapeutic benefit (scientific indications only)	If a supplementation indication is linked to a specific therapeutic benefit, additional supportive scientific evidence is required (as well as the requirement to provide 25% of the RDI for that nutrient).	<i>'Helps prevent dietary vitamin B12 deficiency'. 'Assists in the management of medically diagnosed dietary vitamin B12 deficiency'. 'Provides calcium to improve bone strength'.</i>

Evidence to support indications for listed medicines

The term 'evidence' refers to both information and evidence as described in paragraph 26A(2)(j) and subsection 28(6) of the Act.

As the sponsor of a listed medicine, you must hold evidence to support all the indications you make for your medicine at the time you list the medicine in the ARTG. The evidence you hold must adequately support all indications and demonstrate all claims made for the medicine are true, valid and not misleading. You must keep that evidence for the whole time the medicine remains listed and provide it to the TGA if requested to do so [as provided by subsection 26A(2)(j) and 28(6) of the Act].

What type of evidence do you have to support your indication?

Before deciding the indication/s for your medicine, you must determine the type of evidence you have on which to base the indication. That is, do you have evidence of traditional use or scientific evidence? And, is the evidence you hold supportive of a specific or non-specific indication?

Your evidence must:

- have the same meaning and intent as the proposed indication

- be related to the same medicine or active ingredient/s; and
- have the same therapeutic action and the same context, for example: the same target population or same traditional paradigm.

Where there are differences between the ingredient and reported therapeutic benefit, a justification will be required in your evidence package to address the discrepancy.

Do you have evidence of traditional use?

Traditional medicines are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation and underpins the use of these medicines in a traditional setting. Usually when a medicine or a relevant ingredient in the medicine has been used over a long period of time its dosage and formulation have been refined by experience to maximise therapeutic effectiveness and minimise risk.

Evidence of traditional use for an indication needs to show that the medicine or the relevant ingredients in the medicine have a significant history of use in the specified tradition for the specified therapeutic purpose. You are required to hold documentary evidence that your medicine or its active ingredient has been used for at least three generations (at least 75 years) in the tradition it belongs to. This will establish that it belongs to that tradition and that there is an accumulated repository of observations in humans that underpins the use of the medicine.

For many traditional medicines there has been little quantifiable scientific research, scientific assessment or scrutiny undertaken on the medicine's mode of action or effect. It is inappropriate to use evidence of traditional use to support a scientific claim of efficacy, a mechanism of action or an underlying physiological process, as these are required to be supported by scientific evidence.

If you have determined that the evidence you have is traditional, ['What evidence do you need to support your traditional indication?'](#) provides guidance on compiling your evidence package.

Do you have scientific evidence?

Scientific evidence refers to quantifiable data and usually includes reports of clinical trials in humans, human epidemiological studies, animal studies and other cellular or pharmacological studies. Due to the quantifiable nature of scientific evidence, scientific indications can imply clinical efficacy where the indication is supported by such data.

Examples of scientific evidence include:

- systematic reviews
- reports of clinical studies
- peer-reviewed published review articles; and
- pharmacopoeias and monographs.

If you only have non-clinical studies, cellular or pharmacological studies, these alone are not considered sufficient evidence to support a scientific indication. However, such studies can be used to provide secondary support to human data.

If you have determined that the evidence you have is scientific, ['What evidence do you need to support your scientific indication?'](#) provides guidance on compiling your evidence package.

Do you have a combination of scientific evidence and a history of traditional use (cross-evidence base medicine)?

It is possible for a listed medicine to have scientific and traditional indications where there is a combination of traditional and non-traditional ingredients (cross-evidence base medicine) with a similar therapeutic purpose. Also, it is possible that an ingredient in a cross-evidence base medicine may have evidence of traditional use that is also supported by current scientific literature (cross-evidence base ingredient).

Each scientific or traditional indication requires supportive evidence and the indications must indicate the evidence source (that is, traditional indications must include the [traditional context](#) of use).

If you have a combination of scientific and traditional evidence for your medicine, '[Cross-evidence base medicine: What evidence do you need to support your medicine with a combination of traditional and scientific indications?](#)' provides guidance on compiling your evidence package.

How to source, assess, record and present evidence to support your indication

Before listing your complementary medicine, you should compile an evidence summary to support your traditional, scientific or 'cross evidence base' indications. Your evidence summary should show that you have conducted an objective, comprehensive, transparent and robust review of the literature relating to your indication. The resulting evidence you hold should be of high quality, credible and relevant to your medicine.

[Evidence package checklists](#) available on the TGA website help you sift through the available literature to identify what is appropriate evidence and exclude what is not. The checklists will assist you to collate and compile your evidence summary and determine which evidence items are credible, relevant and of high quality.

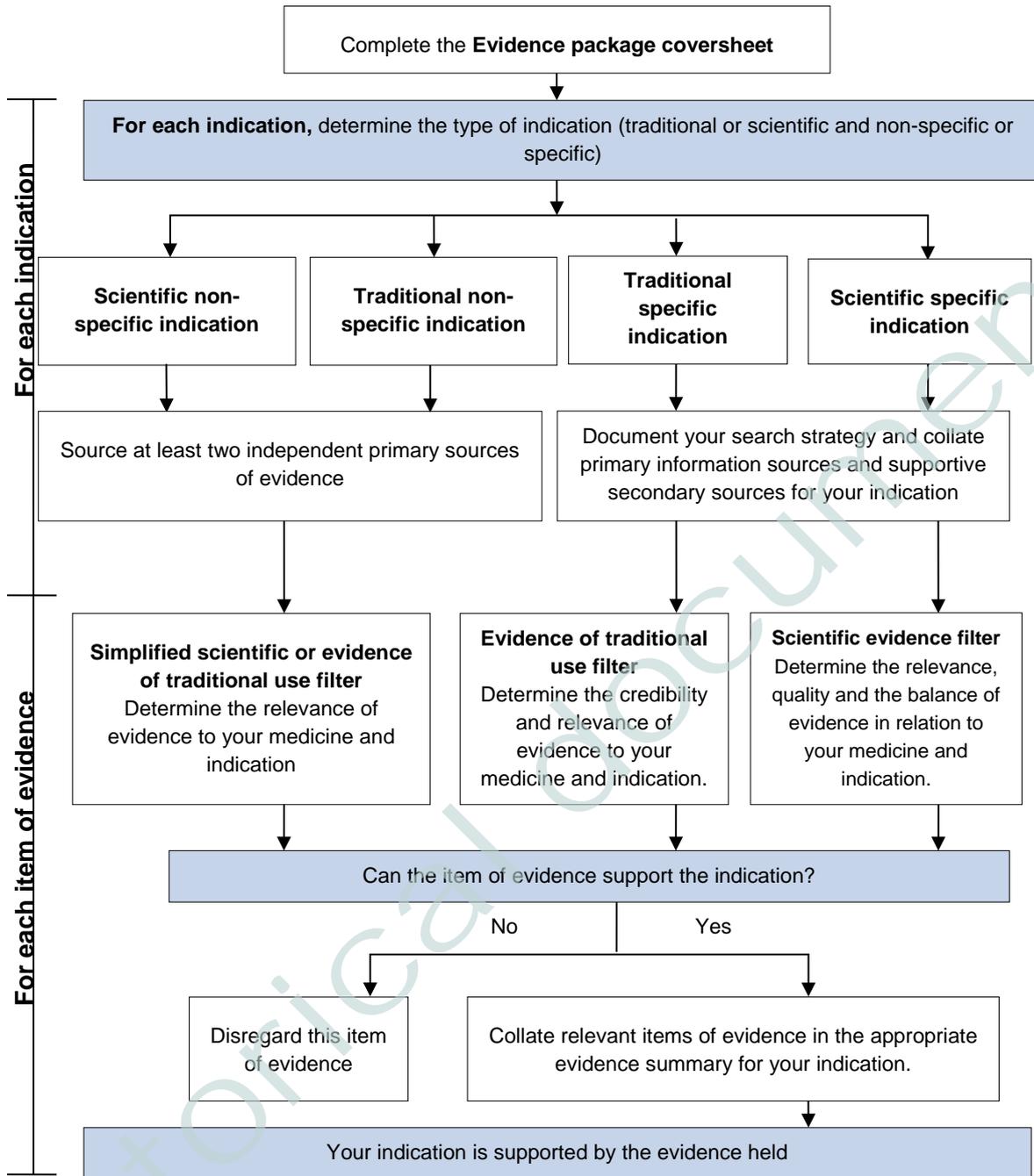
As a mechanism of establishing that you have the evidence to support your indications, you should consider completing the appropriate checklists for your medicine and associated indications, before listing your medicine on the ARTG. You should hold all the information contained within the checklists for your medicine and submit this information to the TGA when requested to do so.

During a compliance review of your medicine, the TGA may request the evidence you hold to support the indications you make for your medicine. At this time, you may include the appropriate checklists (or similar information) as part of your response to the TGA's request for information. While presenting your information in the provided checklist format is not mandatory, submitting information in this format will help facilitate and expedite the compliance review process.

Diagram 2 provides a general flow chart on the steps for compiling your evidence package for your listed medicine. Detailed guidance on compiling traditional or scientific evidence packages is provided in:

- [How to compile a summary of the evidence to support your traditional indication](#)
- [How to compile a summary of the evidence to support your scientific indication.](#)

Diagram 2: Compiling an evidence package to support the indication/s for your listed medicine



Traditional indications: what evidence do you need to support your traditional indication?

Evidence of traditional use

Traditional indications present factual statements of a health benefit relating to a historical record of use within a traditional paradigm. Traditional indications cannot make a scientific claim of efficacy; as such indications require supportive scientific evidence.

Evidence of traditional use to support your traditional indication can be based on the medicine itself as a whole, or on evidence for the individual ingredient about which the indication is made. Each ingredient should be clearly identified and you must hold evidence for each indication. If you chose a traditional indication that is linked to a specific ingredient in the medicine's formulation, then that ingredient should be linked to that indication on the medicine's label.

To claim evidence of traditional use you should ensure that your medicine or ingredient is an established part of a tradition of medicinal use within a particular paradigm or culture for over three generations.



Evidence of traditional use

Traditional indications are based on evidence of a history of medicinal use of the ingredients or medicines that exceeds three generations (75 years) of use.

Many traditional ingredients have a well-established period of widespread traditional use extending well over 75 years, which is extensively recorded in recognised evidence sources for traditional medicine such as *materia medica*, monographs and publications from various international regulatory authorities.

Factors that should be taken into account to establish that a medicine or active ingredient has a well-established tradition of use for its intended purpose include the:

- time over which the medicine or active ingredient has been used
- therapeutic use/s during that time
- continuity of its use
- geographical extent of its use ; and
- use of the medicine is recorded in recognised traditional medicine evidence sources.



Well established traditional of use

Traditional indications based on

- evidence of a history of widespread medicinal use of the ingredient/s or medicine that well exceeds three generations of use (75 years); and
- the traditional use is extensively recorded in internationally recognised evidence sources for traditional medicine use.

If the traditional indication is non-specific (general) and is associated with a well-established tradition of use for a particular ingredient or medicine, then the evidence to support the traditional indication is easier to assess and establish.



Homoeopathic medicines

[Homoeopathic medicine](#) is a traditional paradigm where the manufacturing process of serial dilution and succussion or serial trituration is a major component of the tradition of use. Provided that a substance is prepared according to principles described in a recognised homoeopathic pharmacopoeia and safety requirements are satisfied, indications may be based on traditional use. Evidence of traditional use for homoeopathic medicines can include independent written histories of use in traditional or contemporary homoeopathic literature.

[Evidence package checklists](#) will assist you in compiling an evidence package for your traditional indication.

Multi-traditional paradigm medicines

A listed medicine may contain multiple traditional ingredients that are supported by evidence of therapeutic use within different traditional paradigms (multiple traditional paradigms). Each indication must be supported by evidence and include the traditional context of use (see traditional context in [‘What does an indication look like?’](#)).

The resulting medicine or formulation is not traditional in the context of either of the original traditional paradigms. For example, an ingredient from traditional Chinese medicine may be combined with another ingredient from traditional Ayurvedic medicine. However, since the new formulation is neither a traditional Chinese nor Ayurvedic medicine, the formulation as a whole cannot claim a history of use. Therefore, each indication must refer to the relevant ingredient and specify the traditional paradigm of use.

Your evidence package should include a rationale for the combination of the ingredients in the new formulation which is justifiable in terms of therapeutic use; this includes the dose of each ingredient based on their respective traditional uses.

Example of a traditional indication for a multi traditional paradigm medicine:

‘These herbs are used traditionally in Chinese medicine and Ayurvedic medicine to promote relaxation.’

What are the sources of evidence of traditional use?

Many traditional medicines and ingredients with a long and coherent history of use are well documented in monographs, *materia medica* and other texts. Some traditional medicine paradigms have been recorded by people outside the tradition’s indigenous origin and culture. Other traditional medicine paradigms, particularly those that have been developed within smaller and more localised groups are not well documented; rather they are based on knowledge transmitted orally from generation to generation.

In some instances, you may need different sources of evidence of traditional use to support a particular indication for a traditional ingredient or formulation. Together these sources should form a combined collective of evidence that will be relevant and of high quality.

Note that in general, web searches will not provide sufficient evidence to substantiate traditional indications.

What are the primary sources of evidence of traditional use?

Primary sources of evidence to support traditional indications for your medicine can be derived from sources such as:

- *materia medica*
- official pharmacopoeias
- monographs
- publications from various international regulatory authorities
- texts that are relevant to the traditional paradigm; and
- well recognised evidence-based reference texts.



A pharmacopoeia contains a comprehensive list of medicines and describes their properties and how they are prepared.

A materia medica sets out the body of knowledge on the therapeutic properties of medicines. Different materia medica relate to different types of complementary medicines, for example: Traditional Chinese Medicine and homoeopathy.

While the TGA does not have a list of approved sources of information, [Appendix 3](#) provides some examples of internationally recognised resources and texts.



