This consultation closed on 25 May 2012.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Evidence required to support indications for listed medicines
(excluding sunscreens and disinfectants)

DRAFT

About the Therapeutic Goods Administration

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of 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.

Copyright
© Commonwealth of Australia 2012
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

This consultation closed on 25 May 2012.

Contents

DRAFT

This consultation closed on 25 May 2012.

Executive summary

This document outlines the requirements for evidence[1] held by sponsors to support indications[2] for listed medicines.[3]

For a medicine to be listed in the Australian Register of Therapeutic Goods (ARTG), an applicant must certify that they hold evidence to support each indication made relating to the medicine.[4] It is also a condition of registration of a listed medicine that the sponsor held that evidence at the time the indication was included in the ARTG, that the sponsor retains that evidence at all times while the medicine remains listed and that the sponsor will, if asked to do so by the TGA, give the information to the TGA.[5]

The Government has announced that once updated in consultation with stakeholders, it will be included in the regulations and given legal effect. This means that the evidence held by sponsors to support an indication will need to be provided in a form that complies with these requirements.

The document in divided into 3 main sections:

1. the first section provides information about the nature of listable indications,
2. the second section sets out what is required for an assessment of evidence supporting indications, including guidance about literature searching, and the assessment of the level, relevance, quality, outcomes and overall balance of currently available evidence in order for an expert report to comply with this guideline,
3. the third section provides information about certain required advisory statements.

The document recognises that evidence used to support indications for listable medicines is often retrieved from the available literature rather than sponsor-initiated clinical trials specifically conducted with a proposed product. As such, evidence may come from sources of evidence that describe the effects of single ingredients or combinations of ingredients that are different to those of an intended product. These issues are dealt with specifically in sections that provide guidance regarding the assessment of the relevance of scientific and traditional evidence to a proposed indication.

The document also recognises that the assessment of evidence relating to health outcomes requires particular expertise. It defines the requirements of individuals considered appropriate to assess evidence and aims to assist such individuals in providing a comprehensive and unbiased assessment of the available evidence.

In order to facilitate the review of evidence used to support indications, expert report templates are provided and must be completed. These reports represent the only form acceptable to the TGA and will be used by the Office of Complementary Medicines in its review of compliance with legislative requirements. Evidence provided to the TGA during any evidence based listing compliance review must be provided in the form of a completed summary chart with all relevant publications appended.

A sponsor may provide, in relation to an indication, an expert report that complies with the requirements of this document, however, it does not necessarily follow that the TGA must be satisfied there is evidence to support the relevant indication.

[1] The expression “evidence” is used in the document to refer to both information and evidence as referred to in paragraph 26A(2)(j) and subsection 28(6) of the Therapeutic Goods Act 1989..
[2] The reference to “indication” in this document includes a “claim” as that expression is used in paragraph 26A(2)(j) and subsection 28(6) of the Therapeutic Goods Act.
[3] This document replaces the document titled “Guidelines for levels and kinds of evidence to support indications and claims: For Non-Registerable Medicines, including Complementary Medicines, and other Listable Medicines”.
[4] See paragraph 26A(2)(j) of the Therapeutic Goods Act.
[5] See subsection 28(6) of the Therapeutic Goods Act.

This consultation closed on 25 May 2012.

Overview

Listed medicines are included on the Australian Register of Therapeutic Goods (ARTG) by sponsors through the eBS Listing Facility (ELF). Listed medicines can only contain listable ingredients and listable indications (see Section 1.2), and are subject to postmarket review.

Listable ingredients have been assessed for safety by the TGA and are of low risk. The TGA does not perform safety reviews on each newly listed medicine. Rather, the premarket safety assessment of listed medicines is based on an assessment of the ingredients that a listed medicine can contain. Neither does that TGA assess the efficacy of listed medicines prior to their inclusion on the ARTG. However an applicant to list a medicine on the ARTG must certify that it holds evidence to support any indications included on the ARTG[6]. The sponsor must retain that evidence at all times while the medicine remains listed and must, if asked to do so by the TGA, provide the information to the TGA.[7] All listed medicines must be manufactured according to Good Manufacturing Practice (GMP) to ensure adequate quality. [8]

Listed medicines may be selected for postmarket review. Postmarket review is product specific and may involve an assessment of product quality, safety and/or efficacy. This may be done by means of laboratory testing, review of evidence, and/or assessment of manufacturing documentation or product labels.

Purpose of this document

This document outlines the requirements for evidence[9] held by sponsors to support indications[10] for listed medicines.

In order to facilitate the review of evidence used to support indications, expert report templates are provided and must be completed. These reports represent the only form acceptable to the TGA and will be used by the Office of Complementary Medicines in its review of compliance with legislative requirements. Evidence provided to the TGA during any evidence based listing compliance review must be provided in the form of a completed summary chart with all relevant publications appended.

A sponsor may provide, in relation to an indication, an expert report that complies with the requirements of this document, however, it does not necessarily follow that the TGA must be satisfied there is evidence to support the relevant indication.

DRAFT

[6] *See paragraph 26A(2)(j) of the Therapeutic Goods Act 1989.*
[7] *See subsection 28(6) of the Therapeutic Goods Act 1989.*
[8] *See paragraph 26A(2)(e) and subsection 26A(3) of the Therapeutic Goods Act 1989.*
[9] The expression "evidence" is used in the document to refer to both information and evidence as referred to in paragraph 26A(2)(j) and subsection 28(6) of the Therapeutic Goods Act 1989..
[10] The reference to "indication" in this document includes a "claim" as that expression is used in paragraph 26A(2)(j) and subsection 28(6) of the Therapeutic Goods Act.

This consultation closed on 25 May 2012.

Section 1: Listable indications

1.1 Structure of indications

An indication, in relation to therapeutic goods, must describe the specific therapeutic uses of the goods.[11] Indications refer to a particular health benefit and therefore must include a nominated **action or effect** (such as reduces, improves, maintains, stimulates, or treats) on a defined **target** (such as a biological factor or process, a health state or a clinical condition). Targets may be general—such as pain, fever or general well being—or specific—referring to defined conditions such as knee pain or headache, or a specific receptor, molecule or biological process. Additional qualifying terms may be included to provide information relating to context of use (e.g. within a particular traditional paradigm or a particular subset of the population) or specific qualities of the action (e.g. rapid or sustained) or target (e.g. acute, severe or persistent). Indications can generally be reduced to the following pattern:

(CONTEXT) to/for the (Q_A) ACTION of (Q_T) TARGET

Where:

CONTEXT= potential contextual qualifier, ACTION=action, outcome or effect, TARGET=the clinical condition, health status or biological factor, Q_A=potential action qualifier, and Q_T=potential target qualifier.

Example:

Traditionally used in Australian Indigenous medicine to rapidly reduce high fever

CONTEXT Q_A ACTION Q_T TARGET

For the relief of severe menstrual pain

ACTION Q_T TARGET

1.2 Characteristics of listable indications

Clinical harms associated with medicines may come about in a variety of ways that include direct adverse effects associated with the actions of the medicine, and indirect effects that may be associated with drug interactions. The potential for clinical harm to occur is magnified when medicines are used inappropriately or unnecessarily, such as may occur when indications are not supported by evidence. In these situations, consumers may be exposed to potential adverse outcomes without any clinical benefit. Clinical harms may also occur if consumers treat themselves rather than seeking the advice of a medical practitioner or other health professional for potentially serious medical conditions. Inappropriate or unnecessary use may also be associated with significant financial harms.

Listed medicines are considered 'low risk'. This means that products eligible for listing must be safe for the use for which they are indicated in the absence of health practitioner supervision. In order to minimise potential risk, restrictions are placed on the nature of the ingredients permitted for use in listed medicines, and also on the indications that may be associated with listed medicines. In addition, indications must be supported by evidence that is acceptable to the TGA (as outlined in subsequent sections of this document).

An indication for a listed medicine:

[11] *Therapeutic Goods Act 1989*

- must be supported by appropriate evidence that is held by the sponsor and complies with the requirements outlined in this document, including the requirement to include any relevant disclaimers
- must be associated with a defined dose (and route of administration) of a listable ingredient, combination of ingredients or formulation
- must comply with the requirements of Schedule 4 of the Therapeutic Goods Regulations 1990.[12]
- generally do not refer to a disease, ailment, defect or condition that is not appropriate to diagnose, treat or manage without consultation with, or supervision by, a healthcare practitioner, and includes obesity but does not include being overweight.

1.3 Types of listable indications

Indications may be categorised in a number of ways. Historically the approach has been to recognise three categories of indications that form a hierarchy, each requiring an increasing 'level' of evidence.

Linking the type of indication with the level of evidence in this way is a useful risk-based approach, however the level of evidence of a study must be considered alongside a number of other factors such as the quality of the study, how well the study is reported, the consistency of its findings to those from other studies, the clinical impact of its results, the generalisability of the results to the population for whom the guideline is intended, and the applicability of the results to the Australian population.[13]

Furthermore, type of indication and level of evidence are different and unrelated concepts. Requiring different types of indications to be backed by different levels of evidence creates a situation that is potentially confusing and misleading to consumers, and one that does not provide an incentive for sponsors to market products backed by strong supportive evidence.

Indications may be better classified according to type of supporting evidence, and the type of health benefit expected. This approach maximises transparency and ensures that consumers are able to make informed choices about the products they decide to buy.

Scientific and traditional indications

Indications may be classified into 'scientific indications' or 'traditional indications' according to the type of supporting evidence. The evidence requirements for each type of indication are outlined in Sections 2.2.2 and 2.2.3 respectively. Unlike scientific evidence, evidence for traditional indications relates to a history of use rather than quantifiable assessment of scientific data, and therefore a mechanism must be in place to ensure that consumers are aware of the nature of the evidence supporting the proposed uses of the product so as to make an informed choice. The use of appropriate contextual qualifiers within indications ensures that such information is readily available to consumers.

Types of indication according to type of health benefit

In broad terms, indications may target biological factors, health states or clinical conditions. The following diagram provides a visual representation of all states of health through perfect health to symptomatic illness. It also includes a description of the different types of indications according to the action or effect on the indication target. Indications are conveniently separated into three clusters: health indications; risk reduction/prevention indications; and illness indications.

[12] This means that it cannot be for the treatment of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 of the Therapeutic Goods Advertising Code.
[13] National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. December 2009.