Each item of evidence must be considered on its own merit in relation to your medicine. An item of evidence can only be considered a primary source of evidence if it establishes a tradition of use and is credible and relevant for your medicine/indication.

Some monographs refer to clinical studies or pharmacology of a particular ingredient using citations and reporting study outcomes of auxiliary scientific papers. Such information would be considered a secondary source of scientific evidence and is often associated with scientific indications. Such information is not consistent with evidence of tradition of use and traditional indications.

Can non-reference textbooks be used as sources of evidence?

Non-reference textbooks cite, comment on or build on primary sources of evidence. As such, non-reference textbooks do not usually provide sufficient evidence to substantiate traditional indications. If you use a non-reference textbook, you should locate the original or primary source of evidence of traditional use; that is find copies or quotations from the original documents cited in footnotes. If this is not possible then include the footnotes in your evidence summary to clearly indicate that the textbook is based on original historic records.

Where it is impossible to find the original reference that describes the traditional use, evidence of traditional use may be supported by more recent references reporting the original tradition. However, these references should provide enough information to support that your medicine is consistent, as far as possible, with the one described in the original reference.

Can you use modern textbooks and monographs to support your traditional indication?

Many modern textbooks and monographs include a combination of both traditional and scientific evidence. If you are using a textbook, monograph or similar source to support an indication, you must determine whether the information in the source is traditional (over three generations of use) or scientific.

In a situation where a traditional indication is used in combination with a scientific statement relating to the mechanism of action of the ingredients, the combined indications must not imply clinical efficacy unless supported by primary sources of scientific evidence.

Mechanistic studies [*in vitro* studies or non-clinical (animal studies)] are types of secondary sources of evidence and are appropriate to provide information regarding the biological plausibility of a mechanism of action. However, non-clinical studies are rarely a supportive form of evidence in isolation and cannot be used to imply efficacy of a medicine in the absence of clinical studies.

Can you use independent written histories to support your traditional indication?

When supporting evidence includes independent written histories of use in the classical or traditional literature (such as in relation to oral evidence or testimonials), the significance and clarity of references to any health benefit should be assessed by whether the:

- traditional paradigm is defined
- ingredient(s)/medicine is/are fully characterised (for example: chemically, biologically)
- preparation is described
- dose and dosing details are documented
- route of administration is specified
- target population is defined; and
- traditional indication is described.

Can you use evidence in languages other than English to support your traditional indication?

Evidence in a language other than English can be used, if you provide in your evidence package a:

- copy of the relevant pages in the original language; and
- verified English translation of the relevant pages.

A verified translation is one that is accompanied by a signed statement from an accredited translator, fluent in both languages, verifying that the translation is true and complete.

Are there any other evidence sources you can use to support your traditional indication?

If the traditional indication is from an oral culture, video footage (stored in a digital format, not on film) may be appropriate. To be regarded as high quality, oral evidence must be corroborated from at least two separate sources in different locations.

Assessing the relevance of evidence to your indication

You must ensure that the evidence of traditional use for your indication is comparable to your medicine in terms of:

- ingredient/s
- method of preparation
- dosage; and
- conditions of use (route of administration, frequency and duration of use, target population and risks).

In general, active ingredients may be considered as sufficiently identical if there are no relevant differences in the method of preparation and if the medicine has the same intended purpose, dosage and the same route of administration. This includes traditional medicines in which the therapeutic indication, dosage and administration are based on traditional knowledge but the dosage forms have been modified to modern dosage forms, for example: capsules or tablets.

When evidence relates to an herb or herbal substance, the species (and subspecies where applicable), plant part and route of administration should be identical to that described in the evidence. The method of preparation and processing, the equivalent dry weight and the dose of active component used described in the evidence should be consistent with that in the medicine. Traditional methods of preparation include:

- the use of a whole organism or specific parts (leaf, root, fruiting body, etc.)
- fresh, dried, or preserved with alcohol, honey or sugar
- extracts produced by the application of pressure to the source material
- aqueous extracts such as infusions, decoctions and syrups
- ethanol-based extracts such as tinctures
- glycerine-based extracts
- vinegar-based extracts
- oil, grease or fat-based infusions; and
- beeswax salves and ointments.

Other methods of preparation may be considered traditional if supported by an appropriate reference describing the use of the method within the traditional medicine paradigm. However, non-traditional methods of preparation of otherwise traditional materials, including the use of non-traditional solvents, can change the chemical profile of the preparation. Such changes may affect the efficacy (and safety) of the product. Medicines that have been altered significantly in their constituent profile from the traditional medicine on which the indication is based will require scientific evidence to substantiate their claimed action.

Additional guidance on the [equivalence of herbal extracts in complementary medicines](#) is available on the TGA website.

Medicinal preparations described in early pharmacopoeias, *materia medica* and other traditional references may pre-date modern analytical techniques. These are unlikely to provide a comprehensive and satisfactory specification (for the characterisation and establishment of the quality of the ingredient or medicine). In such situations, your active ingredients and method of preparation should be identical to that described in the classical literature.

Modification of traditional formulations

Modification to the traditional formulations in Traditional Chinese Medicine (TCM) and Ayurvedic medicine should ensure that the traditional method of preparation, traditional formulation principles and dosage for the therapy remain in order for these medicines to make a traditional indication.

That is, to meet the criteria for a traditional claim using a history of TCM use, the overall medicine formulation should reflect the traditional principles of ingredient combinations or substitution of herbal species.

For traditional ingredients or medicines which have been altered significantly in their constituent profile from the classical traditional medicine on which the indication is based, further information may be required to justify the alteration in order to substantiate their claimed indication.

What indication sub-type does your evidence of traditional use support?

The [sub-type of the indication](#) will affect the level of evidence required to substantiate the indication. The more non-specific the traditional indication, the greater likelihood that the evidence to support the indication can be found in [primary sources of evidence of traditional use](#) and the more straightforward the evidence assessment process will be.

Table 3 provides information on the level of evidence generally required to substantiate non-specific and specific traditional indications.

Table 3: Levels of evidence generally required to support sub-types of traditional indications

Level of indication	Evidentiary support required
Traditional non-specific (general) indications	Two primary sources of evidence of traditional use .
Traditional specific indications	At least two primary sources of evidence of traditional use as well as other relevant and credible items of evidence to support the specificity of the indication.

An example of a non-specific indication for a traditional ingredient:

Allium sativum (garlic) (that has a well established tradition of use): ‘Traditionally used in Western herbal medicine to support immune system function in healthy individuals’.

An example of **non-supportive** evidence for a traditional specific indication:

A listed medicine contains a number of herbs commonly used in TCM and has the indication: ‘Traditionally used for the symptomatic relief of heartburn’.

The only evidence the sponsor holds that the ingredients have a tradition of use within TCM is a copy of the relevant pages from a contemporary Chinese reference that indicate one of the herbs present in the medicine was used in ancient times for symptoms such as ‘*stomach fire with rebellious stomach qi*’. However, there is no information on the plant part of the herbal species used, the method of preparation or the recommended dosage.

In this instance, the evidence item is not sufficient to support the proposed indication at the dose recommended.

An example of **supportive** evidence item for a traditional specific indication:

A listed medicine contains a number of herbs commonly used in TCM and has the indication: *'Traditionally used for the symptomatic relief of dry cough'*.

All ingredients are included in the *Pharmacopoeia of the People's Republic of China* (PPRC). The formulation is referred to in a TCM *Materia medica*. Ingredients in the medicine are the same plant part, preparation type and quantity as that referred to in the traditional formula in the *Materia medica*. However, one of the herbal ingredients is not a permitted ingredient in listed medicines in Australia. This ingredient has been substituted in the medicine available in Australia by another herbal ingredient, which is listed in the PPRC as a widely accepted medicinal substitute for the original herbal ingredient.

In this instance, this evidence item is likely to support the proposed indication.

Choosing or deciding upon your traditional indication

Due to the discordance between traditional and contemporary contexts and the potential for consumers to assume that medicines have been assessed scientifically, traditional indications are required to include the traditional context of use in the indication (refer to ['What does an indication look like?'](#)). Evidence of traditional use must clearly identify the traditional paradigm which it refers to, and this context must be conveyed clearly to the consumer. When traditional use is limited to a particular paradigm or geographical region, then this limitation must be referenced in the indication.

Compare your chosen indication with the reported health benefit and context of use in your evidence of traditional use. Your indication should have the same meaning and intent specified in the evidence (including any traditional terminology). The terms used in your indication should be consistent with the specified paradigm to ensure that the indication is not misleading and appropriately supported by the evidence you hold. The use of common English terms in addition to traditional terminology provides clarity to the average consumer regarding the therapeutic use of the medicine.

You should ensure that each ingredient (for which a traditional indication is made) has been prepared using a traditional method for that paradigm (for example: dilution and succussion of mother tinctures for homeopathic medicines). Where your medicine has been modified from a classic formula or individual ingredient –you should show that the formula or ingredient, as modified, is still acceptable within the specified tradition.

When choosing or deciding upon your traditional indication **you should:**

- clearly identify the traditional paradigm that supports the traditional formulation
- base any statement about the medicine's therapeutic benefit on experiences or theories specific to the particular tradition, not on scientific clinical evidence; and
- use the same logic and terminology (in English terms or accompanied by English terms) that belongs to the specified traditional paradigm.

Your traditional indication **should not:**

- refer to anatomical, physiological or pharmacological effects that are not envisaged within the specified paradigm, for example: *'raise haemoglobin levels'*
- imply efficacy based on scientific evidence for the medicine, for example: *'clinically tested'*

- use specialist terminology that belongs to a different paradigm, for example: '*damp heat*' is a specific Chinese medicine term and would be inappropriate for an Ayurvedic medicine
- include indications that require scientific substantiation, for example: '*assists to increase bone density by 10%*'; or
- refer to conditions that cannot be diagnosed within the specified paradigm, for example: '*Traditionally used in Chinese medicine to increase bone mineral density*' is inappropriate as increased bone mineral density cannot be monitored or determined without conventional medical intervention.



If you are aware that there is conflicting evidence between the history of traditional use and contemporary scientific evidence for your medicine, then it is advisable to include a statement to this effect in any labelling and advertising associated with the medicine, for example: 'this traditional use is not supported by scientific evidence'. This will ensure that the advertised information relating to your medicine is truthful, valid and not misleading.



In deciding your traditional indication, ask yourself

- Is the indication suitable for use in listed medicines?
- Are the terms used to describe your indication the same as those in your evidence of traditional use?
- If the terms are different from those in the evidence of traditional use, can you justify the change?

How to compile a summary of the evidence to support your traditional indication

You should compile an **evidence summary** demonstrating that you have conducted an objective, comprehensive review of the literature relating to your traditional indication/s. The resulting evidence you hold should be:

- relevant to your medicine
- be of high quality; and
- adequately demonstrate that all traditional indications you make for your medicine are true, valid and not misleading.

[Evidence package checklists](#) provided on the TGA website assist you to collate your evidence summary and filter evidence items to those that are credible and relevant to your medicine. Refer to [Appendix 1: How to use evidence package checklists](#) for assistance with the process. While presentation in this manner is not compulsory, it will expedite the compliance review process should your medicine be selected for an evidence compliance review.

Scientific indications: what evidence do you need to support your scientific indication?

Scientific evidence refers to quantifiable data and includes: clinical trials in humans; epidemiological evidence; animal studies; and other evidence of biological activity. Due to the quantifiable nature of scientific evidence, scientific indications can imply efficacy to health outcomes.

Example of evidence for a scientific indication

A medicine containing turmeric (*Curcuma longae rhizoma*) has undergone randomised placebo-controlled clinical trials in humans and has been shown to provide a statistical significant decrease in gastrointestinal effects (abdominal pain, discomfort and wind) in this well designed study. An appropriate indication for this medicine may be:

'Turmeric has been shown to relieve symptoms associated with mild digestive disturbances (abdominal pain and discomfort).'

Scientific indications are usually supported with data from relevant controlled human clinical trials, or studies. These studies may be supplemented by other sources of evidence. You may also choose to conduct clinical trials on your medicine. For more information on conducting your own clinical trials refer to the [National Health and Medical Research Council \(NHMRC\) website](#).

What are the sources of scientific evidence?

High quality sources of scientific evidence include:

- Peer-reviewed⁶ original clinical research in well cited journals, for example: *New England Journal of Medicine* or *The Lancet*. Well cited journals are those with high Journal Impact Factors of greater than 5 (refer to [Appendix 2: Journal impact factors](#)).

Peer-reviewed journals are considered a good place to start when searching for supporting scientific evidence.

- Systematic reviews of the clinical research relating to particular subject areas – such as those conducted by the Cochrane Collaboration. Systematic reviews are also reported in high-quality journals.
- Unpublished studies or 'Propriety research' (as long as they fulfil the required criteria).
- Secondary sources or non-clinical studies. Only human studies are considered appropriate to support indications for listed medicines. The scientific uncertainties involved in extrapolating non-human data from animal and in vitro studies limit their usefulness. However, non-human and in vitro studies may be used to support any discussion on biological plausibility.

What databases can you use to search for scientific evidence?

General web search engines are not considered appropriate databases or sources of primary scientific evidence. Similarly, online databases containing a limited collection of scientific abstracts are not considered primary sources of scientific evidence.

⁶ 'Peer review' is the evaluation of research by other people in the same field to maintain the quality of work in that field.

To find scientific journal articles that may be relevant to your indication; you should search a comprehensive electronic database such as MEDLINE (an electronic database produced by the United States National Library of Medicine that indexes millions of articles from 5,000-plus reputable biomedical journals from around the world).

Examples of comprehensive electronic databases include:

- MEDLINE
- EMBASE
- Web of Science
- the Cochrane library
- BIOSIS
- Sciverse Scopus
- Cab Health
- AGRICOLA
- Food Science and Technology Abstracts

Access to MEDLINE is through the [PubMed](#) search facility, where you will also find search instructions, tutorials and FAQs. MEDLINE/PubMed provides abstracts (summaries) and citations for the journal articles listed, and often links to the full-text articles online.



Database searches

Your database search should utilise MEDLINE/PubMed electronic databases and include at least one other relevant database.