DRAFT

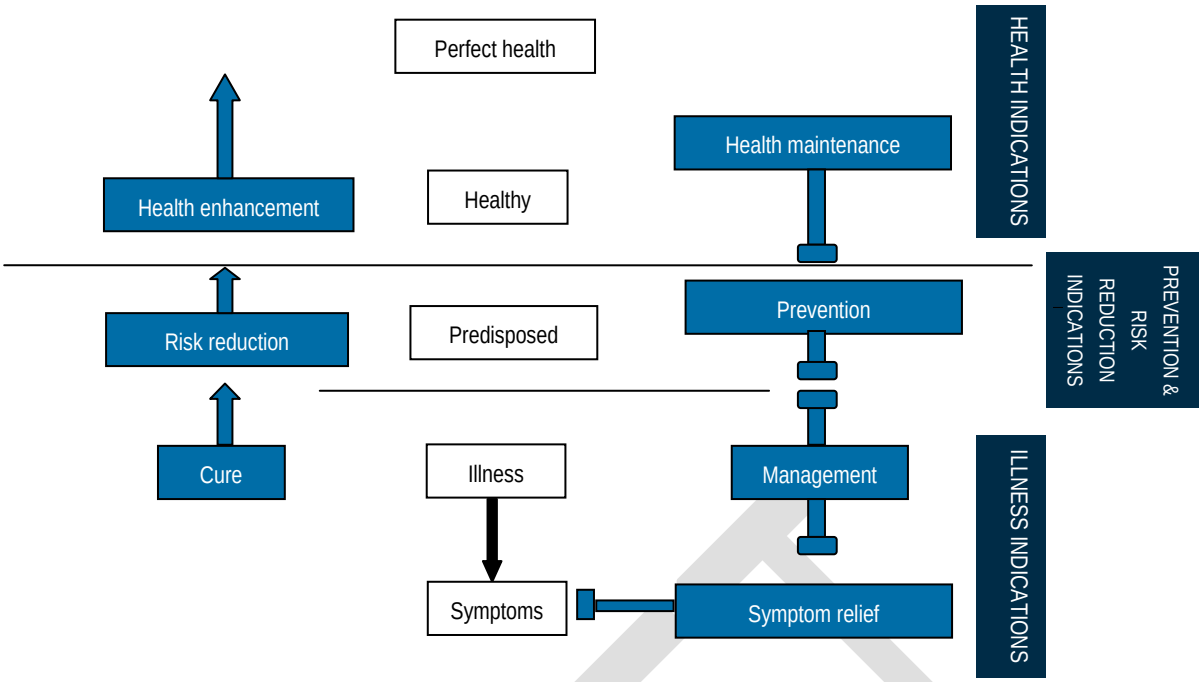


Figure 1. Schematic diagram showing relationships of different types of indications

Cluster 1: Health indications

Health indications target healthy individuals and assist in maintaining or improving their state of health and wellbeing. The health indication cluster includes the following types of indications:

- **Health maintenance**: normal physiological effects of nutrients and other substances in growth, development and normal functions of the body.
- **Health enhancement**: specific beneficial effects of nutrients and other substances on physiological and psychological activities beyond their role in normal growth, development and normal functions of the body.

Cluster 2: Risk Reduction and prevention indications

Risk reduction/prevention indications target individuals at risk of illness and partially or completely reduce the risk. The risk reduction/prevention indication cluster includes the following types of indications:

- **Risk Reduction**: favourable modification of a known risk factor for a specified illness.
- **Prevention**: prevents the development of a named illness.

Cluster 3: Illness indications

Illness indications target individuals suffering an illness (condition, disease or disorder). The illness claim cluster includes the following types of claims:

- **Management**: sole agent or contributing factor in the control of an illness such that morbidity is decreased and quality of life improved without resolution of the illness.
- **Symptom relief**: effectively reduces the frequency and/or severity of a symptom or cluster of symptoms associated with a named disorder.
- **Cure**: effects complete resolution of an illness and all associated morbidity**.**

DRAFT

This consultation closed on 25 May 2012.

Section 2. Evidence requirements: substantiating indications

In order to certify that it holds appropriate evidence to support listable indications, the applicant to list a medicine must demonstrate that the current available balance of relevant evidence is supportive. To ensure that the relevant body of evidence is comprehensively and objectively assessed, an 'expert' with sufficient clinical and critical appraisal skills to perform such a review must prepare a formal 'expert report'. An expert with the appropriate skills may be engaged to prepare such a report for the sponsor. The following sections outline the requirements of the expert report, and provide guidance regarding the interpretation of a potentially complex body of evidence.

In order for a listable indication to be supported by evidence, the following criteria **MUST** be fulfilled:

- The proposed indication must be a 'listable indication' as defined in Section 1.2.
- It needs to be clear in terms of the biological/clinical factor affected and the expected benefit.
- It must be linked to a defined and sufficiently characterised ingredient or group of ingredients.
- It must be supported by appropriate evidence (as described in Section 2.2).
- It must inform consumers of any limitations regarding the generalisability of the health benefit to the general Australian population.
- The expert report provided by the applicant in relation to the indication must be in an appopriate format (as described in Section 2.1).

Section 2.1 The expert report

In order for an applicant for a listable medicine to propose a listable indication, it must provide an objective report that contains a comprehensive analysis of the data relating to the proposed listable indication. This must be prepared by an expert with the appropriate skills to critically assess the available evidence and its relevance to the proposed listable indication. The following sections set out the requirements of the expert and export report provided in support of listable indications.

2.1.1 Scientific listable indications

2.1.1.1 Characteristics and qualifications of an 'expert'

The author of the expert report required for support a listable scientific indication must have both clinical and critical appraisal skills. A scientific expert will have completed, as a minimum, the following:

a. a tertiary degree (of at least three years duration) in a health profession; **and**

b. at least one of the following

   i. a course in critical appraisal or biostatistics from a tertiary institution (this could include a short course or a component of a masters); or

   ii. a PhD in a scientific or health related discipline; or

   iii. a specialist medical qualification.

2.1.1.2 Format of the expert report

The expert report must be either:

- based on a literature review of the existing body of evidence backing an indication for a particular ingredient, **or**
- involve the analysis of new, unpublished clinical trials. In the latter case, a thorough literature review must also be included to ensure that new data is assessed within the context of the existing body of knowledge**.**

The following table outlines the structure of the expert report. It must include the following sections..[14] This list is reproduced as an expert report template in Appendix 1 to assist sponsors in ensuring the expert report contains all necessary information. The report summary contains the essential information required by the TGA and **must be** provided to the TGA if requested.[15]

Section	Information required
Expert details	CV Justification of expert status
Recommendation	Proposed indication/s Ingredient details Grade of recommendation
Identification of evidence	Literature search strategy (including inclusion and exclusion criteria) Literature search results Any additional non-published studies
Relevance of evidence	Assessment of the relevance of retrieved results to proposed indication, proposed formulation, target population and context of use
Study quality	Level of evidence Participant inclusion/exclusion criteria Study method including randomisation and control of confounders Sample size determination Statistical analysis of results
Efficacy	Assessment of statistical and clinical significance Consistency of findings
Balance of Evidence	Body of evidence matrix Final Grade of recommendation

[14] These sections are broadly consistent with the recommendations of the National Health and Medical Research Council (NHMRC) in the document titled *NHMRC levels of evidence and grades for recommendations for developers of guidelines* NHMRC. 2009. <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf>

[15] See the condition of listing in subsection 28(6) of the Therapeutic Goods Act. A sponsor must also provide information or documents requested by the TGA under subsection 31(1) of the Therapeutic Goods Act.

This consultation closed on 25 May 2012.

Information regarding the assessment of evidence is provided in Section 2.2.2. In addition to the parameters described below, any new studies conducted should be conducted according to Good Clinical Practice (GCP) guidelines[16] and, the reporting of trials conducted should adhere to the principles outlined in the CONSORT statement.[17] Sponsors should also be aware of any requirements for listed medicines outlined in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM).[18]

2.1.2 Traditional listable indications

2.1.2.1 Characteristics and qualifications of an 'expert'

The author of the expert report required for support a traditional listable indication must have clinical skills, detailed knowledge of the relevant healing paradigm, and the ability to critically asses the relevant literature. An expert in the assessment of evidence of traditional use must have completed, as a minimum, the following:

a. a three year tertiary degree in a health profession; **and**

b. at least one of the following

   i. five years experience as a practitioner or researcher in the relevant traditional medicine paradigm; or

   ii. five years experience in an advisory or regulatory role related to the relevant traditional medicine paradigm; or

   iii. a PhD involving study of the relevant traditional medicine paradigm.

2.1.2.2 Format of the expert report

The expert report must be based on a review of the relevant literature and must include the components outlined in Section 2.2.3, which align broadly with those required for the assessment of scientific listable indications. The assessment of evidence is addressed in Section 2.2.3 and an expert report template is provided in Appendix 2 to assist sponsors in ensuring the expert report contains all the necessary information.

Section	Information required
Expert details	CV Justification of expert status
Recommendation	Proposed indication/s Ingredient details
Identification of evidence	Sources searched: pharmacopoeias, national formularies, monographs, textbooks, historical references
Relevance of evidence	Assessment of relevance of retrieved results to proposed indication, proposed formulation, target population and context of use

[16] Note for guidance on Good Clinical Practice (CPMP/ICH/135/95). Therapeutic Goods Administration 2000. <http://www.tga.gov.au/pdf/euguide/ich13595.pdf>
[17] Schulz, KF et al (2010). CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine. 152. <http://www.annals.org/content/early/2010/03/18/0003-4819-152-11-201006010-00232.full.pdf+html>
[18] Australian Regulatory Guidelines for Complementary Medicines (ARGCM). Therapeutic Goods Administration. 2012 (for release July 2012). <http://www.tga.gov.au/industry/cm-argcm.htm>

Section	Information required
Quality of evidence	How well is the paradigm, ingredient, preparation, dose, route of administration, target population and health benefit described?
Outcomes	Document the exact phrasing of health benefit described in the sources of traditional evidence
Balance of evidence	Body of evidence matrix Final grade of recommendation

Section 2.2. Evidence required to support listable indications

Scientific and traditional indications are fundamentally different; scientific indications are efficacy based and directed at the general Australian population, while traditional indications refer to a tradition of use within a particular paradigm.

Scientific evidence is derived from the scientific literature and may be used to substantiate indications that refer to health benefits in the general Australian population.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken into their mode of action and effect. The following definition of 'traditional use' has been adopted for the purpose of these guidelines.

Traditional use refers to a consistent body of documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.

Evidence of traditional use can only be used to support indications that refer to the traditional use of a medicine or preparation for a health benefit within a given healthcare paradigm.

Because of the nature of evidence of traditional use, traditional indications **must not** imply efficacy. Indications that are based on traditional use, must be true, valid, not misleading and consistent with its traditional use.In order to reduce the possibility that traditional indications are misinterpreted by consumers to imply efficacy, traditional indications must include a statement to the effect that the health benefit is based exclusively on long-term use and experience.

Appropriate scientific evidence must be available to justify scientific indications, and appropriate evidence relating to traditional use is required to substantiate traditional indications.

In situations where both scientific **and** traditional evidence requirements are met for an active ingredient or medicine, traditional and/or scientific indications may be made.

2.2.1 The assessment of evidence

Indications for listed medicines describe a relationship between using the medicine and a beneficial health outcome. When assessing the evidence base for a listable indication, the following factors must be considered:

- *Relevance of evidence:* for scientific indications, the findings of studies submitted must be relevant to the population targeted by the medicine. For traditional indications this is not necessary as the traditional context of use must be included in the indication. For both scientific and traditional listable indications however, the available evidence must be directly relevant to the proposed indication and ingredient characteristics (such as plant part and dose/posology).

This consultation closed on 25 May 2012.

- *Kind of evidence:* indications made by listed medicines may be substantiated by evidence of traditional use or by scientific evidence. Evidence of traditional use may only be used to substantiate traditional indications.
- *Level of evidence*: listable indications must be supported by evidence that is robust. Case-control studies, cohort studies and other clinical trials are the types of studies that may be appropriate to support scientific indications for listable indications. National pharmacopoeia that prescribe accepted uses for ingredients, national formularies, certain monographs and historical records are appropriate references for traditional listable indications.
- *Quality of evidence:* scientific studies must be critically appraised 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.[19] The quality 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.
- *Efficacy measures:* the results of scientific studies must be assessed for statistical and clinical significance. For scientific listable indication, the evidence available must demonstrate an overall improvement in the relevant parameter that is statistically AND clinically significant. As traditional indications refer to a tradition of use rather than medicine efficacy, efficacy data is not required. However, it is important that terms used to refer to a health benefit in evidence held are identical or equivalent to terms used in a listable indication.
- *Balance of evidence:* the balance and range of evidence available must support indications made by a listed medicine. The balance of evidence is represented by the studies or sources of evidence that are relevant to an indication. In order to support an indication, the available positive evidence must outweigh the equivocal or negative evidence. Plausible explanations need to be put forward to account for any inconsistencies or conflicts in the evidence.
- *Strength of the evidence:* the analyses performed above must then be brought together in the form of a matrix (Sections 2.2.2.6 and 2.2.3.6), with the objective of determining the overall strength of evidence supporting the proposed listable indication.

The following sections describe in detail the nature, quality and kind of evidence required to substantiate listable indications. These sections are designed to provide a guide for the assessment of potentially supportive evidence relating to listable indications, and to provide guidance for sponsors wishing to conduct their own efficacy studies.

2.2.2 Assessing scientific evidence

2.2.2.1 Searching the available literature

A comprehensive, transparent and reproducible review of the available literature that is of potential relevance to the listable indication is required. This process will involve the following steps:

- **Identifying relevant keywords related to the ingredient and health benefit.** The search terms should cover all aspects of the evidence required to be addressed in the expert report or which TGA may subsequently identify as of concern, and should consider synonyms and alternate spellings and terminologies.
- **Identifying relevant electronic databases such as MEDLINE, EMBASE, Web of Science, the Cochrane library, BIOSIS, Sciverse Scopus, Cab Health, AGRICOLA, and Food Science and Technology Abstracts.** The search must utilise MEDLINE and should involve at least one other relevant database. It is important to remember that literature from both the medical and nutritional literature may be of relevance when ingredients are components of foods.

[19] Gardner MJ, Bond J. An exploratory study of statistical assessment of papers published in the British Medical Journal. JAMA. 1990; 263:1355-7.

- **Determining any search limitations such as date ranges or languages. As a minimum, the search must extend backwards at least 10 years from the present day. Non-English language publications will** need to be considered if a substantial amount of scientific work has been reported in the non-English literature.
- **Documenting the search parameters and the results of the search.** The search should be documented to internationally accepted standard**s.**[20] The databases and search interfaces used and the numbers of references retrieved must be documented in the report.

It is recommended that the help of a librarian is sought when conducting the literature review.

Additional unpublished studies: unpublished studies may contribute to the evidence base for a scientific listable indication provided they fulfil the required criteria outlined below and have been reviewed by at least two independent reviewers (one of these may be the expert if not an author on the study). Studies that have been verified through peer review are more likely to be methodologically robust. This is particularly important where original research is used to support a listable indication. To facilitate an accurate interpretation of methodological quality, any original research must be appropriately documented.[21]

2.2.2.2 Level of evidence

NHMRC levels of evidence

Studies with increased methodological rigor are able to produce evidence that more closely reflects the health benefits associated with a particular intervention. Accordingly, the NHMRC has developed the following hierarchy of evidence[22]:

Level	Intervention
I	A systematic review of level II studies
II	A randomised controlled trial (RCT)
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: · Non-randomised, experimental trial · Cohort study · Case-control study · Interrupted time series with a control group

[20] Systematic Reviews: CRDs guidance for undertaking systematic reviews in healthcare. Appendix 3, Documenting the search process. York, UK; Centre for Reviews and Dissemination, January 2009. <http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm>

[21] Schulz, KF et al (2010). CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine. 152. <http://www.annals.org/content/early/2010/03/18/0003-4819-152-11-201006010-00232.full.pdf+html>

[22] NHMRC. NHMRC levels of evidence and grades for recommendations for developers of guidelines. 2009. <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf>

This consultation closed on 25 May 2012.

Level	Intervention
III-3	A comparative study without concurrent controls: · Historical control study · Two or more single arm studies · Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

In circumstances where it is not possible or ethical to perform randomised controlled trials, an appropriate hierarchy for scientific evidence may more closely align with the NHMRC model for assessment of prognosis or aetiology.[10] This may be the case for long-term health benefits where randomised controlled trials are impractical.

Level	Intervention
I	A systematic review of level II studies
II	A prospective cohort study
III-1	All or none of the people with the risk factor(s) experience the outcome and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect
III-2	A retrospective cohort study
III-3	A case-control study
IV	A cross-sectional study or case series

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

· systematic reviews and/or meta-analyses of all relevant RCT

· high quality, preferably multi-centre, RCT

· well-designed controlled trials without randomisation, or

· well-designed analytical studies preferably from more than one centre or research group, including cohort and case-control studies, or from multiple time series with or without intervention.

Clinical trials, particularly randomised 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 listable 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 scientific listable indication.

If a systematic review is used to support an indication, it is necessary to demonstrate that the studies included in the review are relevant and satisfy the requirements outlined in the subsequent sections.

This consultation closed on 25 May 2012.

2.2.2.3 Assessing the relevance of evidence to listable indications

Indications must not, indirectly, or by implication, lead consumers to believe that the medicine will assist in a health benefit that is not explicitly supported by the balance of evidence.

Establishing the relevant evidence base for a proposed indication is a critical step in the review of evidence. This requires an assessment of the relevance of every study retrieved during the literature review to the proposed product ingredient/s, dose and indications. The relevant evidence base for a listable indication includes all studies that are relevant in terms of ingredient, health benefit, population and context of use.

Relevance to health benefit

Indications describe beneficial effects on biological or clinical targets. All (and only) evidence that directly relates to the target described in a listable indication must be considered when assessing the evidence base for a listable indication. 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 (even if these are considered to be related).

Example:

A study that assesses the effect of an ingredient on the duration of the common cold does not contribute to the evidence base for a listable indication that describes a reduced frequency of the common cold or a reduction in symptoms of the common cold.

Example:

Only studies that directly assess weight loss or reduction in body mass index (BMI) can be considered relevant to the evidence base for a weight loss indication. Evidence supporting indications relating to weight maintenance, or changes in body shape and composition, does not contribute to the evidence base for a weight loss listable indication. Similarly, evidence supporting changes in body composition or body shape alone are not sufficient to demonstrate weight loss. An indication of increased lean body mass and decreased fat mass without any weight loss indicates a change in body composition rather than in weight, and would not be considered to meet the requirements for weight loss. Thus, a change in waist circumference without a change in weight would not be sufficient to support an indication for weight loss.

The following table provides representative examples of terms related to weight loss, that cannot be substituted for weight loss in a listable indication.

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

This consultation closed on 25 May 2012.

Example:

A listed herbal medicine containing Black cohosh (*Cimicifuga racemosa*) has the indication 'To assist in symptomatic relief of menopause'. An average consumer is likely to interpret this to mean that the product may assist in the relief of all symptoms associated with menopause—for example, hot flushes, insomnia, irritability, anxiety, vaginal dryness and osteoporosis. The sponsor holds a number of published controlled clinical studies that demonstrate that the subjects taking the herb (using a preparation and dose consistent with that proposed for the product) experienced significant reduction in the frequency and intensity of hot flushes. The primary objective of the studies was to determine the effect of Black cohosh on hot flushes only. The effect on other symptoms and signs were not examined. It could not, therefore, be used to support such an indication.

Ideally the health benefit should be included in the study as a primary outcome. This ensures that the study is sufficiently powered to detect a benefit that is statistically and clinically significant (Section 2.2.2.4). 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 (Section 2.2.2.5).

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.

Example:

An indication relating to weight loss refers to a clinical outcome. Changes in enhanced fat metabolism, thermogenesis, or metabolic rate do not necessarily translate into weight loss and evidence supporting these indications does not substantiate indications for weight loss.

In certain circumstances, it may be necessary to rely on surrogate markers rather than final clinical outcomes. This may occur, for example, with risk reduction claims where favourable manipulation of a known risk factor for a condition can be extrapolated to infer a reduction in risk of the condition, and can therefore be considered to support a risk reduction listable indication. In these cases, the expert must provide an evidence based justification of the extrapolation of data from surrogate marker to clinical outcome, and the listable indication must still satisfy the requirements of a listable indication set out in Section 1.2.

Qualifying a biological or clinical target

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

Example:

A listable indication describing a reduction in pain would draw on an evidence base that includes studies that assess pain outcomes in a variety of conditions and scenarios. In contrast, the evidence base relevant to a listable indication that describes a reduction in mild to moderate pain would be restricted to studies that specifically categorise and assess mild to moderate pain.

Study duration

Relevant studies must be of appropriate duration to validate a health benefit included in a listable indication. In other words, each study must be long enough to demonstrate the health benefit has been clearly achieved. 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 apply, 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

This consultation closed on 25 May 2012.

reduction, and those that produce favourable modulation of biomarkers, 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 to indications relating to these outcomes as longer treatment periods are required.

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

Example:

Acute pain relief: a reasonable trial would measure pain for several hours after an initial dose (related to dosing) and long enough to be representative of the pattern of use expected of a consumer when used to combat pain associated with a non-serious, self-limiting painful condition.

Example:

A reasonable timeline to achieve a significant degree of weight loss is six months. After about six months, the rate of weight loss usually declines as weight plateaus, and some regain is common.[23] Studies assessing weight loss should be of at least six months duration.[24,25] Weight loss is never linear and to extrapolate the effects of early weight loss is misleading and not acceptable. Studies conducted over a few days, weeks or months provide unreliable results. Furthermore, shorter studies may fail to demonstrate the full benefit of an intervention, including the ability of the intervention to sustain weight loss for a longer period. Therefore, studies considered relevant to indications relating to weight loss **must** be of at least six months duration.

Relevance to the proposed medicine

The active ingredient must be well characterised. Preparations used in studies that are cited as evidence to justify listable indication must contain the same substance that is administered in a similar form and preparation as that present in the medicine. In the case of listable indications based on vitamins, minerals, nutrients or known therapeutically active components of herbs, this involves careful consideration of the dose, route of administration and dosing regime employed in the available studies. In order to be considered relevant to the listable indication, all these factors must closely resemble that intended for the medicine.

When evidence 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 in the evidence held must be highly 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 studies, sponsors will need to hold evidence that the chemical profile of the active ingredient(s) is not substantially different from the preparation used in the studies to support the indication. Unfortunately, many trials of otherwise high quality inadequately describe or characterise the composition of the herbal intervention. Even when the herbal product is standardised to known active components or marker compounds, there can be variation in the concentration of other components that may result in different pharmacologic activity *in vivo*.

[23] 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.
[24] 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.
[25] Jull, A, et al. (2009). Chitosan for overweight or obesity (Review). The Cochrane Library 2009(1): 1-44.