Web search engines are not considered appropriate databases or sources of primary evidence.

During your database search, if a substantial number of results (hits) are received, you can refine your search by reducing the date range to the last 5-10 years (a justification for refining the date range should be recorded in your evidence package).

Your database search of the literature should be documented to best practice standards. [The Australian Regulatory Guidelines for Complementary Medicines \(ARGCM\)](#) provides guidance on appropriate search strategy standards. The search terms, databases and search interfaces you use and the numbers of references retrieved should be documented in your evidence package ([Evidence package checklists](#)).

Using internationally recognised monographs or pharmacopoeias to support your scientific indication

High-quality and credible texts such as internationally recognised pharmacopoeias or monographs maintained by other international regulatory bodies (refer to [Appendix 3](#)) or evidence based reference texts may also be appropriate to support [non-specific](#) (general) indications, such as: nutrient supplementation indications when multiple monographs from different independent regulatory bodies report the same therapeutic benefit.

Internationally recognised monographs and pharmacopoeias can also provide additional support to specific indications referring to health enhancement claims, but such items will need

further evidentiary support from primary research articles and/or systematic reviews. The more specific the indication, the more evidence you need to support your indication.

Using clinical studies to support your scientific indication

When citing a publication, you should not rely simply on the fact that a study is published as being sufficient to support your indications. Sometimes the results of published clinical studies are reviewed by others and these thoughts are captured in letters to the editor published separately in the journal. Often clinical studies may indicate that the results are indicative that an effect might be present, but that further work is needed. Such studies cannot be relied on solely to support specific indications.

Studies that have been through a peer review process are more likely to be methodologically robust and valid. You need to evaluate each piece of evidence to ensure that it is relevant and of high quality to support your indication.

Certain clinical studies offer higher quality evidence than others due to their methodological design (NHMRC, 2009). You should select the highest quality of evidence available to support for your indications.

Suitable evidence to support a scientific indication can be obtained from:

- high quality, preferably multi-centre, random controlled trials (RCT)
- well-designed controlled trials with randomisation; or
- well-designed analytical studies preferably from more than one research group, including cohort and case-control studies.

Clinical trials, particularly randomised, placebo-controlled and blinded trials, provide the most robust information regarding the potential efficacy of a particular intervention. Case-control studies and cohort studies may not be practical means of providing evidence for some indications and are limited in their ability to produce unbiased and unambiguous data regarding the true efficacy of an intervention. They can, however, provide valuable supportive data relating to the likely effectiveness of an intervention within the general population. Case studies and epidemiological surveys do not have sufficient strength in their own right to justify a scientific indication.

If you use a [systematic review](#) to support an indication, it is necessary for you to demonstrate that the studies included in that review are relevant and satisfy the requirements outlined in the subsequent sections.

Diagram 3 and Table 4 display the hierarchy of evidence sources.

Diagram 3: Hierarchy of evidence sources

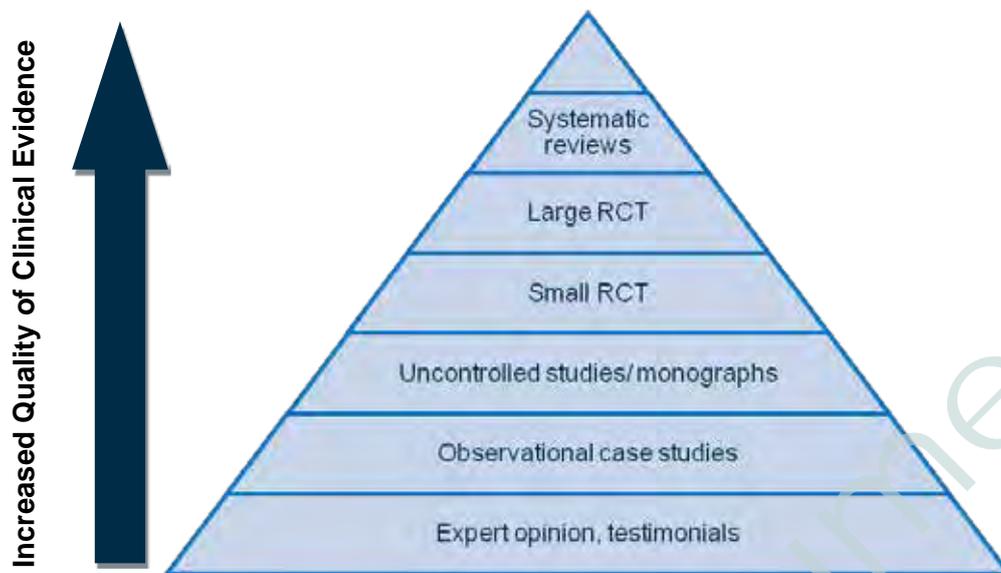


Table 4: Levels of evidence associated with clinical studies (adapted from NHMRC)

Level	Intervention	Definition
I	A systematic review of level II studies.	Cochrane Reviews are examples of such systematic reviews.
II	A randomised controlled trial.	An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.
III	A pseudo-randomised controlled trial (that is: alternate allocation); or A comparative study with concurrent controls: (Non-randomised); or A comparative study without concurrent controls.	A pseudo-randomised controlled trial is a study with an independent, blinded comparison with a valid reference standard between participants with a defined clinical presentation. Comparative studies with concurrent controls include: non-randomised experimental trial; cohort studies; case-control studies; or interrupted time series with a control group. Comparative studies without concurrent controls include historical control studies, two or more single arm studies, cohort studies, case-control studies, and interrupted time series without a parallel control group. Refer to the National Health and Medical Research Council for definitions.

Level	Intervention	Definition
IV	Case series with either post-test or pre-test/post-test outcomes.	In depth description of the factors related to a disease, disorder or condition in a specific individual or group of individuals.

Can you use unpublished studies to support your scientific indication?

Unpublished studies can contribute to your evidence base for a scientific indication if they are relevant and have been reviewed by at least two independent reviewers. To facilitate an accurate interpretation of methodological quality, any original research must be appropriately documented [Schulz *et.al.* (2010)].

Can you use abstracts to support your scientific indication?

Abstracts are not primary sources of scientific evidence and cannot stand alone to support scientific indications. These documents usually do not give sufficient details as to how the research was conducted or the data were analysed, thereby not allowing an objective evaluation of the quality of the research data and the conclusions drawn by the study authors.

Can you use non-clinical studies to support your scientific indication?

Animal or *in vitro* studies cannot stand alone to support scientific indications. The scientific uncertainties involved in extrapolating human health benefits from animal and *in vitro* studies limit their usefulness. Non-clinical studies are considered secondary sources of scientific evidence, and may provide additional weight to a proposed health benefit when limited clinical studies are available. Only clinical (human) studies are considered primary sources of scientific evidence and sufficient to support indications for listed medicines.

Can you extrapolate target population groups from clinical study groups?

Indications may refer to health benefits for the general population or for specific sub-populations (for example: children or elderly). The study should be carried out in a study group representative of the population group for which the indication is intended to be made. Extrapolation of results obtained from subjects outside the target population group is normally not accepted unless it can be appropriately justified. Given the variability of the indications and evidence such justifications can only be made and assessed on a case by case basis.

Using systematic reviews and review articles to support your scientific indication

Systematic reviews are reports of the outcome of analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. In a systematic analysis only those trials that meet a number of pre-set conditions in relation to research design (for example: sample size, randomisation) are included in the final meta-analysis. Cochrane Reviews are examples of such systematic reviews.

Review articles report the study outcomes of a collection of study articles with a common theme or on a particular topic. The review author/s will assess the published research, conduct research regarding the major research advances or report on any significant data gaps then present findings in a coherent view. Review articles provide broad information about a given topic, but are limited in their ability to provide support to specific indications. These limitations

are primarily driven by limited scientific assessment or scrutiny of the studies reported in the review article, as review author/s often report the study outcomes as reported by study authors without further assessment of the study methodology.

Using Cochrane Reviews to support your scientific indication

Often a good source of high-quality evidence for scientific indications will be the [Cochrane Library](#), a searchable database of the systematic reviews done by the Cochrane Collaboration. The Cochrane Collaboration is highly regarded, internationally recognised source of independent research. Cochrane reviews are systematic surveys of primary research (that is: experimental research) on healthcare topics.

Each Cochrane review starts with a clear question, for example: *'Does Echinacea reduce the occurrence of the common cold?'* It then searches for and collates all the existing primary research from around the world that meets certain quality standards. Carefully following protocols that are designed to minimise bias, it then assesses that evidence against strict guidelines to establish whether there are conclusive findings that answer the question. The reviews are updated frequently.

Cochrane reviews concentrate on research conducted using randomised controlled trials (RCT). A randomised controlled trial is a study in which people are randomly allocated to one of two groups. One of the groups receives the treatment being tested (for example, a pill containing *Echinacea purpurea*). The other, known as the control group, receives a placebo treatment (for example: a sugar pill). No-one in either group knows which treatment they received. The study is controlled so that all participants have similar care in all ways other than the treatment being tested. Ideally the study participants, the scientists running the trial and those assessing the outcomes are also unaware of which group participants are in – this is called 'double-blinding'.

Cochrane reviews are written by and for scientists but each has a plain language summary (under 400 words) explaining the background, methods, results and weaknesses of the review. Even if you are not a scientist, these summaries can help you assess whether the evidence is relevant to your medicine's indication, but it would be beneficial for a person with expertise in critical appraisal to review the full study to determine if it actually supports your claim.

Systematic reviews and RCT are often associated with higher quality evidence and are appropriate to support scientific indications for listed medicines. However, various levels of clinical trials may be of high quality, but offer lower level of clinical significance due to the design of the study. For instance, random placebo-controlled trials are often seen as higher level or quality of evidence compared to cohort studies (refer to glossary for definition of terms) due to a lower level of potential confounders or bias in RCT studies.

Your evidence package should predominately consist of primary sources of evidence that are relevant to your medicine and of high quality. Multiple low-quality sources of evidence are unlikely to be adequate to support indications for listed medicines.



When using any evidence source, including systematic reviews or publications in a peer-reviewed journal, you must ensure that the evidence is relevant to your ingredient/medicine and relevant to your indication (see [Using clinical studies to support your scientific indication](#)).

Assessing your evidence

Relevance of the evidence to your indication

During your search for evidence you may come across many different types of evidence from a variety of different sources of literature. Review of the literature to produce an existing body of high-quality evidence that is relevant to the indication or medicine is known as 'filtering' ([Evidence package checklists](#) provide a checklist to assist you with this process).

Establishing the relevant evidence base for your proposed indication is a critical step in the review of evidence. This requires an assessment of the relevance of every item retrieved from the literature review of your proposed medicine, dose and indications. The relevant evidence base for your proposed indication includes all studies that are relevant in terms (amongst others) of ingredient, health benefit, population and context of use.

You must determine whether the evidence you have obtained is relevant to support your proposed scientific indications for your medicine.

Below are the concepts to allow you to assess whether the item of evidence is relevant to your medicine/indication.

Health benefit (indication)

You should ensure that the research is relevant to your proposed specific indication for your medicine. In drafting indications, you should take care to make sure that they match the underlying evidence you hold. Indications that do not match the science, no matter how sound that science is, are unlikely to be supported. Indications should not exaggerate the extent, nature, or prominence of the effects achieved in a study (the study outcomes), and should not suggest greater scientific certainty than that which actually exists.

All indications based on scientific evidence must be supported by primary evidence, such as clinical studies. The scientific uncertainties involved in extrapolating human data from animal and *in vitro* studies limit their usefulness as an evidence base to support your indication. Non-human and *in vitro* studies may, however, be used to support any discussion on biological plausibility of a potential mode of action in humans.

Participants enrolled in studies used to justify indications for your listed medicine should fit the following eligibility criteria, unless your medicine is directed to a specific population sub-group:

- male and female participants
- generally healthy
- aged 18–65 years; and
- socioculturally similar to the Australian population.

Secondary evidence or non-clinical studies (such as mechanistic studies) are normally insufficient to support indications implying efficacy. However, secondary evidence may be used in conjunction with primary evidence to strengthen the wording of an indication.

Dosage

For scientific indications, the recommended dosage and duration or frequency of administration of the medicine must be consistent with the evidence supporting the indication.

Active ingredient and route of administration

The evidence must relate to the whole medicine, the same active constituent(s) with a similar dosage regimen, dose form and route of administration to the medicine for which a claim is being made. For specific scientific indications for example, the different formulation between your medicine and that of the formulation reported in the scientific evidence is very important (for example: the use of a novel tablet matrix). If there are differences noted, then further justifications will be required to address the data gaps identified using the checklists provided.

Assessing the quality of the evidence

In addition to determining the relevance of the item of evidence, you need to determine whether the evidence is of high quality. Importantly, to facilitate the assessment of balance view of evidence, both relevant non-supporting and supporting items of evidence will need to be assessed for quality.

Methodology, blinding and randomisation

The clinical research being used to support your scientific indication should be conducted in a reliable manner to yield meaningful and reproducible results. The design, implementation, and results of each piece of research are important in assessing the adequacy of the substantiation of the health benefit or study outcome.

There are some principles generally accepted in the scientific community to enhance the validity of test results. However, there is no single set protocol for how to conduct research. For example, a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist and better evidence to identify potential safety concerns.

You should critically appraise scientific studies in terms of methodological quality and the possibility of bias and/or confounding. Studies that have been peer-reviewed may be more likely to be methodologically robust. You should assess the results of scientific studies for statistical significance and meaningfulness (clinical significance) of the reported therapeutic benefit. Your evidence should demonstrate an overall improvement in the expected health benefit that is statistically and clinically significant. Additionally, studies that incorporate randomisation process of assigning trial subjects to treatment or control groups are often considered of greater quality due to the reduction of potential for bias. The randomisation method should be described in the study report and meet contemporary standards (such as using post-study questionnaires' of study participants to confirm that they remained blinded). Similarly, the incorporation of good blinding methods in the study design tends to result in studies that are methodologically robust.