When evidence supports a listable indication for one or more ingredients in the medicine (but not the medicine as a whole) indications **must** specify the ingredients for which evidence is held. Indications must only refer to medicines/substances for which a favourable evidence base exists (as described in subsequent sections). In order to establish the relevance of medicine to indications that relate to combinations of active ingredients, all studies included must involve the same combination of ingredients at comparable doses. This is discussed further in Section 2.2.5.

Other characteristics of products used in clinical trials may also impact on relevance to a proposed indication. For example, modified release forms of a medicine designed for slow or delayed release of an active ingredient may not be relevant in support of indications that refer to outcomes that are achieved rapidly.

Relevance to target population

Only human studies are considered sufficient to support indications for listed medicines. The scientific uncertainties involved in extrapolating non-human data from animal and in vitro studies limit their usefulness. Non-human and in vitro studies may, however, be used to support any discussion on biological plausibility.

General factors

Studies used to justify scientific listable indications should be conducted in populations that are reasonably representative of the general Australian population. Participants enrolled in studies used to justify indications for listed medicines should fit the following eligibility criteria, unless the medicine is directed to a specific population sub-group:

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

Health status

The health status of the study population must be representative of the target population. Many listed medicines target healthy individuals, individuals in a preliminary state of illness, or individuals with a borderline condition that places them at risk of illness. Data obtained from studies with participants that have serious disorders can not generally be extrapolated to a healthy population and, as such, these studies do not contribute to the evidence base for a listable indication. However, data collected from individuals with non-serious disorders and—in situations where a continuum of health and disease exists—individuals in early disease states may contribute to the relevant evidence base.

Example:

For listable indications on reducing gastro-intestinal discomfort (in the general population) evidence in patients with irritable bowel syndrome may be relevant. However, for indications on maintenance of normal joints (in the general population), evidence derived from studies of osteoarthritis patients would not be considered relevant. Osteoarthritis patients are not considered to be representative of the general population with regard to the status of their joint tissues; normal cells and tissues are different from osteoarthritic cells and tissues, and therefore may respond differently to an intervention with exogenous substances.

Establishing relevant study populations for listable indications that claim favourable modulation of measurable validated biomarkers of disease (such as BMI, blood pressure, blood glucose and cholesterol) in the healthy Australian population poses a particular challenge. Although a small change in a given biomarker may be associated with negligible biological dysfunction and minimal increase in risk of serious disease, larger changes are more likely to be associated with pathophysiological processes and increased risk of overt illness that require health practitioner involvement. For these reasons, it is unlikely that study populations with baseline biomarker levels

This consultation closed on 25 May 2012.

greater than 10 to 15 per cent above the accepted upper limit of 'normal' would be considered relevant to support indications relating to favourable modulation of measurable biomarkers of disease in the healthy Australian population.

Example:

Obese individuals have a higher basal metabolic rate (BMR) in absolute terms than lean individuals, but a lower BMR when expressed per kilogram of body weight. In addition, obese people expend more energy for a given activity because of their larger mass. Therefore, for the same level of dietary energy and physical activity, the magnitude of the effect will be different for obese and overweight individuals. This difference may be negligible for small increments in BMI but is likely to become increasingly significant as BMI increases. Furthermore, the degree of weight loss and number of dropouts in each group may be discordant for overweight and morbidly obese individuals within a study. [26] Because of these factors, weight changes observed in obese individuals with a BMI >35 kg/m^2 are not applicable to overweight persons. As such, studies that include obese participants with a BMI >35 kg/m^2 should not be generalised to otherwise healthy overweight groups.

For studies that involve specific cohorts (e.g. subjects with a disease) rather than the target group for a claim (e.g. the general population), it is the responsibility of the expert to provide an evidence based justification that results from a study group other than the target population are generalisable to the target population. This process must consider biological factors as well as environmental and behavioural factors including the influence of health practitioner intervention which may differ between healthy and unwell populations.

The following table summarises the characteristics of biomarker ranges for relevant study populations when included in biomarker listable indications targeting the general Australian population. In principle, the values given for the relevant study population lie within approximately 10 to 15 per cent of the upper limit of normal and include predisposed states but not overt disease.

Target population	Parameter	Australian population healthy reference range	Relevant study population*
Healthy population	Weight	20-24.9 kg/m2	18-30 kg/m2
	Blood sugar	Fasting <5.5mmol/L	Fasting < 7.0 mmol/L (and negative Glucose Tolerance Test)
	Blood pressure	<120/80 mmHg	<140/90 mmHg
	Blood cholesterol (total)	<5.5mmol/L	<6.0mmol/L
	Blood cholesterol (HDL)	Male: 0.9-2.0 mmol/L Female: 1.0-2.2 mmol/l	Male: 0.8-2.3 mmol/L Female: 0.9-2.5 mmolL
	Blood cholesterol (LDL)	2.0-3.4mmol/L	<4.0mmol/L
	Blood TAG	<2.0 mmol/L(opt)	<2.5 mmol/L

[26] Teixeira, P, et al. (2004). Pretreatment predictors of attrition and successful weight management in women. International Journal of Obesity, 28: 1124-1133.

Target population	Parameter	Australian population healthy reference range	Relevant study population*
Overweight	Weight	BMI 25-29.9 kg/m2	BMI 25-34.9 kg/m2

*All must be otherwise healthy

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

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 results 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 generalisability of study findings.

Listable indications directed at sub-groups of the general Australian population

When an indication is directed at a specific sub-group of the population, eligibility criteria will reflect the indication and may include additional requirements. When an indication is directed at a sub-group of the population, the sub-group must be specified in the indication. The results of studies that target specific subgroups cannot be generalised to the general population.

The following table provides guidance regarding the characteristics of study populations that provide relevant information for several indications:

Indication	Relevant population
For weight loss in overweight individuals when used in conjunction with a calorie or kilojoule controlled diet and physical activity (or exercise)	· male and female participants · aged 18-65 years · generally healthy population with BMI 25-34.9 kg/m^2 · socioculturally similar to the Australian population
Reduces pain	· male and female participants · aged 18-65 years · generally healthy population with a range of painful (non-serious) conditions
Relieves fever in children	· male and female participants · aged 2-18 years · generally healthy population with cough associated with a range of (non-serious) conditions
Calcium helps maintain healthy strong bones	· male and female participants · aged 18-65 years · generally healthy population · dietary and lifestyle pattern similar to the Australian

This consultation closed on 25 May 2012.

Indication	Relevant population
	population

Listed medicines **must not** target individuals with serious medical disorders, as referring to such disorders within an indication may be lead consumers to believe that the medicine provides treatment for the disorder.

DRAFT

This consultation closed on 25 May 2012.

Relevance of context

It is important to recognise that the body of evidence relevant to a listable indication is generally derived under conditions that are more restrictive than those experienced by consumers of listed medicines. 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 medicine *efficacy* but may overestimate medicine *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 confounding and bias due to differences in environmental conditions, participant characteristics and compliance.

Provided that measures are taken to ensure that the characteristics of the medicine, its indications, and its target population are consistent with the supportive evidence base, well controlled efficacy studies are considered the 'gold standard' for assessing health benefits provided by listed medicines. 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 (see Section 2.2.2.5) and this should be justified in the expert report.

However, where supportive evidence for a health benefit is limited to a particular context, this must be explicitly stated in the listable indication. Conversely, contextual qualifiers can only be introduced into a listable indication when the balance of supportive evidence within that specific context fulfils the requirements of the subsequent sections of this document.

Example:

The evidence base surrounding a modulating effect of Factor X on levels of calcium demonstrate a consistent increase in bone density but all studies have been conducted in postmenopausal women. The indication would need to include a contextual qualifier such as 'Used in postmenopausal women'.

Determining which studies to include for further analysis

It is important that only studies that are relevant to proposed listable indications are included in any subsequent analysis. The following table provides guidance regarding the inclusion and exclusion of studies from further analysis based on relevance to a proposed listable indication.

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
Relevance to medicine	Identical active ingredient, dose, formulation and route of administration	Identical active ingredient and route of administration, Consistent dose and formulation	Identical route of administration Consistent active ingredient, dose and formulation	Different ingredient or route of administration
Relevance to target population	Population studied is identical to the target population	Population studied is similar to the target population	Some differences between study and target populations but 'clinically reasonable' to apply evidence to the target population	Major differences or differences of uncertain clinical significance exist between study and target populations

This consultation closed on 25 May 2012.

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
Relevance to health benefit	Study directly measures health benefit in listable indication as primary outcome	Study directly measures health benefit in listable indication as secondary outcome	Study directly measures health benefit in listable indication as post-hoc analysis	Study does not directly measure health benefit in listable indication
Relevance to context	Study context directly applicable to Australian self care context	Study context applicable to Australian self care context with few caveats	Probably applicable to Australian self care context	Study context not applicable to Australian self care context

Only studies achieving ratings of 'satisfactory' or above in ALL four relevance categories are considered relevant to a proposed listable indication. All studies achieving four ratings of 'satisfactory' or above must then be included in subsequent analysis, and studies not achieving this must be excluded.

An Average Relevance Score (ARS) can then be produced by assigning a value to each rating (excellent=3, good=2, satisfactory=1, Poor=0) and calculating the average relevance score in the following way:

For each included study, add together all four relevance rating scores to produce the study relevance score.

$$R_S = R_M + R_P + R_B + R_C$$

Where R_S=study relevance score, R_M=relevance to medicine, R_P=relevance to target population, R_B=relevance to health benefit, and R_C=relevance to context.

Add together the study relevance score for all studies and divide by the total number of included studies

$$\text{Average relevance score (ARS)} = \frac{\sum R_S}{n}$$

Where R_S=relevance score for each study and n=number of relevant studies.

The ARS may vary between 4 and 12. For the purposes of assessing the balance of evidence (Section 2.2.2.6): an ARS above 9 indicates high relevance; an ARS of 7-9 indicates good relevance; an ARS of 4-6 indicates satisfactory relevance; and an ARS below 4 represents unsatisfactory evidence. Relevance scores for all studies retrieved during the literature review must be calculated and included in Section 3 of the Summary Chart at Appendix 2.

2.2.2.4 Quality of Evidence

Assessing the quality of studies that make up the relevant balance of evidence for an indication is essential in order to determine the validity of study results. A reliable assessment of study quality can only occur if the study design, methods and analyses are appropriately documented.

Methods

Studies must 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 participant cohorts must be described. The baseline distribution of potential confounders must be shown and any potential confounding must be considered and accounted for during the analysis. In addition, the limitations and generalisability of the study should be discussed.

Intervention and control groups

All participants enrolled in a clinical trial are considered to be derived from a common population and may be allocated to control or intervention 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 review to assess the possibility of corruption. Baseline characteristics of the intervention 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-intervention differences in health benefit between groups.

Interventions

Ideally, trials should be conducted under conditions where the only difference between groups is that one is exposed to the intervention, 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 systematic biases may impact on study results and must be considered and accounted for in the analysis. This may need to include behavioural and lifestyle factors such as diet and exercise.

Number of participants

It is important that trials enrol sufficient numbers of participants to detect a significant and reliable intervention effect. The number of participants needed to be reasonably certain of a reliable result needs to account for the degree of health benefit expected (in general a minimum clinically significant effect), 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 than those predicted by power calculations.