Statistical analysis

A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of a placebo effect or chance. The results should translate into a meaningful health benefit for consumers. Some results that are statistically significant may still be so small that they may not provide a positive effect to consumer health.

Filtering relevant evidence to those of high quality will involve, as a minimum, an assessment of the following:

- characterisation of the ingredient/s
- study design/methods
- participant eligibility (inclusion/exclusion criteria)

- adequacy of randomisation and blinding of participants (for example Randomised Controlled Trials (RCT))
- sample size justification
- controlling for potential confounders
- study attrition (for RCT and cohort studies); and
- statistical analyses undertaken.

For each study, the meaningfulness of the observed effect/s to consumers at an individual and/or population level (clinical significance) must be assessed.

Balanced view of your scientific evidence

Studies cannot be evaluated in isolation of the surrounding context. The context of the scientific evidence is just as important as the internal validity of individual studies. You need to consider all relevant research relating to the claimed benefit of your medicine and should not focus only on research that supports the effect, while discounting research that does not. A well-constructed literature search should normally be undertaken to help ensure that the general body of evidence related to a specific indication is identified.

Before you list a medicine in the ARTG you must be satisfied that the balance of evidence supports your indication. In other words, a reasonable person making an objective assessment of all the relevant, high-quality evidence about your medicine would conclude that the weight of good evidence is in favour of your indication rather than against it. Your indications must not, indirectly, or by implication, lead consumers to believe that your medicine will assist in a health benefit that is not explicitly supported by the balance of evidence.

The evidence you hold to support your indication should consist of studies that are largely consistent with the surrounding body of evidence. Where there are inconsistencies in the evidence, it is important that you examine whether there is a plausible explanation for those inconsistencies, for example: in some instances the differences in results will be attributable to differences in dosage, the form of administration, the population tested, or other aspects of study methodology. You should assess how relevant each piece of research is to your medicine and the specific indication you wish to make, and also consider the relative strengths and weaknesses of each. If a number of studies of different quality have been conducted on a specific topic, you should look first to the results of the studies with more reliable methodologies (that is, RCTs or systematic reviews).

You should also ensure that the evidence supporting your indications remains valid for the life of the medicine, and this is best achieved using a body of evidence approach. As research advances, the body of scientific evidence supporting a particular health benefit may change. Newer clinical studies may enhance the strength of the evidence supporting your claim, or it may be inconsistent with the strength of previous research. Having a body of supporting evidence will allow you to ensure that the indications claimed for your medicine remain true, valid, are not misleading and consistent with scientific evidence for the life your medicine.

What indication sub-type does your scientific evidence support?

Depending on the [indication sub-type](#), the required evidence to support the indication will be different. Non-specific indications such as '*may assist with general health and well-being*' can be supported by scientific evidence from monographs or pharmacopoeias. Whereas specific

indications should be supported by specific scientific evidence such as results of clinical studies, or systematic reviews (refer to table below).

Table 5: Levels of evidence generally required to support sub-types of scientific indications

Scientific indication	Evidence required to support indication
Non-specific indication	Descriptive studies, case series or reports of relevant expert committees. Reference texts, such as pharmacopoeias or monographs, or other evidence-based reference texts, may be provided to support non-specific indications.
Specific indication	<p>You must hold scientific evidence to support the specific indication. Such as</p> <ul style="list-style-type: none"> • Evidence obtained from well-designed controlled trials with randomisation; OR • Evidence obtained from well-designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies; OR • Evidence obtained from multiple time series with or without intervention, including within country and between country population studies.



All indications / claims relating to symptoms must be accompanied by the advice “If symptoms persist consult your healthcare practitioner” or words to that effect.

Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the medicine provides at least 25% of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Indications / claims 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.

Choosing or deciding upon your scientific indication

Scientific indications are usually supported with clinical data from relevant human studies that have likely undergone some scientific assessment or scrutiny. Due to this quantifiable scientific research undertaken into their mode of action and/or health benefit, this evidence type is appropriate to support efficacy for your listed medicine.



Scientific indications must not specify or refer to traditional paradigms.

The use of the term 'clinically proven' in scientific indications infers a level of certainty in the implied health benefit associated with the listed medicine in that it has been clinically trialled and proven to be effective. These terms are not acceptable unless supported unequivocally by robustly designed, published peer-reviewed clinical trial(s) conducted on the actual medicine being advertised, or an identical formulation and dose (as a minimum). The use of the terms 'clinical', 'clinically', 'scientifically' coupled with 'trialled' or 'tested' implies a higher level of certainty associated with the health benefit of your medicine and unless matched by well-designed clinical studies on your specific medicine, may mislead consumers about the effectiveness of your medicine.

You must compare your indication with the quoted health benefit in your evidence identified from scientific sources. Your indication will refer to the same clinically significant study outcomes as that reported in the clinical study.

In developing your scientific indication you should:

- make sure that the indication is suitable for use in listed medicines
- base any statement about the medicine's therapeutic benefit on the demonstrated clinical study outcomes; and
- imply only the same level of certainty in clinical effectiveness as that reported in clinical studies, for example 'clinically proven to...' compared to 'may assist to...'

How to compile a summary of the evidence to support your scientific indication

You should compile an evidence package demonstrating that you have conducted an objective, comprehensive and transparent review of the literature relating to your indication/s. The resulting evidence you hold should be of high quality and relevant to your medicine and adequately demonstrate that all indications you make for your medicine are true, valid and not misleading.

[Evidence package checklists](#) provided on the TGA website assist you to collate your evidence summary and filter evidence items to those that are credible and relevant to your medicine. You are required to hold all the information contained within the relevant forms for your medicine before listing it. Refer to the [Appendix 1: How to use evidence package checklists](#) for assistance with the process. While presentation in this manner is not compulsory, it will expedite the compliance review process, should your medicine be selected for an evidence compliance review.

Cross-evidence base medicine: What evidence do you need to support your medicine with a combination of traditional and scientific indications?

A listed medicine can have a combination of scientific and traditional indications where:

- an ingredient in the medicine is supported by both scientific evidence and evidence of traditional use ('cross-evidence base ingredient')
- the medicine contains both traditional and non-traditional ingredients with associated traditional and scientific indications ('cross-evidence base medicine').

It is important that the indications for your listed medicine accurately describe the evidence base for the indication. You are also required to have supportive evidence for all your traditional and scientific indications. Refer to:

- [Traditional indications: what evidence do you need to support your traditional indication?](#)
- [Scientific indications: what evidence do you need to support your scientific indication?](#)

Cross-evidence base ingredient (scientific and traditional)

In cases where you have supportive evidence of traditional use and scientific evidence for an ingredient, both scientific and traditional indications may be made for that ingredient.

Examples of indications for a 'cross-evidence base ingredient'

'Echinacea pupurea has been traditionally in Western herbal medicine for hundreds of years to reduce the risk of common colds. This herb now has scientific evidence showing that it helps support immune function.'

'Citrus fruits have been used traditionally in Western herbal medicine to maintain good health and wellbeing. Citrus fruits contain vitamin C which helps maintains healthy gums, blood vessels and connective tissue.'



If you are aware that there is conflicting evidence between the history of traditional use and contemporary scientific evidence for your medicine, then it is advisable to include a statement to this effect in any labelling and advertising associated with the medicine, for example: 'this traditional use is not supported by scientific evidence'. This will ensure that the advertised information relating to your medicine is truthful, valid and not misleading.

Cross-evidence based medicine

A medicine with a mixture of scientific and traditional indications (mixed paradigm medicine) with traditional and non-traditional ingredients requires scientific evidence to support the scientific indications and evidence of tradition of use to support the traditional indications.

Where your medicine contains multiple ingredients, with some associated with scientific indications and others with traditional indications, the kind of evidence supporting each indication must be clearly communicated to the consumer.

Evidence may refer to a formulation or an ingredient of the medicine. Indications must only refer to entire formulations or specific combination of ingredients for which the evidence is held. When evidence supports a health benefit for one or more ingredients in the medicine (but not the medicine as a whole) indications must include this information.

Example of an indication for a cross paradigm medicine

A medicine that contains *Echinacea purpurea* and ascorbic acid (vitamin C) may have the following indication (if supported by evidence):

'This medicine has been formulated from traditional and modern ingredients, to help support healthy immune system function, specifically:

Echinacea purpurea has been traditionally used in Western herbal medicine to boost the immune system

Vitamin C supports the immune system'.

How to compile a summary of the evidence to support your indication for your cross-evidence based medicine

You should compile an evidence summary demonstrating that you have conducted an objective, comprehensive and transparent review of the literature relating to your indication/s. The resulting evidence you hold must be relevant to your medicine, be of high quality and adequately demonstrate that all indications claimed for your medicine are true, valid and not misleading.

[Evidence package checklists](#) provided on the TGA website assist you to collate your evidence summary and filter evidence items to those that are credible and relevant to your medicine. You are required to hold all the information contained within the relevant forms for your medicine before listing it. Refer to the [Appendix 1:How to use evidence package checklists](#) for assistance with the process. While presentation in this manner is not compulsory, it will expedite the compliance review process, should your medicine be selected for an evidence compliance review.

Part B: Further technical guidance

Part B of this guide provides additional technical information on specific subjects and clinical issues relating to listed medicines. Additionally, case studies are provided for greater clarity of particular technical issues, such as indications relating to biomarkers, nutritional supplementation and weight loss.

Equivalency of ingredient, preparation, dosage and dosage form between the evidence and your medicine

The active ingredient should be well characterised in the evidence supporting your indication. Preparations used in the evidence should contain the same ingredient preparation and dosage form as your medicine.

In the case of indications based on vitamins, minerals, nutrients or known therapeutically active components of herbs, this involves careful consideration of the dose, route of administration and dosage regimen employed in the available scientific literature. In order for a piece of evidence to be relevant to your indication, all these factors should closely resemble that intended for the medicine.

Evidence that relates to a herb or herbal substance, the species (and subspecies if applicable), plant part, method of preparation and processing, the equivalent dry weight and the dose of active component used should be consistent with that of the herb or herbal substance in the medicine. If the processing used to prepare a particular herbal product is different to that used in the literature, you will need to hold evidence that the chemical profile of the resulting active ingredient(s) is not substantially different from the active ingredient used in the evidence to support your indication. Unfortunately, many trials inadequately describe or characterise the composition of the herbal treatment. Even when the herbal ingredient is standardised to known active therapeutic components or marker compounds, there can be variation in the concentration of other components in the herbal extract for example that may result in different pharmacological activity in vivo.

Other characteristics of medicines used in clinical trials may also impact on relevance to your proposed indication. For example, modified release dosage forms of a medicine designed for slow or delayed release of an active ingredient may not be relevant to support indications that imply health outcomes that are achieved rapidly (for example: '*for the rapid relief of pain*').

Scientific studies

Study populations

As indicated in Part A of this guidance, only human studies are considered sufficient as primary evidence to support indications for your listed medicine. Studies used to justify the scientific indications for your medicine should be conducted in populations that are representative of, or can reasonably be extrapolated to the general Australian population.

Relevance of the study population

The health status of the study population should be representative of the target population for your medicine. Many listed medicines are used by healthy individuals. Data collected from study populations with non-serious disorders and in situations where a continuum of health and disease exists, such as individuals in early disease states, can influence the relevance of the evidence for your indication.

In general, data obtained from studies with participants who have serious diseases, conditions or ailments cannot be extrapolated to a healthy population and, as such, are not relevant evidence to support an indication for a listed medicine.

However, in circumstances where a positive modulation of a health benefit is noted in a diseased study population, it may be possible to use these clinical outcomes to provide secondary evidentiary support for your indication. Such an indication should be carefully worded to accurately reflect the evidence base supporting to the indication.

For example:

'May assist with maintaining normal healthy cholesterol levels'.

Justifying the differences between study and target population

When you use clinical studies that employ specific study population groups (for example: subjects with a disease) rather than the target population group for your indication (for example: the general healthy population), you should provide an evidence-based justification.

This process should consider biological factors as well as environmental and behavioural factors including the influence of health practitioner intervention which may differ between healthy and unhealthy populations.

In vitro studies or non-clinical data can provide additional justification to support the outcomes of the primary clinical study using diseased populations. Data generated from diseased study participants could be used to demonstrate that the active ingredients have positive pharmacological effects; however such data may not be appropriate to support an indication that is intended to be used by healthy people to maintain normal [biomarker](#) levels. You should also consider the mechanism of action of the medicine or ingredient and whether it is applicable to the general healthy population. The pathophysiological changes in a disease population may result in the ability of a particular ingredient or medicine to be effective. The same result may not be achieved in a general healthy population as it may be dependent on pathophysiological changes associated with the diseased population. Further, any favourable modulation is likely to be dose-dependent; therefore consideration should be given to the effect, if the dose requires modification.

Target sub-populations of the general Australian population

When an indication is directed towards a specific subgroup of the population (for example: elderly or pregnant women), it needs to be supported by evidence derived from the same subgroup of the population. The results from studies of target specific subgroups are not relevant to the general population. For example, clinical studies that use females as the treatment group are not relevant to the general population.

Table 6 provides examples of the characteristics of study populations that are relevant to the target population.

Table 6. Characteristics of study populations that are relevant to the target population

Indication	Relevant population
<i>For weight loss in overweight individuals when used in conjunction with a calorie or kilojoule controlled diet and physical activity (or exercise).</i>	Male and female participants aged 18-65 years; generally healthy population with BMI 25-30kg/m ² socioculturally similar to the Australian population

Indication	Relevant population
<i>Reduces pain.</i>	Male and female participants aged 18-65 years; generally healthy population with a range of painful (non-serious) conditions.
<i>Relieves cough in children.</i>	Male and female participants aged 2-18 years; generally healthy population with cough associated with a range of (non-serious) conditions.
<i>Calcium helps maintain healthy strong bones.</i>	Male and female participants aged 18-65 years; generally healthy population; dietary and lifestyle pattern similar to the Australian population.

Study duration

Relevant studies should be of appropriate duration to validate a health benefit included in an indication. Each study should be long enough to clearly demonstrate the health benefit. The appropriate duration of studies depends on the nature of the health benefit. If an indication refers to a short-term benefit such as acute pain relief, trials of several hours duration may be adequate. Conversely, for indications where long-term benefits are implied, studies must be of sufficient duration to establish a sustained response that is likely to be meaningful. This is particularly important for indications relating to maintenance of health or risk reduction, and those that produce favourable modulation of biomarkers and body weight, as the body's homeostatic processes may reduce early gains. Therefore, studies assessing cardiovascular risk factors, weight, or changes in muscle mass or bone strength that are not long enough to establish a sustained clinical benefit are not relevant.

For these reasons, the duration of each study is an important factor and must be considered when assessing the body of evidence relevant to an indication. The minimum relevant study duration should be determined and justified in relation to the relevant indication, and all studies of insufficient duration should be omitted from the primary analysis.

CASE STUDY 1: Study duration for pain relief

A listed herbal medicine containing willow bark (*Salix alba*) has the scientific indication: '*Helps relieve short-term back pain*'.

A clinical trial reports a long-term pain relief effect in subjects suffering osteoporosis and back pain beginning 2 weeks after the initiation of treatment.

The above indication is not supported by the outcomes of this study.

CASE STUDY 2: Study duration for weight loss

A listed herbal medicine has the scientific indication: *'Helps assist weight loss'*.

Evidence held to support the indication was a clinical trial of 6 weeks duration.

A reasonable timeframe to achieve a significant degree of weight loss is six months (clinical significance). After about six months, the rate of weight loss usually declines as weight plateaus, and some regain is common [Franz (2007)].

Shorter studies fail to demonstrate the full benefit of a treatment, including the ability to sustain weight loss for a longer period. Therefore, studies will generally be at least six months duration to be considered relevant to indications relating to weight loss must be of at least six months duration.

The above indication is not supported by the outcomes of this study.

Study outcomes**Primary and secondary clinical study outcomes**

Ideally the health benefit of your medicine will be included in the study as a primary outcome with an adequate sample size. This ensures that the study is sufficiently powered to detect a benefit that is statistically and clinically significant. However, inclusion of the health benefit as a secondary outcome may be acceptable provided that the observed result is shown to be statistically and clinically significant.

Evidence that describes an effect on a biological process generally does not contribute to the evidence base for an indication that refers to a clinical outcome. Such data may, however, be useful in demonstrating biological plausibility of a clinical outcome.

Evidence held to support indications referring to beneficial effects on biological or clinical targets should directly relate to the target described. Evidence relating to a particular clinical outcome, physiological process or health benefit cannot be drawn from data describing different clinical outcomes, physiological processes or health benefits.

CASE STUDY 3: Duration versus symptomatic relief

A clinical study that assesses the effect of an ingredient on the *duration* of the common cold does not support an indication that describes *symptomatic relief* of the common cold. Therefore, the indication can only refer to reducing the duration of a cold and not to relief of symptoms.

Assessing the significance of study outcomes**Attrition rates (drop out rates)**

Attrition rates are commonly high in studies that evaluate health gains that are modest and require long-term commitment. High attrition can introduce serious bias (attrition bias) into these studies because the reasons for non-completion vary across initially randomised groups. High attrition rates may also diminish the general applicability of the treatment to the Australian population. The resulting data from a high attrition study should be interpreted with caution.

An Intent-To-Treat (ITT) analysis, in which outcomes of the original randomised groups are compared, provides a means of accounting for the effects of dropouts. In an ITT analysis, dropouts from the study are included in the analysis. When an ITT is performed, all efforts should be made to obtain outcome measurements from dropouts at the end of the study. In cases

where this is not possible, baseline measurements of study parameters should be carried forward (for example, for a study outcome related to weight loss, body weight recorded at the beginning of treatment would be the same at the end of the study). A treatment effect demonstrated in an ITT analysis underestimates the efficacy of the treatment but may be a good reflection of effectiveness under real world conditions [Koepsell & Weiss (2003)]. When dropouts are not accounted for in the analysis of results, attrition bias (exclusion bias) may result.

Number of participants (power calculations)

It is important that studies enrol sufficient numbers of participants to detect a significant and reliable treatment effect. The number of participants required to be reasonably certain of a reliable result needs to account for the degree of health benefit, the variability of individual results and the number of participants dropping out of the study (attrition rate). As a consequence, studies may need to include larger numbers of participants to account for a high attrition rate.

How many patients are needed for a clinical trial?

An essential part of critically appraising a clinical study is to determine if a sufficient number of study participants were included in the trial in order to reliably detect and measure effects of the intervention.

This is described as the studies 'power'. The larger the number of participants, the greater the potential statistical power.

The number of study participants required for a study to demonstrate clinical significance depends on several factors: the study aim and design, the type and sensitivity of the primary end-point, how the data will be analysed, the significance level and allocation ratio of treatment to control as well as the anticipated standard deviation or the anticipated results in the control group.

There are many published resources available in which these factors are explained including good and bad practices for sample size calculation.



Often high quality clinical studies have been designed to provide meaningful statistical calculations. Study clinicians have considered the factors that are important to achieve the desired outcome and have designed the study accordingly. If you choose to use a clinical study to support a scientific indication, you are not expected to perform power calculations, but to consider any limitations of the statistical calculations that the study authors have reported, including the number of drop outs and the impact this may have on the reported study outcomes.

Appropriate statistical methods must be used to compare the effects of treatment between groups, and to compare the number of individuals achieving a clinically significant result in each group. The analysis should also account for any potential confounders. An Intent-to-Treat (ITT) analysis should also be performed, particularly when attrition rates are high. Previously unplanned analyses undertaken after the completion of a trial (post-hoc analyses) are to be avoided as they are unlikely to have been considered in power calculations and study design.

An indication can only be justified when the available evidence supports the described health outcome. The balance of evidence should support an outcome that is:

- statistically significant; and
- clinically significant (or meaningful to the consumer).

Statistical significance (p-value)

When considering a study result, it must be unlikely (probability of less than 5%) that the observed health benefit could have been a chance occurrence. The 'p' value indicates the probability that an effect is due to chance, assuming there is no real difference between intervention and control groups. Therefore, a 'p' value of less than 0.05 indicates with acceptable certainty that an observed effect or health benefit is unlikely to be due to chance.

Confidence intervals provide an alternative measure of statistical certainty. Confidence intervals of 95% are commonly employed to show the range within which the true outcome value could be expected to occur with 95% certainty. When 95% confidence intervals are generated for primary study outcome measures, the 95% confidence intervals of the intervention and exposed groups must not overlap.

However, statistical significance does not provide information about the degree of benefit produced or whether it is likely to be meaningful.

Clinical significance

Not all statistically significant differences are clinically significant (Berry (1986), Sackett *et al.* (1985), Levitt (1981)). A statistically significant outcome indicates only that there is likely to be a relationship between intervention and outcome. Clinical significance is more difficult to define but is commonly considered to represent a degree of benefit that is worthwhile in real life to justify intervention, and may consider factors such as cost, side effects and inconvenience.

A number of general principles can provide guidance about clinical significance. For listed medicines, it might be regarded as a degree of benefit that is meaningful to the consumer. The number of participants required to detect a clinically significant difference between treatment and control groups depends on the type and level of health benefit, the standard deviation of the health effect, the significance level (p-value) and statistical power of the study and the type of hypothesis being tested.

In general terms, most research studies contain 0.8 sample power, meaning that there is an 80% probability of finding a significant difference with a given sample size, if a real difference truly exists and having excluded the role of chance. High quality studies will recruit many more subjects than required in order to maintain adequate numbers in the trial even when there are drop outs recorded throughout the study. The meaningfulness of a predetermined 'significant clinical benefit' may then vary between patients depending on a number of factors such as state of disease, comorbidities, personal circumstances, and alternative options for treatment.

Judgements about clinical significance are often made by experienced clinicians within a context of ongoing monitoring and supervised care. Listed medicines, however, are freely available to consumers and may not involve practitioner intervention or supervision. Determining the clinical significance of health outcomes associated with listed medicines is particularly difficult for the following reasons:

- Listed medicines are self-selected by consumers from a wide variety of backgrounds, with varied expectations and variable educational and financial resources.
- The health outcomes provided by listed medicines may be modest, not readily apparent, and/or achieved over long periods of time.
- Healthy consumers may be satisfied with smaller gains in health than individuals with a pre-existing condition.

Notwithstanding these factors, consideration should be given to the likely significance (meaningfulness) of an observed health outcome to the intended target population. Table 7 provides a useful approach to the assessment of clinical significance for listed medicines.

Table 7: Approach to the assessment of clinical significance for listed medicines

	Excellent	Good	Satisfactory	Poor
Clinical impact	Meaningful health benefit very likely to be achieved by consumers	Meaningful health benefit likely to be achieved by consumers	Impact on target population uncertain-health benefit possible.	Unlikely to be meaningful

Ethnic, cultural and social factors

The characteristics of study participants must also reflect the characteristics and lifestyle of the target population for the medicine. Consideration of genetic, ethnic and socio-cultural factors is important when assessing the relevance of scientific evidence used to substantiate indications as differences in any of these may result in discrepancies between results reported in study data and expected results in an Australian population. The Australian population is culturally and ethnically diverse. Scientific data obtained from studies conducted in homogenous ethnic populations may be limited in their relevance to the general Australian population. Factors such as diet, lifestyle, support networks and religious beliefs may all impact on the study findings. Your evidence summary should include a justification to illustrate that the results derived from clinical studies that employ homogenous ethnic study populations are relevant to the general Australian target population, and therefore adequate supportive evidence for your medicine.

Relevance of context for your evidence

It is important to recognise that the body of evidence relevant to your indication is generally derived under conditions that are more restrictive than those experienced by consumers of listed medicines in 'real-world' situations. In research studies, tight control of experimental conditions and intensive monitoring are important in controlling for confounding across treatment and placebo groups. Studies conducted in this way are ideal for estimating potential **efficacy** but may overestimate **effectiveness** within its target population.

Studies that are less prescriptive may provide useful adjunctive information about 'real-world' medicine effectiveness. However, such studies may not accurately predict potential medicine efficacy, as the results of such studies may be subject to bias due to differences in environmental conditions, participant characteristics and compliance.

Provided that measures are taken to ensure that the characteristics of your medicine, its indications, and its target population are consistent with the supportive evidence base, well controlled efficacy studies are considered the 'gold standard' for supporting health benefits associated with your listed medicine. However, in situations where real-life effectiveness is likely to be significantly less than that observed in trials, the expected result in the general population should still be clinically meaningful.

Contextual qualifiers can be included in an indication so that it accurately reflects the evidence base held to support the indication.

For example:

'May assist with weight loss when used with calorie controlled diet and exercise'.

'May assist with weight management when used with calorie controlled diet and exercise'.

For indications that imply an ability of a listed medicine to assist with weight loss, the same level of evidence (that is, relevance, high quality, statistical & clinical significance and balance of the evidence) is required as for any other indication for a listed medicine. Specifically:

- the proposed indications should be appropriate for listed medicines (that is the indications cannot refer to obesity or a serious condition)
- the proposed indications should be consistent with the evidence held to support such indications
- the design and quality of the study should allow accurate conclusions of study outcomes to be drawn
- the study aims and the limitations identified by the study authors should be taken into account when developing your indication
- the clinical trial duration needs to be sufficiently long to support indications that refer to long term benefits, for example: sustainable weight loss is greater than 6 months; and
- the study should be carried out in a study group representative of the population group for which the indication is made. Any extrapolation of results obtained from subjects outside the target population group must be appropriately justified.

The use of qualifiers relating to the biological or clinical target of an indication restricts the applicability of the indication to a specific type of a condition or process (such as mild pain rather than pain more broadly) and narrows the relevant evidence base:

For example:

'may assist with reducing pain'; is less limiting than: 'may assist with reducing mild pain'.

CASE STUDY 4: The use of qualifiers to limit the health benefit

A listed herbal medicine containing *Actaea racemosa* (Black cohosh) has the scientific specific indication:

'May help to relieve menopausal symptoms'.

This indication may imply the relief of all symptoms associated with menopause (that is: hot flushes, insomnia, irritability, anxiety, vaginal dryness and so on).

The evidence base to support the indication using the same preparation and dose of *Actaea racemosa* reports a significant reduction in the frequency and intensity of hot flushes only. The effect on other menopause symptoms and signs were not examined. A more appropriate limiting indication that is supported by the evidence is:

'Helps reduce the frequency and severity of menopause hot flushes'.

Qualification may provide additional clarity to a particular indication, such as 'assists', 'helps', 'when used in conjunction with x or y' to convey that the strength of the evidence held to support a particular health benefit may not be as strong as other instances whereby a qualifier was not used.

Study design and methods

Studies should clearly document aims and methods. Study design (including the presence or absence of randomisation and blinding), measurement techniques and statistical methods must be clearly outlined. Inclusion and exclusion criteria and the baseline characteristics of study participants should be described. The baseline distribution of potential confounders must be shown and any potential confounding factors must be considered and accounted for during the analysis. In addition, any limitations and ability to apply the results to the general population should be discussed.

Intervention and control groups (study trial arms)

All participants enrolled in a clinical trial are considered to be derived from a common population and may be allocated to control (placebo) or intervention (treatment) groups. Randomisation of participants to intervention and control arms of the trial helps reduce innate inter-group differences and potential bias. The method of randomisation must be clearly described so as to enable the reviewer to assess the possibility of unblinding. Baseline characteristics of treatment and control groups should always be documented to establish equivalence in key areas such as age, weight, diet and other factors that may contribute to non-treatment differences in health benefit between groups.

Ideally, trials should be conducted under conditions where the only difference between groups is that one is exposed to the intervention (treatment), while the other is not. This is often achieved in controlled trials, but is less likely to occur in cohort studies and case-control studies. In these methodologies, the presence of potential confounders and study biases may impact on study results and must be considered and accounted for in the analysis of the study. When confounders exist within a study, they lessen the study's quality and the degree of confidence in the reported study outcomes. Under these circumstances, care should be taken in describing the indication.