Power calculations should be used to estimate the minimum number of participants in the trial needed to detect a clinically significant health benefit. Clinical significance is often difficult to define, however a number of general principles can provide guidance. These are discussed in Section 2.2.2.5. Clinical significance should be clearly defined and factored into power calculations and study design. The number of participants required to detect a clinically significant difference between treatment and control groups depends on the degree of health benefit considered 'clinically significant', 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, calculations should be based on two-sided tests of significance at the five per cent level and at least 80 per cent power. As power calculations only predict the number of individuals required to complete the study, extra people must be recruited into a study to compensate for potential dropouts.

Attrition 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 may be differential across initially randomised groups. Changes in the composition of study groups may also diminish the generalisability of the intervention. As a result, data based on the health benefit to those who completed the program 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 measures should be carried forward. 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.[27] Sensitivity analyses provide an additional means of assessing the effect of dropouts on study results.

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

Analysis

Appropriate statistical methods must be used to compare the effects of an intervention 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.

Documenting quality of evidence

Studies of higher methodological quality carry more weight in an assessment of the relevant evidence base for a particular indication. A checklist is included in Appendix 2 to aid with the assessment of study quality, and **must** be completed for every study included in the review. The checklist enables the expert to determine a quality score (out of 15) for each study considered and requires the expert to tabulate the number of high quality (score 8-15) and lower quality studies (score 0-7).

2.2.2.5 Efficacy measures: Evidence of a health benefit

Efficacy measures

Ensuring that the body of evidence is relevant to the indication, medicine and target population makes it likely that the target population can achieve the indicated health benefit of a medicine. However, it is also important that medicines deliver health benefits that are unlikely to be due to chance and clinically significant.

Assessing the significance of outcomes

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

- statistically significant, and
- clinically significant.

For health claims, the effectiveness of substances in producing an outcome may be less distinct and less easily measured than for illness indications.

Statistical significance

It must be unlikely (probability of less than 5 per cent) 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. Ninety five per cent confidence intervals are commonly employed to show the range within which the true outcome value could be expected to occur with 95 per cent certainty. When 95 per cent confidence intervals are generated around outcome measures, the 95 per cent 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.[28,29,30] A statistically significant outcome indicates only that there is likely to be a relationship between intervention and outcome.

[28] Berry G Statistical significance and confidence intervals [Editorial]. Med J Austr. 1986;144:618-9.
[29] Sackett DL, Haynes RB, Tugwell P Clinical Epidemiology—A Basic Science for Clinical Medicine. Boston: Little, Brown & Co.; 1985.
[30] Levitt SH, Boen J, Potish RA Rebuttal to letter entitled 'Clinical trials: statistical significance and clinical importance.' Int J Radiation Oncology Biol Phys. 1981;7:1741-2.

This consultation closed on 25 May 2012.

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 measures of effect size have been used to help assess the clinical significance of a particular health outcome. These measures and their general interpretation are included in the following table for reference.

Interpretation	d	r	AUC (%)	RD (%)	NNT
Very large	≥1	≥0.7	≥76	≥52	≤1.9
Large	0.8	0.5	71	43	2.3
Medium	0.5	0.3	64	28	3.6
Small	0.2	0.1	56	11	8.9

Extracted from Kraemer et al 2003[31]
d= effect size, r=correlation coefficient, AUC=area under the receiver operating characteristic [ROC] curve, RD=risk difference, and NNT= number needed to treat

A detailed description of these measures is beyond the scope of this document, however it is important to understand that some of these measures, particularly 'd' value and number needed to treat (NNT), can often be calculated from data reported in studies even if not explicitly stated. The 'd' value represents a measure of the size of the outcome relative to the standard deviation of the study population. NNT represents the inverse of the absolute reduction in risk (ARR). Dividing ARR by the rate of events recorded for the control group then gives the relative risk reduction (RRR) which is equal to one minus the relative risk (RR). An odds ratio (OR) rather than RR may be calculated for case-control studies as data regarding the total number of individuals is not known. The OR provides a reasonable estimate of RR provided that the outcome being assessed is relatively uncommon.

Although these measures are useful as a guide, determining clinical significance is a complex and subjective process. Consumers and researchers judge clinical significance by weighing up factors such as clinical benefit, cost and side effects.[32] 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.

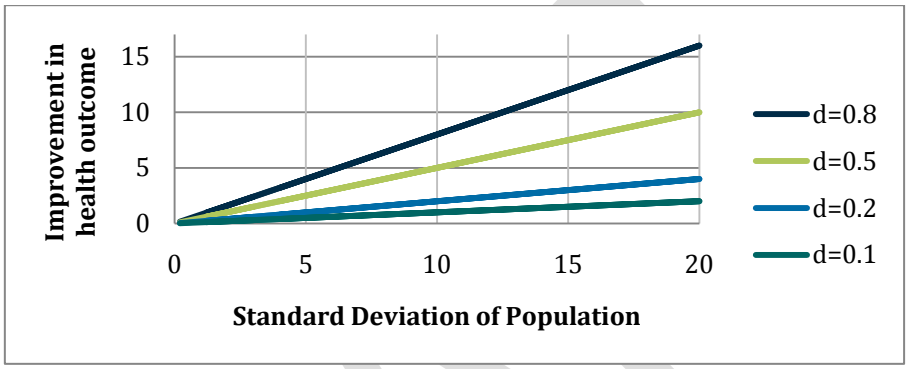
Judgements about clinical significance are often made by experienced clinicians within a context of ongoing monitoring and supervised care. Listed medicines, however, are freely available to consumers and may not involve practitioner intervention or supervision. Determining the clinical significance 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 an established disease.

[31] Kraemer HC, Morgan GA, Leech NL et al. Measures of clinical significance. J. Am. Acad. Child & Adolesc. Psychiatry;2005. 42(12): 1524-9
[32] Ibid

- Because listed medicines are unscheduled[33] and readily available to the Australian population, small benefits that do not produce clinical benefits that are significant at the individual level, may be meaningful at the population level.

In general terms, no further justification is required if the body of evidence supports an effect size (d) of 0.5 or above (or equivalent r, AUC, RD or NNT). For listable indication where the evidence supports an effect size less 0.5, the expert must justify the clinical significance of the effect size for the given listable indication. This justification may involve consideration of benefits to the consumer or to the population more broadly. In general, effect sizes below 0.2 (or equivalent) would not be considered clinically meaningful. In circumstances where the TGA requires a sponsor to submit an expert report,, the TGA will consider the clinical significance (irrespective of d score)on a case by case basis. The following diagram illustrates the relationship between 'd' value for various differences in health outcomes for different population standard deviations. The following table provides some guidance based on typical population standard deviations of a variety of biomarkers.



Indication biomarker	Typical population standard deviation	Improvement for d=0.8	Improvement for d=0.5	Improvement for d=0.2	Improvement for d=0.1
BMI*	4.3 kg/m^2	3.4 kg/m^2 (approx 11.5% body weight)	2 kg/m^2 (approx 7% body weight)	0.9 kg/m^2 (approx 3% body weight)	0.5 kg/m^2 (approx 1.5% body weight)
Systolic BP	20 mmHg	16 mmHg	10 mmHg	4 mmHg	2 mmHg
Diastolic BP	10 mmHg	8 mmHg	5 mmHg	2 mmHg	1 mmHg
Total cholesterol	1.2 mmol/l	0.96 mmol/l	0.6 mmol/l	0.24 mmol/l	0.12 mmol/l
Blood sugar	3 mmol/l	2.4 mmol/l	1.5 mmol/l	0.6 mmol/l	0.3 mmol/l

*additional requirements apply, see below.

[33] That is, are not included in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

This consultation closed on 25 May 2012.

Special requirements for indications related to weight loss

Registered medications targeting obese populations are required to demonstrate an absolute reduction in weight loss of at least 10 per cent over one year.[34] This degree of weight loss may not be desired or appropriate for overweight individuals.

It is commonly accepted that a loss of five per cent of initial body weight represents a minimum clinically significant degree of weight loss[35] and is considered a minimum degree of weight loss required for listed medicines indicated for weight loss. Lesser degrees of weight loss are unlikely to be clinically significant and are inadequate to support therapeutic indications. It is possible for lifestyle modification alone to produce weight loss of this degree that is maintained over periods greater than six months.[36, 37, 38]

However, in weight loss trials the control group commonly also achieves some degree of weight loss. Listed medicines must demonstrate an added benefit that is meaningful and unlikely to be attained through diet and exercise alone. Rose and Day[39] postulated that a mean reduction in BMI of one kg/m^2 across a population could make significant impacts on the prevalence of obesity and overweight. This has been borne out in subsequent studies.[40] A mean weight loss of three per cent is likely to represent a mean loss of one BMI point in the population enrolled in a clinical trial (BMI 25-34.9 kg/m^2). This will translate to an expected weight loss of greater than three per cent of initial body weight for the target population of the medicine (BMI 25-29.9 kg/m^2). In non-randomised controlled studies, the treatment group must show at least five per cent 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. Mean values may be misleading and it is important that the effect of a substance or medicine represents a consistent effect across a target population. At least 50 per cent of participants in the treatment group must achieve a loss of at least five per cent of initial body weight, making it 'more likely than not' that consumers will achieve a clinically significant benefit from appropriate use of the medicine.

Therefore, in order to justify indications relating to weight loss in overweight individuals (BMI 25-30 kg/m^2) supporting evidence must demonstrate:

- a mean overall loss of at least five per cent initial body weight in the treatment group, which is at least three per cent greater (for RCT) OR five per cent greater (for non-RCT) than that of the placebo/control group. In both cases the difference **must** be statistically significant ($p<0.05$);

AND

- at least 50 per cent of participants in the treatment group **must** have achieved a loss of at least five per cent of initial body weight.

[34] European Medicines Agency (2007). Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96). London. <http://www.emea.europa.eu/pdfs/human/ewp/028196enfin.pdf>

[35] NHMRC (2003). Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults. Canberra. <http://www.health.gov.au/internet/main/publishing.nsf/Content/obesityguidelines-guidelines-adults.htm/$FILE/adults.pdf>

[36] 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.

[37] 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.

[38] 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.

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

[40] 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.

This consultation closed on 25 May 2012.

2.2.2.6 Assessing the balance of evidence

Once the characteristics of individual studies have been assessed, the balance of the scientific evidence must be determined. All relevant studies must be considered and the results of a hand-picked study or studies will not constitute evidence in the absence of an assessment of the totality of currently available relevant evidence. Evidence will **only** be taken to support an indication if the balance of currently available relevant evidence is positive.

Once the key features of relevant studies have been assessed, the expert must summarise the relevant body of evidence and provide an overall assessment of the balance of evidence supporting the indication. This process involves three steps:

1. preparation of an evidence statement matrix
2. formulation of a recommendation based on the body of evidence
3. determination of the grade for the recommendation.