Reference to secondary methods of assessment

In some clinical studies, the study authors may refer to secondary methods to assess study outcomes (for example, visual analogue scales as a method to subjectively assess study outcomes (pain, hunger etc)). While this reference to secondary methods is appropriate, it is important that these methods are accurately validated, to ensure the results can be reproduced. The characteristics of the secondary methods are often reported in other studies or publications, and it is this original research that validates the scales.

If your scientific evidence relies on secondary methods of analysing study outcomes, then these original studies will also need to be cited and provided to the TGA on request.

CASE STUDY 5: Reference to secondary methods of assessment

A clinical study was provided to support the indication

'assists with the reduction of appetite'.

The supporting clinical study used a visual analogue scale (VAS) secondary assessment method [reference: Silverstone *et. al.* (1981)] to determine the changes in four parameters associated with the assessment of appetite ('hunger', 'thoughts of food', 'urge to eat', and 'fullness of stomach').

However, the method of determining appetite in the clinical study that administered VAS at thirty day intervals, was inconsistent with the method reported by Silverstone *et. al.* (1981), which administered the VAS at hourly intervals.

As the changes to this secondary method of assessment (VAS) were not appropriately validated in the clinical study, the study does not support the indication.

Indications relating to biomarkers

Your indication may refer to the favourable modulation of measurable biomarkers of disease (such as Body Mass Index (BMI), blood pressure, blood glucose and cholesterol) in healthy individuals. This is difficult to substantiate when the primary evidence is derived from a diseased population. The extrapolation of study findings from a diseased study population to the healthy Australian population can be problematic and potentially misleading. A small change in a

given biological surrogate may be associated with negligible biological dysfunction and minimal increase in risk of serious forms of disease, whereas larger changes are more likely to be associated with pathophysiological processes and an increased risk of overt illness which requires health practitioner involvement.

Evidence may also need to be sourced to illustrate that favourable modulation of biomarkers in a diseased population does not result in serious conditions in a healthy population, for example: a study reporting the significant reduction of blood glucose in hyperglycaemic patients in the trial should not result in hypoglycaemia in healthy individuals. In these cases, further justification is required to demonstrate that your medicine is safe for its intended purpose.

If your evidence uses study populations with baseline biomarker levels that lie outside normal healthy levels it is unlikely to be considered relevant to support indications relating to biomarkers levels in the healthy Australian population.

For example:

'May assist with maintaining normal cholesterol levels in healthy individuals'.

In addition, indications should only target healthy individuals with biomarker levels that lie within the normal healthy range (as outlined in the Table 1 above). Because of the continuum between health and disease, all biomarker and risk reduction indications should include a disclaimer that recommends consumers consult a healthcare practitioner if they are concerned about their health status.



Indications that refer to the modulation of biomarker levels cannot be supported by evidence of traditional use.

Table 8 summarises the characteristics of values of biomarker ranges for healthy study populations.

Table 8: Summary of common biomarker ranges for healthy study populations

Biological Parameter	Value
Body weight (BMI)	20-24.9 kg/m ²
Blood sugar	Fasting 4.0-5.5mmol/L
Blood pressure	100/60-140/90mmHg
Blood cholesterol (total)	<5.5mmol/L
Blood cholesterol (LDL)	2.0-3.4mmol/L

Indications relating to weight loss

Indications relating to weight loss or management require supporting scientific evidence that demonstrates that the initial weight loss is meaningful to the consumer (that is, clinically significant) and can be maintained after the initial weight loss period.

In Australia, registered medicines targeting obese populations are required to demonstrate an absolute reduction in weight loss of at least 10% over one year (EMA (2007)). This degree of weight loss may not be desirable or appropriate for mildly overweight individuals. It is commonly accepted that a loss of 5% of initial body weight over six months is likely to represent a clinically significant degree of weight loss and is considered a minimum degree of weight loss required for listed medicines that are indicated for weight loss. Lesser degrees of weight loss are unlikely to be clinically significant and therefore generally considered inadequate to support indications associated with weight loss. It is possible for lifestyle modification alone to give similar weight loss results (Franz *et al* (2007), Wu (2009), Sacks (2009), Rose and Day (1990)).

In weight loss trials the control group commonly achieved some degree of weight loss due to changes in lifestyle, such as dietary intake and exercise. Evidence supporting weight loss indications claimed for listed medicines should demonstrate that the degree of weight loss is meaningful and unlikely to be attained through diet and exercise alone.

Rose and Day (1990) postulated that a mean reduction in BMI of approximately 1 kg/m² (one BMI unit) across a population could make significant impacts on the prevalence of obesity and overweight individuals within the population. A mean body weight loss of 3% is likely to be equivalent to a mean loss of one BMI unit in the population enrolled in a clinical trial. However, the clinical study population will often include obese individuals which are different to a healthy target population.

Obese people expend more energy for a given activity because of their larger body mass. Therefore, for the same level of dietary energy and physical activity, the reduction in body weight will be different for obese (BMI >30 kg/m²) and overweight individuals (BMI 25-30 kg/m²). This difference may be negligible for small increments in BMI but is likely to become increasingly significant as BMI increases.

Thus the degree of weight loss is likely to be different when comparing overweight and obese individuals when given the same treatment protocol. As such, studies that include obese participants with a BMI >30 kg/m² cannot be generalised to otherwise healthy overweight individuals.

It follows therefore, that in non-randomised controlled studies, the treatment group (BMI 25-29.9 kg/m²) should show at least a 5% greater weight loss than the placebo group to counter for potential confounding. There must be a reasonable chance that meaningful weight loss will be achieved in consumers investing in the medicine. Single mean values may be misleading and it is important that the effect of an ingredient or medicine represents a consistent effect across the whole target population. At least 50% of participants in the treatment group must achieve a loss of at least 5% of initial body weight, making it 'more likely than not' that consumers will achieve a clinically significant benefit from appropriate use of the medicine.

For each clinical study used to support weight loss indications, the meaningfulness of the observed effect to the general Australian population should also be assessed. Study outcomes that report statistical significant changes in weight loss parameters must also demonstrate clinical significance, or provide a meaningful health benefit to the consumer of your medicine.

Weight loss indications and scientific evidence

In general, for indications relating to weight loss in overweight individuals (BMI 25-30 kg/m²), clinical significance (that is a health benefit that is meaningful to the consumer) is only achieved if supporting scientific evidence demonstrates:



- a mean overall loss of at least 5% initial body weight in the treatment group, which is at least 3% greater (for RCT) OR 5% greater (for non-RCT) than that of the placebo group. In both cases the difference must be statistically significant ($p < 0.05$); and
- at least 50% of participants in the treatment group must have achieved a loss of at least 3% or 5% of initial body weight, respectively; and
- the study duration is a minimum of 6 months.

CASE STUDY 6: Primary and secondary clinical outcomes

A clinical study reporting the ability of *Caralluma fimbriata* to reduce hunger (primary outcome), does not support a weight loss indication, as only studies that directly assess weight loss can be considered relevant to the evidence base for a weight loss indication.

Changes in fat metabolism, thermogenesis, metabolic rate or reduction in hunger do not necessarily translate into weight loss and evidence supporting these indications cannot be extrapolated to support an indication for weight loss.

Table 9 provides examples of terms that are often related to, or used to convey weight loss that should not be substituted for the term weight loss in an indication. The evidence should support your indication, thus if your evidence refers to the reduction of hunger, then your indication could refer to reducing hunger, without extending this to weight loss or management.

Table 9: Terms that should not be substituted for the term 'weight loss' in an indication.

Metabolism	Body shape and composition	Weight-related	Appetite
Increased metabolic rate	Fat loss	Weight maintenance	Appetite suppression
Enhanced metabolism	Increased muscle mass	Weight control	Enhanced satiety
Enhanced fat metabolism	Cellulite	Weight management	Fasting
Thermogenesis	Slimming		
Increased calorie burning			

Indications relating to nutrient supplementation



If a listed medicine states that it is intended to supplement a named nutrient, it must provide at least 25% of the Recommended Dietary Intake (RDI), Adequate Intake (AI) or nutrient reference value for that nutrient and the nutrient should be in a form that is available for absorption by the body.

Supplementation non-specific indications

Non-specific supplementation indications are those commonly linked to medicines that only contain vitamins, minerals or nutritional substances as ingredients.

Statements relating to supplementation with vitamins, minerals or other essential nutrients (for example: a source of calcium) that imply a general health benefit (such as the maintenance of good health) are often supported by high-quality and credible scientific literature, such as internationally recognised pharmacopoeias or monographs, descriptive studies, case series or reports of relevant expert committees.

Providing the listed medicine provides the required amount of the nutrient, vitamin or mineral; reference texts, such as pharmacopoeias or monographs, or other evidence-based reference texts, are sufficient to support non-specific claims.

Supplementation specific indications

When the supplementation claim is linked to a specific therapeutic benefit, then additional scientific evidence is required to support the claim.

The salt of the nutrient/mineral/vitamins should be in a form that is readily absorbed by the body. The dosage directions for the medicine should ideally optimise the effect of the medicine (for example, take with food). For each nutrient, availability from non-food sources depends on the dosage, transport mechanism, age, gender, deficiency status and whether the supplements are taken with a meal (for example: Calcium citrate is 2.5 times more bioavailable (rate and extent of availability in plasma) than calcium carbonate when taken with a meal (Heller *et al* (2001)). Where vitamins, minerals or other nutrients are the subject of other indications, the dose must be consistent with the evidence to support the indication.

All indications for nutrient-containing medicines, whether implicit or explicit, must be appropriate for listed medicines. In general the indication must not refer to serious forms of a disease, condition, ailment or defect. Often the term 'dietary' is used as a qualifier to limit potential references to serious diseases and nutrient deficiencies.

For example:

'Helps to prevent dietary vitamin B12 deficiency.'

'Assists in the prevention of dietary iron deficiency.'

'Prevention of dietary vitamin [XX] deficiency.'

'Prevention of dietary mineral [YY] deficiency.'

'For the management of medically confirmed dietary vitamin [XX] deficiency.'

'For the management of medically confirmed dietary mineral [YY] deficiency (This indication is not to be used for the treatment of iron deficiency conditions).'

Appendix 1: How to use evidence package checklists

The following guidance assists you complete the evidence package checklists (provided on the TGA website and listed below) for the indications for your listed medicine.

List of checklists

Checklist title	Applicable for: Scientific evidence	Applicable for: Evidence of traditional use
Checklist 1: Evidence package cover page	Yes	Yes
Checklist 2: Evidence search strategy	Yes	Yes
Checklist 3: Evidence of traditional use filter Guidance to filter your evidence to identify those items that are credible, relevant and of high quality	No	Yes
Checklist 4: Scientific evidence filter Guidance to filter your evidence to identify those items that are credible, relevant and of high quality.	Yes	No
Checklist 5: Evidence of traditional use summary	No	Yes

The evidence which supports an indication for each ingredient is drawn from evidence of traditional use, or from other scientific research into the ingredient. Refer to the Evidence Guidelines for information on type of indications and evidence required to support them.

An indication may be related to one or more active ingredients, or to a fixed combination of active ingredients. For each indication-ingredient relationship, you need to complete the appropriate checklists to document:

- your search for evidence
- the findings from your search
- the credibility of the evidence you wish to use to support the indication or claim; and
- the relevance and consistency of the evidence, indication and medicine.

Your evidence package should include a summary of the evidence you hold supporting all the indications of your medicine and attached copies of evidence items.

If you have a traditional indication with evidence of traditional use

You are advised to include checklists 1, 2, 3 and 5 in your evidence package.

If you have a scientific indication with scientific evidence

You are advised to include checklists 1, 2, 4 and 6 in your evidence package.

If you have a both evidence of traditional use and scientific evidence

You are advised to include all checklists (1, 2, 3, 4, 5 and 6) in your evidence package.

Checklist 1: Evidence package cover page

Complete all sections of this document and attach to the front of your evidence package.

1a: Identification of listed medicine and sponsor details

Provide:

- the medicine name
- the medicine's AUST L number [when this has been assigned to the medicine - upon completion of your medicine application via the TGA's eBusiness services (eBs)]
- your name; and
- your contact details (as recorded in eBs).

1b: Listed medicine details

Provide general information on your medicine:

- dosage form, for example: tablet, capsule, oral liquid
- route of administration, for example: oral or topical
- intended population, for example: general, children, adults, elderly
- recommended dose unit, for example: 2 tablets
- maximum recommended daily dose (MRDD), for example: 6 tablets per day
- directions for use, for example: 'take 2 tablets before a meal'
- duration of use (where relevant): 'take for 2 weeks'; and
- cautions and contraindications, for example: 'not suitable for use in children'.

1c: Listed medicine active ingredients

For each active ingredient in your listed medicine, provide:

- the Australian Approved Name (AAN) for the ingredient
- plant/animal part (where relevant), for example: herb, flower, rhizome
- preparation (where relevant), include all extraction details:
 - number of extraction steps
 - solvent used
 - concentration
 - equivalent weights; and
 - any other relevant details.
 - For example: 'dried powder', '5:1 extract (in 25% ethanol) equivalent to 1g fresh leaf'.
- equivalent dose of substance per unit dose, for example: 500 mg per dose; and
- maximum recommended daily dose (MRDD), for example: 2 g per day.

1d: Listed medicine indication details

For each indication, you should assign a reference number (for evidence package) and record:

- the indication (health benefit of the medicine). Where the indication is traditional, the indication should use terminology appropriate to the traditional medical paradigm
- the active ingredient to which the indication relates to (as provided in 1c); and
- indicate whether the indication is traditional or scientific.

For medicines with more than one active ingredient, evidence to support the indications can be for the formulated medicine or be derived for each individual active ingredient.

A single active ingredient medicine can have more than one indication, for example: a medicine formulated with a single active ingredient might have two indications attributed to it: '*decreasing nausea*' and '*aids digestion*.' You should hold evidence for each of the medicine's indications.