The evidence statement matrix provides ratings for key characteristics of the evidence across the body of relevant evidence. The following table provides guidance on how to complete the matrix. [41]

Element	A (excellent)	B (good)	C (satisfactory)	D (poor)
Relevance	Average relevance Score 10-12	Average relevance Score 7-9	Average Relevance Score 4-6	N/A*
Evidence base	· at least one level I study, OR · three level II studies with a low risk of bias	· one or two level 2 studies, OR · a systematic review, OR · at least three level III studies with a low risk of bias	· One or two level III studies with a low risk of bias · one or two level I or II studies with a moderate risk of bias	· Level 4 studies, OR · level 1-3 studies, OR · systematic review with a high risk of bias
Consistency	All high quality studies show SS positive effect	Most high quality studies show SS positive effect	High quality studies equivocal, lower quality studies mostly consistent with respect to a SS positive effect	Inconsistent (equivocal)
Clinical impact	Very large (d>0.8)	Large (d= 0.5-0.79)	Medium (d<0.5 justified)	Small (d<0.5 not justified)

Level of Study derived from NHMRC 2009[42] (See Section 2.2.2.2)
*If only one study then consistency rated as N/A

The relevance, evidence base and clinical impact have been discussed in sections 2.2.2.2-6. An assessment of the consistency of evidence requires consideration of both the quality and outcomes of the studies included in the report. The expert is asked to firstly consider the outcomes observed in high quality studies, and then only consider the consistency of outcomes observed for lower

[41] The table has been adapted from the NHRMC document titled "NHMRC levels of evidence and grades for recommendations for developers of guidelines".
[42] NHMRC. NHMRC levels of evidence and grades for recommendations for developers of guidelines. 2009. <http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf>

This consultation closed on 25 May 2012.

quality studies if the outcomes observed for high quality studies are not clearly consistent. Section 5 of the Summary Chart at Appendix 2 guides the expert through this process.

The expert must then use the information summarised in the matrix to assess support for the proposed indication and determine the grade for the recommendation. The following table provides definitions for grading the recommendation. [43]

The grade for the recommendation is given by the lowest rating achieved in any of the four categories (relevance, evidence, consistency, clinical impact). Recommendation grades of C and above indicate acceptable support for listable indications. However, if a grade C is achieved, additional qualification of the indication may be required in order to ensure that consumers remain informed regarding potential limitations of the evidence.

Grade of recommendation	Description
A	Body of evidence strongly supports listable indication
B	Body of evidence broadly supports listable indication
C	Body of evidence supports listable indication with qualification
D	Body of evidence inconclusive
E	Body of evidence does not support listable indication

Example:

A sponsor plans to promote a herbal product for the relief of nocturnal leg cramps. A well documented literature review reveals one relevant randomised, placebo-controlled study in eight volunteers demonstrating the product to be effective in reducing the frequency and severity of nocturnal leg cramps. However, there are several other relevant RCTs that do not show such a benefit. It is not clear whether the different results of the various studies are a consequence of differences in product formulation or dosage or some other factor.

Even though the single study is positive, it does not provide adequate substantiation because the totality of existing evidence does not suggest that the herbal ingredient ameliorates nocturnal leg cramps. Moreover, the very small study size represents a weakness. If no plausible explanation can be found to explain the disparate results (selection of different population groups—men, women, age—dose, preparation, etc), given the weakness of study and the weight of contrary evidence, the available evidence is not adequate to substantiate the indication.

As the body of evidence for complementary medicines is constantly changing it is possible that the balance of evidence for a listable indication may change over time. Because of this: unsupported indications may become supported if favourable evidence emerges that tips the balance

2.2.3 Assessing evidence of traditional use

Traditional medicine includes a diverse range of health practices, approaches, knowledge and beliefs incorporating medicines of plant, animal, and/or mineral origin, spiritual therapies, manual techniques and exercises applied singularly or in combination. Traditional medicine is an integral element of some cultural practices, such as traditional forms of Asian medicine and Aboriginal and Torres Straits Islander healing practices. Traditional medicine may also be referred to as indigenous, folk, holistic or natural medicine, and other variations.

[43] The table has been adapted from the NHRMC document titled "NHMRC levels of evidence and grades for recommendations for developers of guidelines".

Some traditional systems of medicine are highly developed and well documented. They are based on systematized knowledge, a comprehensive methodology and rich clinical experience obtained over long periods of time. Many forms of traditional medicine have been adopted by populations outside their indigenous origin and culture. There are also a large number of less complex traditional medicine practices that have been developed within small and localised ethnic groups or areas. Such practices are based largely on empirical experiences of treatment and include the use of complementary medicines. The knowledge may not be documented and is transmitted orally from generation to generation.

Traditional medicines have an extensive history of use, sometimes measured over thousands of years. Factors that should be taken into account to establish that a Listed complementary medicine or an active ingredient(s) has a well established traditional of use for its intended purpose, includes the time over which the medicine or active ingredient has been used and certain quantitative aspects of its use. This includes the extent of use (local, national or global) of the medicine or active ingredient and the continuity of its. Therefore different periods of time may be necessary for establishing that a listed complementary medicine or an active ingredient has been used traditionally. In any case the period of time required for establishing a traditional medicinal use of a listed complementary medicine or an active ingredient must not be less than 75 years from the first documented use of the medicine or active ingredient(s)[44]. This provides for 3 generations of human experience and an accumulated repository of observation that underpins the use of these medicines. Medicines that have been used over a long period of time usually result in preparations where the dosage and formulation have empirically evolved to maximise their therapeutic effectiveness and minimise risk.

Traditional medicines and ingredients that have a long and coherent history of use are expected to have useful bibliographic data and information published in the form of official pharmacopoeia, materia medica, ethnological/cultural monographs, national regulatory authority reports and other authoritative sources. Evidence that a medicine has been used traditionally for a particular therapeutic purpose can be used to support indications for listed medicines provided that they meet the requirements of the following sections of this guideline.

2.2.3.1 Searching the available literature

A comprehensive, transparent and reproducible review of the literature that is of potential relevance to identify evidence of traditional use of active ingredients and products and their associated traditional therapeutic use. A systematic literature review must be undertaken to assess the breadth of available evidence and the relevance of each item then considered in relation to the indications, medicine composition and target population. Literature to be searched should include national pharmacopoeias, national formularies, national materia medica and other monographs and other historical or authoritative texts that are relevant to the traditional paradigm.

Selecting and combining terms is of fundamental importance in searching electronic databases, as is an understanding of the structure of each database. Searches should not be limited to English, but every effort should be mage to obtain translations of key references. See the Australian Regulatory Guidelines III – Section 5.9. Searching the Literature on Complementary Medicines for general help in identifying information sources, search terms and developing a search strategy. Sponsors are also encouraged to refer to authoritative online sources, including, but not limited to, regulatory authorities and other reputable agencies. It is recommended that the help of a specialist librarian is sought, particularly when searching non-English databases when conducting the literature review.

It is particularly important to determine whether the product to be listed in the ARTG is essentially the same as detailed in the supporting reference(s). For example, source species are the same, the respective quantity of crude extract are the same, the method of preparation is the same, and the particular combination of active ingredients is identical.

[44] In regulatory jurisdictions where a shorter period of traditional use has been specified, such as Canada and the European Community, the evidence or information supporting traditional use claims is assessed by the competent authority prior to market entry.

This consultation closed on 25 May 2012.

Use of secondary references such as abstracts, reviews, general textbooks, research focused journal articles etc. as primary references to support the traditional use of the medicinal ingredient is unacceptable

This process will involve the following steps:

- identifying relevant paradigm (e.g. Western herbal medicine, traditional Chinese medicine, Ayurvedic medicine)
- identifying relevant sources (including national pharmacopoeias, national formularies, authoritative texts, historical records)
- wherever possible, using primary sources of information (these may be cited in scholarly or authoritative texts and journal articles) and tracing back references in any pharmacopoeia and authoritative texts so as to establish primary references.
- eliminating duplicate references
- documenting the search parameters and the results of the search.

2.2.3.2 Level of evidence

Substantiating traditional listable indications depends on identification of evidence that supports the use of a substance within a particular paradigm over three or more generations for a specific health related or medicinal purpose. National pharmacopoeias (that include information related to therapeutic use), national monographs and the inclusion of a medicine for a particular use in a national formulary provide high level evidence that the use is established and broadly accepted within a given context. The pharmacopoeias must be issued or endorsed by the relevant government authority. (Note that the word 'pharmacopoeia' in the title of a text does not mean it is a government-endorsed text.). Such pharmacopoeias include the British, European, United States (of America), Chinese, German, Indian and Japanese Pharmacopoeias.

Certain other monographs and material medica that have been reviewed by the TGA are also acceptable evidence of traditional use (Appendix 1). Independent historical records[45] can provide useful information. However, isolated reports may not be representative of well established traditional use. Because of this, historical records used to substantiate traditional indications must demonstrate coherent use over a period of at least 75 years. This may involve multiple historical records or records that include information relating to use over time.

Textbooks provide useful information in guiding the expert towards sources of primary evidence but are not sufficient evidence to substantiate traditional indication. Where textbooks are referenced, traditional evidence must be followed back to the original supporting documentation. These may then be used as original independent historical records. When textbooks are not referenced, the source of evidence supporting the reference is not clear and therefore not acceptable unless the text is considered authoritative and thus represents a primary source of information.

Evidence held by the sponsor to support traditional indications must be in the English language, or be a certified transcript translated from the native language.

The potential sources of traditional evidence may be considered within a hierarchy. This is shown below.

Level	Intervention
I	National formulary, monograph or pharmacopoeia
II	TGA accepted traditional monograph or material medica (see Appendix 1)

[45] Independent historical records are references that do not cite the same source or each other as the main source of information regarding the traditional use

Level	Intervention
III	Original historical records
IV	Non-TGA approved reference texts

Texts such as the Natural Medicines Comprehensive Database, Natural Standard, Physicians Desk Reference, general textbooks and scientific journal articles (other than papers reporting original ethnobotanical research) cannot be used to support traditional listable indications.

Oral histories of use

In some cultures the transmission of information relating to traditional medical practices may occur solely through verbal communication. Where this is the case (such as for traditional Indigenous Australian medicine) oral histories of use may substitute for original historical records provided that evidence is obtained independently from multiple practitioners or members of indigenous group(s) who maintain such a history. Such evidence must be collected by an ethnographic professional with the appropriate expertise to gather the required information.

When evidence is obtained from multiple practitioners, full narratives must be obtained from each practitioner on an individual basis and interviews with different practitioners must occur at different times and places without the opportunity for collaboration. In order to generate one item of evidence equivalent to an original historical record, the multiple accounts must yield a consistent approach (substance, dose, route of administration and use) within a particular locale or group. Enough information relating to the traditional practice must also be obtained to enable an adequate assessment of the relevance of the evidence to health benefit, medicine, population and context as outlined in Section 2.2.3.3.

The ethnographic professional collecting the information must gauge the regional breadth of the practice by interviewing practitioners in different locales. Consistent approaches in three separate locales may equate to three original historical records and provide sufficient evidence to support indications couched within a context of traditional use within the appropriate cultural paradigm (e.g. traditional Indigenous Australian medicine). On occasions where use is restricted to fewer than three locales, due to geographic factors such as limited availability of a particular herb, sufficient evidence may be present to support an indication. However, additional qualifications may be necessary to inform consumers that the traditional use was restricted to a particular regional area, locale or group.

2.2.3.3 Relevance of traditional evidence

Relevance to health benefit

Indications must remain true to the context of use from which substantiating evidence has been derived and must refer to a 'tradition of use'. When traditional use is limited to a particular paradigm or geographical region then the paradigm/region must be referenced in the indication.

Terms used in traditional listable indications must be consistent with those referenced in the traditional evidence source and must **not**:

- reference specific anatomical, physiological or pharmacological effects that are not envisaged within the paradigm and/or require scientific substantiation such as stimulation or modulation of the immune system or antioxidant functions
- reference conditions that cannot be diagnosed within the identified healing paradigm such as the maintenance of normal glucose levels, blood pressure or cholesterol
- be interpreted or extrapolated to infer benefits that were not readily recognised within the traditional paradigm such as weight loss, addiction cessation and providing specific vitamins, minerals or essential fatty acids

- contain vague or ambiguous terms that may be misinterpreted by consumers to infer use in serious disorders, such as 'useful for chronic inflammation' or 'used as a healing aid for urinary disorders'
- refer to serious disorders, or symptoms that may imply a serious disorder (as per all listable indications).[46]

Example:

Terms used to describe weight loss in indications must be identical to terms referenced in the evidence held. Only evidence that directly refers to use for 'weight loss' may be used to support traditional weight loss indications. Evidence relating to traditional use for suppression of hunger and promotion of fasting are **not** acceptable justification for traditional weight loss indications. Sources that contain paradigm-specific terms that may imply weight loss do not provide substantiating evidence for weight loss indications. Such terms are also generally not permissible in listable indications as they may be poorly understood or misinterpreted by consumers within the general Australian population.

Relevance to the proposed medicine

Evidence may refer to a formulation or an ingredient of the medicine. Indications must only refer to formulations/ingredients for which 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:*

*e.g. '**Contains ingredients** traditionally used in Ayurvedic medicine to aid sleep'.*

For non-herbal ingredients, the route of administration, dose, and dosing regime for each active ingredient (or combination of active ingredients) contained in the medicine must be consistent with the evidence base. When evidence relates to a herb or herbal substance, the species (and subspecies where applicable), plant part, and route of administration must 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 in the evidence held must be highly consistent with that of the herb or herbal substance in the medicine. When evidence for a range of preparations is held, the preparation used in the medicine must fall within this range.

A judgement may need to be made to determine whether the product to be listed in the ARTG is essentially the same as detailed in the supporting reference(s). Active ingredients can be considered as sufficiently identical (a corresponding product[47]) if the specification is the same and there are no relevant differences in the method of preparation and that the product, irrespective of the excipients used, has the same intended purpose, dosage and posology and the same route of administration. This includes traditional medicines in which the therapeutic indication and claims, dosage and administration are based on traditional knowledge but the dosage forms have been modified to modern dosage forms, e.g. capsules or tablets.

To make a traditional indication for a product the method of preparation of the active ingredient(s) must be those traditionally used. Traditional methods of preparation include:

- the use of a whole organism or specific parts (leaf, root, fruiting body, etc.);

whether 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;

[46] Therapeutic Goods Advertising Code. Appendix 6 Part 2

[47] A corresponding product is characterised by having the same active ingredients (but not necessarily the same excipients); the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration.

This consultation closed on 25 May 2012.

- glycerine-based extracts;
- vinegar-based extracts;
- oil, grease or fat-based infusions;
- beeswax salves and ointments.

Other methods of preparation may be considered traditional if supported by an appropriate and authoritative reference describing the method's use within the traditional medicine paradigm. However, non-traditional methods of preparation of otherwise traditional materials, including the use of non-traditional solvents, can quantitatively and/or qualitatively 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 claim is based require scientific evidence in order to substantiate their claimed action.

Relevance to population

Sources of evidence for traditional indications are likely to be derived from culturally homogenous populations that do not closely resemble the general Australian population. This reduces the generalisability of the expected health benefit(s) to the Australian population, but is acceptable provided that efforts are made to ensure that consumers remain informed. Because of this, the context of use (paradigm/region) **must** be referred to in the indication.

Evidence of traditional use in populations or individuals with serious medical disorders can generally **not** be extrapolated to the healthy population and, as such, these sources can not contribute to the evidence base for a listable indication. Listed medicines **must not** refer to or target populations with serious medical disorders.

In some traditional medicine paradigms may specifically exclude certain subgroups of the populations from access to a medicine. This information may be provided in language that is specific to that healing paradigm or culture. In cases where it is not evident to the consumer that the risk information is traditional in nature, an appropriate traditional qualifier must be included, e.g. “Do not use in pregnancy.

Relevance of context

Sources of evidence must be relevant to a common traditional context or paradigm. For traditional listable indications, the body of evidence relevant to a listable indication is generally derived under conditions that do not resemble those experienced by consumers of listed medicines as the historical and cultural context of use is far removed from self-selection and self-use use by consumers in contemporary Australia. Because of the discordance between traditional and contemporary contexts, and the potential for consumers to assume that products have been assessed scientifically, traditional listable indication are **required** to include the context (traditional paradigm) in the indication:

*e.g. ‘**Traditionally used** as a sleep aid in **Ayurvedic medicine’.***

Determining which sources of traditional evidence are relevant

All (and only) information that is relevant to proposed listable indications must be considered as part of the relevant body of evidence. The following table provides guidance on the inclusion and exclusion of studies from further analysis based on relevance to a proposed listable indication.

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
Relevance to medicine	Identical ingredient, dose and formulation	Consistent with ingredient, dose and formulation	Consistent with ingredient and dose	Not consistent with dose and ingredient
Relevance to target population	Population studied is identical to the	Population studied is similar to the target population	Some differences between study and target populations	Major differences or differences of uncertain clinical

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
(excluding ethocultural factors)	target population		but 'clinically sensible' to apply evidence to the target population	significance exist between reference and target populations
Relevance to health benefit	Indication in reference source is identical to listable indication	Indication in reference source is clearly equivalent to listable indication	Indication in reference source is equivalent (taking into account historical and cultural trends) to listable indication	Indication in reference may be interpreted as different to listable indication
Relevant to context	Clearly identified within the relevant healing paradigm	Identified (with some interpretation) with the relevant healing paradigm	Consistent with (in terms of time and location) the relevant healing paradigm	Not consistent with the relevant healing paradigm

Only studies achieving ratings of 'satisfactory' or above in **ALL four** relevance categories are considered relevant to a proposed listable indication. All studies achieving four ratings of 'satisfactory' or above must be included in subsequent analysis, and studies not achieving this must be excluded.

An average relevance score (ARS) can then be produced by assigning a value to each rating (excellent=3, good=2, satisfactory=1, poor=0) and calculating the ARS in the following way:

For each included source add together all four relevance scores (relevance to health benefit, medicine, target population and context) to produce the total study rating score.

$$\mathbf{R_S = R_M + R_P + R_B + R_C}$$

Where R_S=source relevance, R_M=relevance to medicine, R_P=relevance to target population, R_B=relevance to health benefit, and R_C=relevance to context.

Add together the source relevance score for all items of evidence and divide by the total number of included items

$$\textbf{Average relevance score (ARS)=} \quad \frac{\sum R_S}{n}$$

Where R_S=relevance score for each study and n=number of relevant studies.

DRAFT

This consultation closed on 25 May 2012.

The ARS may vary between 4 and 12. For the purposes of assessing the balance of evidence (Section 2.2.2.6), an ARS above 9 indicate high relevance, an ARS of 7-9 indicates good relevance and an ARS of 4-6 indicates satisfactory relevance. Relevance scores for all studies retrieved during the literature review must be calculated and included in Section 3 of Summary Chart at Appendix 3.

2.2.3.4 Quality of traditional evidence

The quality of evidence relating to traditional use may be highly variable. National pharmacopoeia, formularies and certain monographs provide high quality evidence of traditional use and may be used to support traditional listable indications.

When supporting evidence includes independent written histories of use in the classical or traditional literature, the significance and clarity of references to any health benefit must be assessed. In some cases, references to health benefits may be vague and difficult to interpret. Similarly, some sources may not provide clear information about the route of administration, dose or preparation. In some cases, the context of use may be unclear and some texts may not accurately document the accepted uses of a preparation within established norms. Such limitations reduce the quality of evidence. Texts that lack or contain ambiguous information relating to health benefit, target population, ingredient, dose and, when relevant, nature of the preparation, can not be used to justify indications based on a history of traditional use.

In cases where modern texts reference historical sources, only the historical source can be used as evidence to substantiate indications relating to a health benefit. Modern texts that reference common historical sources cannot be used as additional items of evidence. In certain cases, texts may rely on a combination of traditional and scientific evidence. In these cases, only references to traditional use can be used to support traditional indications.

Section 4 of Appendix 3 includes a quality checklist for traditional evidence that must be completed for every source reviewed.

2.2.3.5 Efficacy and traditional evidence

In many cases, traditional evidence will not provide an indication of the degree of a given health benefit achieved using an intervention, and will not clearly document other factors potentially contributing to a positive outcome (confounders). Often it is unclear whether an outcome was achieved at all, or in other cases it will be unclear whether the reported health benefits were regularly achieved. For traditional listable indications, efficacy is implied through a tradition of use rather than scientific and statistical evaluation of outcomes. For these reasons it is important that indications describe the 'use' of the substance or medicine and not its 'efficacy' or 'effectiveness'.

It is important to ensure that the traditional use of a substance or combination of substances is consistent with the use described in an indication. The exact terms used by each piece of traditional evidence to describe the intended health benefit must be explicitly documented in Section 3 of Appendix 3.

2.2.3.6 Assessing the balance of traditional evidence

As listed medicines are available for self-selection by consumers in the general Australian population, it is important that traditional listable indications accurately reflect treatments used to bring about health benefits that were broadly accepted and available within a defined cultural paradigm.

In order to establish this, a comprehensive assessment of the relevant traditional literature is required. A thorough literature review must be undertaken to assess the breadth of available evidence and the relevance of each item then considered in relation to the indications, medicine composition and target population. This must include national pharmacopoeias and monographs, national formularies, TGA accepted monographs and material medica, and other historical reports that are relevant to the paradigm specified in the listable indication as outlined in the preceding sections.

References in reference or textbooks must be traced back to original historical references and do not constitute evidence of traditional use in their own right (unless the authoritative text is a historical record in its own right).

National pharmacopoeias, national monographs, national formularies and TGA accepted monographs and material medica represent items of evidence in their own right as they indicate broad acceptance within a specified population. Isolated historical records of use may not be representative of the application of a particular use within a population. For this reason, three independent written histories of use are required to establish one item of traditional evidence.

Traditional references that do not contain indications for a particular health benefit do not necessarily constitute negative primary evidence, however references that specifically advise against use for that health benefit do constitute negative evidence.

The following matrix is reproduced in Section 5 of Appendix 3 and aims to assist the expert in the assessment of the balance of traditional evidence.

Element	A (excellent)	B (good)	C (satisfactory)	D (poor)
Level	Included in TGA approved national pharmacopoeia, national formulary or monograph	Included in non-TGA approved national pharmacopoeia, national formulary or monograph	>3 historical references spanning at least 75 years	Not included in national pharmacopoeia and national formulary and in fewer than three historical references
Relevance	Average relevance score 10-12	Average relevance score 7-9	Average relevance score 4-6	N/A
Quality	Average quality score 11-14	Average quality score 8-10	Average quality score 5-7	Average quality score <5

The expert must then use the information summarised in the matrix to assess support for the proposed indication and determine the grade for the recommendation. The following table adapted from the NHMRC provides definitions for grading the recommendation.