1e: Evidence package details

Use this table to confirm that your evidence package includes:

- a completed cover page (checklist 1)
- scientific and/or traditional evidence search strategy (checklist 2)
- evidence filter for your traditional indication (checklist 3); and/or
- scientific filter for your scientific indication (checklist 4)
- summary of evidence of traditional use for your traditional indication (checklist 5); and/or
- summary of scientific evidence for your scientific indication (checklist 6)
- copies of supporting evidence for your indication (as listed in your evidence summary) attached: and
- an indication of the number of attachments and the total number of pages in the evidence package.

Next step

Complete checklist 2 to record your literature research.

Checklist 2: Evidence search strategy

You should undertake a literature search for your scientific or traditional indication. [The Australian Regulatory Guide for Complementary Medicines \(ARGCM\)](#) provides guidance on performing a literature search. It is recommended that the help of a specialist librarian is sought, particularly when searching non-English databases, when conducting the literature review.

Use checklist 2 to document the outcomes of your search of all items of evidence associated with your medicine. You should complete a separate document for each indication for your medicine. Add as many rows to the table as you need to record all evidence sources identified. This information is important to demonstrate that you have conducted an objective, comprehensive, transparent and reproducible review of the literature relating to your indication.

The quality of evidence will determine the nature of any claim and the wording that can truthfully be used. You are encouraged to refer to credible online sources, such as other regulatory authorities and other reputable agencies. New and unpublished data may be relevant, but they must be assessed within the context of the existing published body of knowledge.

Selecting and combining terms is of fundamental importance in searching electronic databases. You should document the search terms (online and within books) and databases you use and the number of references retrieved.

As traditional indications refer to a tradition of use rather than efficacy, efficacy data is not required (such as clinical trials or studies). However, it is important that the terms used to refer to a health benefit in the evidence held are identical or equivalent to those used in an indication.

Include all references that you find: even those you may discard later because they are irrelevant or poor quality. In particular include those references which do not support your proposed indication to show that a balance of evidence approach has been considered. You may be required to provide a justification to the TGA as to why this evidence was considered irrelevant.

The search must extend retrospectively for at least 10 years from the present day. Searches should not be limited to English, but every effort must be made to obtain translations of key references. Non-English language literature will need to be considered if this is a source of significant scientific work. All publications appended to the final report must be in the English language, or be a certified English transcript from the native language

Search strategy

Provide the following information in the table provided:

- Source searched:
 - identifying bibliographic details
 - exclude duplicate sources; and
 - include any website links.
- Date range of search: applicable for scientific literature searches.
- Search terms: include key words and specific exclusion terms.
- Type of evidence: Indicate if the evidence is scientific (such as: random control trial, evidence based text, Cochrane review) or evidence of traditional use (traditional pharmacopoeia, materia medica).

Example of entries in the search strategy table:

Search strategy for evidence package			
Source searched	Date range of search	Search terms	Type of evidence
Medline	01/01/2003- 10/10/2012	<i>Echinacea</i> and common cold NOT: influenza ,flu	Scientific: RCTs, non-clinical studies, mechanistic studies
<i>British Herbal pharmacopoeia</i>	NA	<i>Echinacea species</i>	Traditional: monograph

Next step

The items of evidence that you have collated through this process should be filtered in checklist 3 (evidence of traditional use) or checklist 4 (scientific evidence). The filtering process will determine the relevance and quality of each evidence item. This should be completed for all items of evidence.

Checklist 3: Evidence of traditional use filter

Use this checklist for traditional non-specific (general) and specific indications. Complete the checklist for each item of evidence.

Checklist 3 provides a filtering process to help you assess your item of evidence to determine:

- that the evidence supports a tradition of use for your indication
- the credibility of the item of evidence; and
- the relevance of the evidence to your medicine/indication.

The filter assists you reduce the number of evidence items to those that are credible and relevant, or to those that you can justify their inclusion into your evidence summary.

If you wish to use evidence for several ingredients to support an indication, each ingredient should be supported by evidence that meets the majority of checklist 3.a.

3a Filter for evidence of traditional use

Evidence item

Provide the details of the item of evidence that you are assessing.

Part 1: Tradition of use

This section of the checklist aims to establish if the evidence supports a history of traditional use (3 generations or 75 years) for your indication.

Your evidence of traditional use should refer to primary sources of evidence and you should check if they are adequately referenced. Some literature items cite, comment on or build on primary sources of evidence. If you use such an evidence item, you must locate the original or primary source of evidence of traditional use so as to establish primary references. That is, find copies or quotations from the original documents cited in footnotes. If this is not possible then include the footnotes in your evidence summary to clearly indicate that the textbook is based on original historic records.

Where it is impossible to find the original reference that describes the traditional use, evidence of traditional use may be supported by more recent references reporting the original tradition. However, these references should provide enough information to support that your medicine is consistent, as far as possible, with the one described in the original reference.

Part 2: Filter for credibility of evidence

This section of the checklist establishes whether the evidence item is from a credible source, such as internationally recognised monographs and pharmacopoeias. The credibility of evidence of traditional use may vary with the nature of the reference source, and the degree of clarity of references to a health benefit.

Part 3: Filter for relevance of evidence

The available evidence should be directly relevant to the proposed indication and ingredient characteristics (such as plant part and dose). This section of the checklist asks you questions relating to specific concepts to determine the level of relevance of the item of evidence. This will allow you to make an assessment on whether to include the item in your evidence summary.

You assess whether your item of evidence of traditional use is relevant by determining how similar it is to your medicine/indication. You determine this by answering by selecting either 'identical', 'similar', 'different' or 'unknown' to the questions for each piece of evidence you hold.

Indication

Your evidence should refer to the same specific health benefit (with the same meaning and intent) as your medicine.

If your indication is a specific traditional indication, the evidence should support this specific health benefit and context of use, for example: target population

Evidence of traditional use may be derived from populations that do not closely resemble the general Australian population (which is the target population for listed medicines in Australia). Further, some traditional medicine paradigms may specifically exclude certain subgroups of the populations from using a particular medicine (for example: children, pregnant women). Your indication should reflect this evidence

Active ingredient characterisation and traditional methods of formulation

The active ingredient should be clearly identified and characterised in the evidence, including:

- name:
 - Latin binomial for herbal species; or
 - correct scientific name (including relevant salt) for minerals, vitamins or other non-herbal substances)
- plant part; and
- preparation and extraction method.

Route of administration

How similar to your medicine is the description of intended route of administration (for example: inhalation as opposed to a chest rub) to that specified in the evidence?

Dosage

The dose, dosage form, dosage range and dosage frequency of the ingredient/medicine should be consistent with your evidence and the composition and preparation of the medicine should be consistent with the principles of the tradition about which the indication is made.

Duration of use

How similar to your medicine is the duration of use specified in the evidence, for example: long term, short term?

Risks, cautions or contraindications

How similar to your medicine is the information regarding any risks, cautions or contraindications (including identification of no known risks, cautions or contraindications) in the evidence to those of your medicine?

For example: if the evidence refers to the ingredient being contraindicated for use in children, your medicine should also reflect this restriction in use.

Assessment of evidence to support your indication

If you answer 'yes' and 'identical' to the majority of questions in checklist 3a, then your evidence item is likely to have a history of traditional use, be credible and relevant to your medicine. Such an item would be considered a primary source of evidence and can be used to support your indication.

If you answer 'no', 'similar' or 'different or not specified' to the majority of questions in checklist 3a, it is likely that the evidence does not support your indication and you should disregard it. If you choose to include this item of evidence in your evidence package you should provide justification as to why that item of evidence is included (see 3b).

3b Justification of evidence

It is recognised that it may be difficult to provide evidence for traditional indications that fulfil all aspects of the credibility and relevance criteria.

Some sources of evidence may not include sufficient details to meet the majority of the relevance and quality criteria in the traditional checklist filter (3a). In this situation, you should hold several sources of evidence that meet most of the relevance criteria in the traditional checklist and when these are combined, the collective source should provide all aspects of the evidence for all concepts raised in the filter. That is the combined items of evidence should address data gaps identified in 3a. This process allows you to use multiple sources of evidence of traditional use to accurately support your traditional indication.

If the evidence summary table lists evidence items that are not relevant (and no justification has been provided for their inclusion into your evidence summary), you may be asked for further clarification as to why you have included evidence that appears irrelevant.

Traditional ingredient changes

Traditional ingredients or medicines which have been altered significantly in their constituent profile from the classical traditional medicine on which the indication is based, further information may be required to justify the alteration in order to substantiate their claimed indication.

Next step

Once you have filtered your evidence to those references that are credible and relevant, or have a justification for their inclusion in your evidence summary, then these references should be included and summarised in Checklist 5: Summary table for evidence of traditional use.

Checklist 4 Scientific evidence filter

Checklist 4 has been provided to assist you with the decision on which items of evidence are relevant to your medicine and are of high-quality. Use this document to assess the relevance, quality and balance of your scientific evidence.

During your search for evidence you may come across many different types of evidence from a variety of different sources of literature and you must review the literature to collate high-quality evidence that is relevant to the indication or medicine – known as ‘filtering’.

All indications based on scientific evidence must be supported by primary evidence, such as clinical studies. The scientific uncertainties involved in extrapolating human data from animal and *in vitro* studies limit their usefulness as an evidence base to support your indication. Non-human and *in vitro* studies may, however, be used to support any discussion on biological plausibility of a potential mode of action in humans.

Establishing the relevant evidence base for your proposed indication is a critical step in the review of evidence. This requires an assessment of the relevance of every item retrieved during the literature review to your proposed medicine, dose and indications. The relevant evidence base for your indication includes all studies that are relevant in terms (amongst others) of ingredient, health benefit, population and context of use.

Additionally, you will be able to determine which items of evidence can be classified as a primary source of evidence (either supporting or non-supporting of your indication), and which item should be relegated to a secondary source of evidence.

If your medicine has more than one indication, you should fill out a new version of checklist 4 for each indication.



Use the scientific evidence filter to reduce the number of evidence items to those that are relevant and of high-quality, or to those that you can justify their inclusion into your evidence summary.

You should also ensure that the evidence supporting your indications remains valid for the life of the medicine, and this is best achieved using a body of evidence approach. As research advances, the body of scientific evidence supporting a particular health benefit may change. Newer clinical studies may enhance the strength of the evidence supporting your claim, or it may be inconsistent with the strength of previous research. Having a body of supporting evidence will allow you to ensure that the indications claimed for your medicine remain true, valid, not misleading and consistent with scientific evidence for the life your medicine.

4a: Simplified filter for non-specific supplementation indication

Vitamin, mineral and nutrient supplementation is often supported by high-quality and credible scientific literature. Use this simplified checklist if your medicine provides a vitamin, mineral or nutrient and the indication refers to general health and wellbeing and *does not* claim a specific health benefit.

Evidence item

Provide the details of the item of evidence that you are assessing.

Part 1: Filter for credibility of evidence

The questions in this part aim to establish that your evidence item is from a well-recognised and credible source.

Part 2: Filter for relevance of evidence

This part establishes that you have the same ingredient as in the evidence, it is absorbable by the body and the medicine provides 25% of the Recommended Daily Intake (RDI).

Assessment of evidence item

If you answered yes to the majority of questions above and have 2 sources of primary evidence, it is likely your indication will be supported by the evidence.

4b: Scientific evidence filter: relevance and quality

This section assists you determine which items of evidence in your evidence summary are relevant to your medicine and assess the quality of evidence that are relevant.

Provide details of the item of evidence at the top of the table

Evidence item

Provide the details of the item of evidence that you are assessing.

Part 1: Relevance of the evidence source to the indication.

The checklist includes questions to allow you to assess whether the item of evidence is relevant to your medicine. You assess whether your item of evidence of traditional use is relevant by determining how similar it is to your medicine/indication. You determine this by answering by selecting either 'identical', 'similar', 'different' or 'unknown' to the questions for each piece of evidence you hold.

Indication

You must ensure that the research is relevant to your proposed specific indication for your medicine. In drafting indications, you should take care to make sure that they match the underlying evidence you hold. Indications that do not match the science, no matter how sound that science is, are unlikely to be supported. Indications should not exaggerate the extent, nature, or prominence of the effects achieved in a study (the study outcomes), and should not suggest greater scientific certainty than that which actually exists.

Specificity

Your evidence should refer to the same specific health benefit (with the same meaning and intent) as your medicine.

If your indication is a specific traditional indication, the evidence should support this specific health benefit and context of use, for example: target population

Active ingredient characterisation

The active ingredient should be clearly identified and characterised in the evidence, including such things as plant part, preparation and extraction method.

For specific scientific indications, the different formulation between your medicine and that of the formulation reported in the scientific evidence is very important (for example: the use of a

novel tablet matrix). If there are differences noted, then further justifications will be required to address the data gaps identified using the checklists provided.

Active ingredient name

The evidence must be relevant to the ingredient name used in your medicine, such as the:

- Latin binomial for herbal species; or
- correct scientific name (including relevant salt) for minerals, vitamins or other non-herbal substances).

Dosage

For scientific indications, the recommended dosage and duration or frequency of administration of the medicine must be consistent with the evidence supporting the indication.

Route of administration

The evidence must relate to the whole medicine, the same active constituent(s) with a similar route of administration to the medicine for which a claim is being made.

Duration of use

The recommended duration of use for your medicine should reflect the evidence.

Risks, cautions and contraindications

Your medicine should restrict us to any risks, cautions or contraindications included in the evidence.

Part 2: Quality of the evidence item

In addition to determining the relevance of the item of evidence, you need to determine whether the evidence is of high quality, as the quality of evidence is important. Only items of evidence that are relevant to your medicine need to be filtered in this part of the scientific filter.

Clearly stated hypothesis

The item of evidence should clearly state the hypothesis or purpose of the study/research.

Study methodology

The clinical research being used to support your scientific indication should be conducted in a reliable manner to yield meaningful and reproducible results. The design, implementation, and results of each piece of research are important to assessing the adequacy of the substantiation of the health benefit or study outcome.

There are some principles generally accepted in the scientific community to enhance the validity of test results. However, there is no single set protocol for how to conduct research. For example, a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist and better evidence to identify potential safety concerns.

You should critically appraise scientific studies in terms of methodological quality and the possibility of bias and/or confounding. Studies that have been peer-reviewed are more likely to be methodologically robust, but may not be.

Filtering to relevant evidence to those of high quality will involve, as a minimum, an assessment of the following:

- characterisation of the ingredient/s
- study design/methods
- participant eligibility (inclusion/exclusion criteria)
- adequacy of randomisation and blinding of participants (for example Randomised Controlled Trials (RCT))
- sample size justification
- controlling for potential confounders
- study attrition (for RCT and cohort studies); and
- statistical analyses undertaken.

For each study, the meaningfulness of the observed effect/s to consumers at an individual and/or population level (clinical significance) must be assessed.

Participants enrolled in studies used to justify indications for your listed medicine should fit the following eligibility criteria, unless your medicine is directed to a specific population sub-group:

- male and female participants
- generally healthy
- aged 18–65 years; and
- socioculturally similar to the Australian population.

Secondary evidence or non-clinical studies (such as mechanistic studies) are normally insufficient to support indications implying efficacy. However, secondary evidence may be used in conjunction with primary evidence to strengthen the wording of an indication.

Participant dropouts

Attrition rates are commonly high in studies that evaluate health gains that are modest and require long-term commitment. High attrition can introduce serious bias (attrition bias) into these studies because the reasons for non-completion vary across initially randomised groups. High attrition rates may also diminish the general applicability of the treatment to the Australian population. The resulting data from a high attrition study should be interpreted with caution.

Confounders

Do any of the study's confounders or variable affect the relevance of the evidence to your indication?

Method of randomisation

Studies that incorporate randomisation process of assigning trial subjects to treatment or control groups are often considered of greater quality due the reduction of potential for bias. The randomisation method should be described in the study report and meet contemporary standards (such as using post-study questionnaires' of study participants to confirm that they remained blinded). Similarly, the incorporation of good blinding methods in the study design tends to result in studies that are methodologically robust.

Blinding protocol

Blinding protocols aim to avoid bias. A double blind protocol is where neither the experimenter nor experimental subjects have knowledge of the identity of the treatments or the results until after the experiment is complete.

Statistical analysis

Statistical significance of study outcomes is important. A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of a placebo effect or chance. The results should translate into a meaningful benefit for consumers. Some results that are statistically significant may still be so small that they may not provide a positive effect to consumer health.

Study limitations

You need to consider if any study limitation affect the relevance of the evidence to your indication.

Clinical significance

You should assess the results of scientific studies for statistical significance and meaningfulness (clinical significance) of the reported therapeutic benefit. Your evidence should demonstrate an overall improvement in the expected health benefit that is statistically and clinically significant.

Assessment of evidence to support your scientific indication

If you have answered yes or identical to the majority of questions it is likely that the item of evidence is relevant and of high quality and supports your indication.

Items that are considered to be of low quality should be disregarded unless you can provide a justification (refer to 4d) for its inclusion into your evidence summary as a secondary source of evidence.

4c: Balanced view of evidence

Part 4c assists you in make a balanced assessment of the evidence, which is an important criterion in evaluating the validity of your package is whether your evidence package represents a balanced view of the currently available body of evidence.

Before you list a medicine on the ARTG you must be satisfied that the balance of evidence supports your indication. In other words, a reasonable person making an objective assessment of all the relevant, high-quality evidence about your medicine would conclude that the weight of good evidence is in favour of your indication rather than against it. Your indications must not, indirectly, or by implication, lead consumers to believe that your medicine will assist in a health benefit that is not explicitly supported by the balance of evidence.

Studies cannot be evaluated in isolation of the surrounding context. The surrounding context of the scientific evidence is just as important as the internal validity of individual studies. You need to consider all relevant research relating to the claimed benefit of your medicine and should not focus only on research that supports the effect, while discounting research that does not. A well-constructed literature search should normally be undertaken to help ensure that the general body of evidence related to a specific indication is identified.

Your evidence should rely on studies that are largely consistent with the surrounding body of evidence. Where there are inconsistencies in the evidence, it is important that you examine whether there is a plausible explanation for those inconsistencies. In some instances, for example, the differences in results will be attributable to differences in dosage, the form of

administration, the population tested, or other aspects of study methodology. You should assess how relevant each piece of research is to the specific indication you wish to make, and also consider the relative strengths and weaknesses of each. If a number of studies of different quality have been conducted on a specific topic, you should look first to the results of the studies with more reliable methodologies (that is, RCTs or systematic reviews).

To facilitate the assessment of balance view of evidence, both relevant non-supporting and supporting items of evidence will need to be assessed for quality.

Checklist 4c provides a mechanism to determine the number of high-quality items that are relevant to your medicine. You will need to have regard to irrelevant studies noted during the search of the available literature to make an assessment of the balance of evidence for supporting your indication. Only if the balance of high quality evidence is equivocal are the outcomes of lower quality studies to be included in assessing the balance of evidence.

This checklist is designed to help you assess whether a reasonable person making an objective assessment of all the relevant, high-quality evidence about your medicine would conclude that the weight of high-quality evidence is in favour of your indication rather than against it.

When the balance of scientific evidence supports your proposed indication then complete the Scientific Evidence summary. Otherwise, you should reconsider your indication and modify the indication such that it is consistent with the evidence that you hold.

4d: Justification of evidence

If you choose to include a piece of evidence in your evidence summary that is not relevant, of high quality or reflective of the balance of evidence, you should provide justification for doing so. Otherwise you may choose to reconsider the wording (or strength/specificity) of your indication and evaluate the evidence for a modified indication.

If your evidence does not include certain details (for example: frequency of dose or dosage form) you should provide justification for the inclusion of these specific details on your medicine and this may be derived from another item of evidence.

Justification can consist of written explanations, documents and supportive evidence.

Next step

Once you have filtered your evidence to those references that are credible and relevant, or have a justification for their inclusion in your evidence summary, then these references should be included and summarised in Checklist 6: Summary table for evidence of scientific use.

Checklist 5: Evidence of traditional use summary

Use this document to summarise your evidence items that when considered together support your traditional indication (combined collection of evidence). You should only need to complete this summary document once for all indications related to your medicine.

5a: Reference list for indications

Provide the indications as listed in checklist 1; Evidence package cover page, part 1d.

5b: Reference list for items of evidence

Enter full citation details of the evidence into the table, and then use the corresponding 'Evidence reference number' to add detail on each of these references to the table in 5c.

You should record the following, where relevant, for each item of evidence you find in the summary of evidence of traditional use table:

- the bibliographic details
- author name
- article title
- journal title
- journal volume/issue number
- month and year of publication; and
- page numbers.

5c: Evidence summary for traditional indications

Use this section to summarise the findings and how they relate to your medicine. Ensure that the reason for including each item of evidence is clear from the information included in the list. If aspects of the evidence such as dosages, preparation types, indications or patient populations differ from those applicable to your medicine, include the justification of the relevance of the evidence in the 'Summary of findings' column.

You should attach a copy of each item of evidence to the checklist that applies to it, and make sure you note the correct publication details.

Examples of the type of the types of evidence included in the summary for a traditional indication include:

- copies of primary sources of information, for example: the relevant pages of a recognised pharmacopoeia such as the *British Herbal Pharmacopoeia*
- verified translations of those pages if the sources are in languages other than English
- video footage (digital format, not on film) or transcripts of any video footage being used as evidence; and
- any additional information to support justifications for inclusion of evidence items.

Checklist 6: Evidence summary for scientific indications

The evidence summary table is what the whole evidence-filtering process leads up to. Checklist 6 includes all the required summary information for your listed scientific indication.

If the evidence summary table lists items of evidence that are not relevant or includes poor quality studies (without providing justification for their inclusion into your evidence summary), the TGA may ask for further clarification as to why you have included evidence that appears irrelevant.



Does the Evidence summary table only include relevant, high quality evidence?

If not, then you will need to provide justifications as to why you have included these items in your evidence summary.

6a: Reference list for indications

Provide the indications as listed in checklist 1; Evidence package cover page, part 1d.

6b: Reference list for items of scientific evidence

Enter full citation details of the evidence into the table, and then use the corresponding 'Evidence reference number' to add detail on each of these references to the table in 6c.

You should record the following, where relevant, for each item of evidence you find in the summary of evidence of traditional use table:

- author name
- article title
- journal title
- journal volume/issue number
- month and year of publication; and
- page numbers.

6c: Evidence summary for scientific indications

Use this checklist to assist you to summarise your evidence and justify how it supports the scientific indications you claim for your medicine. You will take the items of evidence from checklist 4 which have been classified as supporting and summarise these in checklist 6.

You should attach a copy of each item of evidence and any additional information (for example: to support justifications for inclusion of evidence items) to your evidence package.

Appendix 2: Journal impact factors

The 'Impact Factor' (IF) is a measure of 'citation rate per article', and is calculated by dividing 1 year's worth of citations of a journal's articles published in the previous 2 years by the number of major articles published by that journal in those 2 years. Scientists strive to have their research published in journals with high IFs, as this has practical implications for their future funding and employment prospects.

Limitations of the IF

Generally, while high IFs are indicative of the (high) quality and "impact" of research published by a given journal, low IFs do not necessarily correlate with low quality research. A given journal may for example consistently publish 'good research', but have a low IF, if the field of research is narrow and therefore has a small readership/ authorship base.

Journals with high IFs (for example Science 31, for 2011) tend to have been established for many decades, and accept manuscripts from a broad range of disciplines. Because they have a high IF, researchers attempt to publish in them first, so they get "first right of refusal" on all the best research. IF is dependent on net readership, and therefore journals that publish weekly or are free to air have higher IF value compared to journals that are published monthly, but in general a higher IF value the better the research.

What constitutes a 'high IF'?

As a rough rule of thumb, the following can be used to assess the potential usefulness of papers published in a journal with a given IF:

Table Title

Impact Factor Range	Implication
0 ("not yet available") to < 5	Ambiguous/ uninformative
5 to < 10	Suggestive of "quality" research (i.e. rigorous peer-review and high interest-value)
≥ 10	Highly suggestive of quality research

Various companies provide IF values as well as other information of all journals to provide guidance regarding the level of quality of journals (website search for impact factors will find this information).

Appendix 3: Examples of internationally recognised resources and texts - monographs and pharmacopoeias

The TGA does not review the information included in internationally recognised resources and texts for example – monographs, pharmacopoeias, other text publications. It is your responsibility to ensure that the evidence you provide to support your indications is relevant to your medicine and is of sufficient quality.

The texts that are listed in this appendix are examples of internationally recognised texts that may provide evidentiary support to your indications.

Monographs

- Blumenthal M et al (eds) (2000) *Herbal Medicine – Expanded Commission E monographs*, American Botanical Council, Austin, Texas.
- European Scientific Co-operative on Phytotherapy (ESCOP) series (1996) *Monographs on the Medicinal Uses of Plant Drugs*, ESCOP, Exeter.
- World Health Organization (WHO) (1999) *Monographs on Selected Medicinal Plants, Vol 1*, WHO, Geneva.

Pharmacopoeias

- *British Herbal Pharmacopoeia*, British Herbal Medicines Association, West Yorkshire.
- *European Pharmacopoeia*, Council of Europe, Strasbourg.
- *Martindale: the Extra Pharmacopoeia*, Pharmaceutical Press, London.
- *The British Pharmaceutical Codex*, Pharmaceutical Press, London.
- *The British Pharmacopoeia*, Her Majesty's Stationery Office, London.
- *The United States Pharmacopoeia* and *National Formulary*, USP Convention Inc, Rockville, Maryland.
- *Pharmacopoeia of the People's Republic of China Vol 1*

Appendix 4: References

Benedict, M & Arterburn, D (2008). Worksite-based weight loss programs: A systematic review of recent literature. *American Journal of Health Promotion* 22(6): 408-416.

CONSORT website ([Consolidated Standards of Reporting Trials](#))

[European Medicines Agency \(2007\). Guideline on clinical evaluation of medicinal products used in weight control](#) (CPMP/EWP/281/96). London.

Franz M, *et al.* (2007). Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trials with a minimum of 1-year follow-up. *Journal of the American Dietetic Association* 107: 1755-1767.

Franz, M, *et al.* (2007). Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trial with a minimum of 1-year follow-up. *Journal of the American Dietetic Association* 107: 1755-1767.

Heller HJ, Greer LG, Haynes SD, Poindexter JR, and Pak CY (2000) Pharmacokinetic and Pharmacodynamic comparison of two calcium supplements in postmenopausal women. *J Clin Pharmacol Nov*; 40(11): 1237-44.

Jull, A, *et al.* (2009). Chitosan for overweight or obesity (Review). *The Cochrane Library* 2009(1): 1-44.

Koepsell, T & Weiss, N (2003). *Epidemiologic Methods: Studying the occurrence of illness.* Oxford University Press, New York.

National Health and Medical Research Council (2003). [Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults.](#) Canberra.

[National Health Medical Research Council. levels of evidence and grades for recommendations for developers of guidelines. 2009.](#)

[Note for guidance on good clinical practice](#) (CPMP/ICH/135/95). Therapeutic Goods Administration 2000.

Rose G and Day, S (1990). The population mean predicts the number of deviant individuals. *British Medical Journal* 301: 1031-1034.

Sacks F, *et al.* (2009). Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *New England Journal of Medicine* 360(9): 859-873.

Schulz, KF *et al.* (2010). CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. *Annals of Internal Medicine.* 152.

United States Federal Trade Commission's (FTC's) "[Business Guide for Dietary Supplement Industry Released by FTC Staff](#)". (The full version of the FTC's guidelines are available from the website.

Wu T, *et al.* (2009). Long-term effectiveness of diet-plus-exercise interventions vs. diet only interventions for weight loss: a meta-analysis. *Obesity Reviews* 10: 313-323.

Laaser U, *et al.* (2001). Can a decline in the population means of cardiovascular risk factors reduce the number of people at risk? *Journal of Epidemiology and Community Health* 55: 179-184.

Historical document

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au/>