The grade for the recommendation is given by the lowest rating achieved in any of the four categories (relevance, evidence, consistency, clinical impact). Recommendation grades of C and above indicate acceptable support for listable indications. However, if a grade C is achieved, additional qualification of the indication may be required in order to ensure that consumers remain informed regarding potential limitations of the evidence.

Grade of recommendation	Description
A	Body of evidence strongly supports listable indication
B	Body of evidence broadly supports listable indication
C	Body of evidence supports listable indication with qualification
D	Body of evidence inconclusive
E	Body of evidence does not support listable indication

DRAFT

This consultation closed on 25 May 2012.

Example:

A sponsor wants to market a product with a claim 'For the symptomatic relief of hangovers'. The product contains a number of herbs commonly used in traditional Chinese medicine. The only evidence the sponsor holds is a copy of the relevant pages from a contemporary Chinese reference that indicates one of the herbs present in the medicine was used in ancient times for symptoms that overlap with the symptoms of hangover. There is no information on the plant part used, the method of preparation or the recommended dosage. In this instance, the evidence would not be sufficient to support the proposed claim.

2.2.4 Potential clashes between traditional and scientific evidence

The potential exists for apparent clashes between the conclusions of traditional and scientific evidence. Substances or preparations used traditionally for a particular purpose may not be shown to be efficacious when subjected to scientific scrutiny. The significance of this depends on the nature of the indication. When used appropriately, traditional indications present factual statements regarding an historical record of use within a given paradigm. The availability of evidence that disputes the efficacy of the preparation does not disprove the history of use and the traditional indication remains valid. However, issues may arise if traditional indications fail to place therapeutic use within an appropriate context or use vague terms such as 'has been shown to produce weight loss'. For this reason, traditional indications must refer to the tradition of use. In additional, all indications and claims based on traditional use must include a statement to the effect that the efficacy of the product is based exclusively on long-term use and experience.

In situations where traditional indications are used in tandem with factual statements relating to the mechanism of action of ingredients, the combined statements **must not** imply efficacy.

Products with combinations of active ingredients, some of which have a history of traditional use and others which do not, cannot be regulated as traditional medicines. Therapeutic indications for these products must be supported by scientific

2.2.5 Evidence requirements for listed medicines containing multiple ingredients

Multiple ingredient listed medicines are common. Multi-ingredient listed medicines will contain indications that are associated with either

- single ingredients substantiated by scientific evidence, or
- single ingredients substantiated by evidence of traditional use within a single paradigm, or
- single ingredients substantiated by evidence of traditional use within multiple paradigm, or
- an established formulation (fixed combination) substantiated by scientific evidence, or
- an established formulation (fixed combination) substantiated by evidence of traditional use within a single paradigm, or
- combinations of the above

General points

Evidence relating to listable indications based on combinations of ingredients must fulfil the criteria outlined in Section 2.2.2 or Section 2.2.3. In order to establish relevance of an indication to a proposed medicine, all items of evidence included must involve the same combination of ingredients at comparable doses as the sole active ingredients. When combining ingredients, it is the sponsor's responsibility to ensure that the final formulation is rational and fully supported by evidence.

Single ingredients substantiated by scientific evidence

When evidence supports a listable indication for one or more ingredients in the medicine (but not the medicine as a whole) indications **must** specify the ingredients for which evidence is held. Where statements implying synergistic effects of multiple ingredients are made, evidence must be identified to support the synergistic effect.

This consultation closed on 25 May 2012.

Established formulations (fixed combination) substantiated by scientific evidence

When evidence supporting a particular listable indication is based on a particular combination of ingredients, then the evidence can only apply to that particular combination (ingredients, preparation, formulation and posology) and cannot be extrapolated to any individual ingredients. The active ingredient/s must be clearly identified and justification must be provided if a constituent of the fixed combination is considered to be an excipient (e.g. to improve the taste or to influence physical properties of the product) rather than an active ingredient. Whether a constituent of the medicine is an active ingredient or excipient will have important consequences for the consideration of the evidence base.

Single ingredients substantiated by evidence of traditional use within a single paradigm

Therapeutic indications for combination products must be consistent the traditional use of each active ingredient in the product. If all the individual ingredients in a combination product are traditionally indicated for a similar therapeutic purpose, it would be appropriate to apply this to the therapeutic use of the product without specifying the individual ingredients.

For example,

If all the active ingredients are traditionally used for alleviating the symptoms of the common cold (cough, fever, sore throat), the indications for each ingredient could be described separately, or applied to the product (Traditionally used in herbal medicine for relieving cold symptoms).

Single ingredients substantiated by evidence of traditional use within multiple paradigms

Where multi-ingredient products comprise active ingredients from different traditional paradigms, therapeutic indications must be based on, and consistent with, the traditional use of each active ingredient in the product. The rationale for the combination must be justifiable in terms of therapeutic purpose, including the dose of each ingredient based on their respective traditional uses. Each indication must refer to the relevant ingredient and healing paradigm.

For example,

A product containing *Panax ginseng* and *Bacopa monnier* for which there is evidence of traditional use in TCM and Ayurvedic medicine respectively could state "*Panax ginseng* has been used in Traditional Chinese Medicine for X. *Bacopa monnieri* has a tradition of use in Ayurvedic medicine for Y".

Established formulations (fixed combination) substantiated by evidence of traditional use within a single paradigm

A rationale is not required where there is documentary evidence that a specific (fixed) combination has been traditionally used for a period of at least 75 years. In such cases the combination must be documented in its entirety in a traditional monograph, including methods of preparation. Evidence for the traditional use of fixed combination products must include the respective dose for each active ingredient in the combination and the traditional therapeutic purpose for the combination.

Section 3. Disclaimers and required advisory statements

In situations where the use of listable ingredients for listable indications may potentially be associated with an unacceptable degree of risk under particular circumstance or to a subset of the population, mitigation of risk through mandatory labelling advisory statements is required. Mandatory advisory statements for listed medicines are detailed in the following:

- Therapeutic Goods Order (TGO) No 69 General Requirements for Labels for Medicines
- Required Advisory Statements on Medicine Labels (RASML)
- Therapeutic Goods Advertising Code (TGAC)

In addition, certain advisory statements may be associated with standard indication included in the EBS Listing Facility (ELF).

In general terms, advisory statements relating to specific ingredients are contained in TGO 69 and RASML. Examples include:

- listed medicines containing shark cartilage must include the advisory statement *'Derived from seafood'*
- listed medicines containing royal jelly must include the advisory statements '*Not to be taken by asthma and allergy sufferers'* and *'This product contains royal jelly which has been reported to cause severe allergic reactions and in rare cases fatalities—especially in asthma and allergy sufferers'*.

The TGAC and ELF contain advisory statements that specifically relate to indications. Examples include:

- listed medicines indicated for modulation of cardiovascular risk factors (including weight loss) the label must advise individuals who are concerned about that risk factor to consult a health practitioner
- listed medicines indicated for weight loss must indicate that the product is to be used in conjunction with a calorie- or kilojoule- controlled diet and physical activity (or exercise).

DRAFT

Appendix 1: TGA accepted monographs and authoritative texts

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,* Volume 1, WHO, Geneva.
- Yu HC, Kosuna K and Haga M (Eds) (1997) *Perilla: the Genus Perilla*, Harwood Academic Publishers, Amsterdam.

Pharmacopoeias (use current edition)

- *British Herbal Pharmacopoeia*, British Herbal Medicines Association, West Yorks, England.
- *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 Pharmacopeia and National Formulary* USP Convention Inc, Rockville, Maryland.
- *Pharmacopoeia of the People's Republic of China* Vol 1.
- *British Homoeopathic Pharmacopoeia*, British Homoeopathic Society, London.

Other TGA-approved pharmacopoeias on advice from expert committees

Materia medica and repertory

- Boericke W (1927) Pocket Manual of Homoeopathic Materia Medica, comprising the characteristic and guiding symptoms of all remedies (clinical and pathogenetic), Boericke and Runyon Inc, New York, USA.
- Boger CM (1983) Boenninghausen's Characteristics and Repertory, B Jain, New Dehli.
- Boger CM (1992) Boenninghausen's Characteristics Materia Medica and Repertory with Word Index, Jain Publishing, New Dehli.
- Julian OA (1979) Materia Medica of New Homoeopathic Remedies, Beaconsfield Publishers, Beaconsfield, Bucks, UK.
- Kent JT (1935) Repertory of the Homoeopathic Materia Medica, Enrart & Karl, Chicago.
- Kent JT (1978) Repertory of the Homoeopathic Materia Medica, 6th American edition, Jain Publishing, New Dehli.
- Murphy R (1999) Lotus Materia Medica, 2nd edition, Lotus Star Academy, Colorado, USA.
- Reckeweg HH (1991) Materia Medica, volume 1, Aurelia Verlag, Baden Baden, Germany, ISBN 3-922907-16-4.
- Vermeulen F (1997) Concordant Materia Medica, 2nd edition, Emryss bv, Haarlem, The Netherlands.
- Vermeulen F (1993) Synoptic Materia Medica I, Emryss, The Netherlands.
- Vermeulen F (1996) Synoptic Materia Medica II, Emryss, The Netherlands.

Appendix 2: Expert report (scientific)

1. EXPERT DETAILS

Name:

Qualifications:

Experience:

2. RECOMMENDATION

Listable indication	
Ingredient details	Ingredient: Route of Administration: Dose: Other details:
Recommendation	
Signature	

DRAFT

3. IDENTIFICATION OF RELEVANT EVIDENCE (Sections 2.2.2.1 and 2.2.2.2)

Search Date	Search terms

Source searched	# References
Duplicates	
TOTAL	

Reference	Published (Y/N)	Study type	Relevance (score each from 0-3)				Total Relevance Score (0-12)	Included (Y/N)
			Medicine	Population	Indication	Context		

Average Relevance Score of included studies (4-12)	

DRAFT

Guidance for assessing relevance (Section 2.2.2.3)

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
Relevance to medicine	Identical active ingredient, dose, formulation and route of administration	Identical active ingredient and route of administration, Consistent dose and formulation	Identical route of administration Consistent active ingredient, dose and formulation	Different ingredient or route of administration
Relevance to target population	Population studied is identical to the target population	Population studied is similar to the target population	Some differences between study and target populations but 'clinically reasonable' to apply evidence to the target population	Major differences or differences of uncertain clinical significance exist between study and target populations
Relevance to health benefit	Study directly measures health benefit in listable indication as primary outcome	Study directly measures health benefit in listable indication as secondary outcome	Study directly measures health benefit in listable indication as post-hoc analysis	Study does not directly measures health benefit in listable indication
Relevance to context	Study context directly applicable to Australian self care context	Study context applicable to Australian self care context with few caveats	Probably applicable to Australian self care context	Study context not applicable to Australian self care context

4. EVIDENCE QUALITY (for each included study)

Experimental studies (e.g. randomised controlled clinical trials)

Item	Parameter	Yes (1) or No (0)
Inclusion/exclusion criteria	Inclusion and exclusion criteria reported?	
Sample size	Power calculation performed? Attrition reported? Reasons for attrition given?	
Group allocation	Randomised? Randomisation method reported? Randomisation appropriate? Allocation concealed?	

Item	Parameter	Yes (1) or No (0)
Blinding	Were subjects blinded? Were the researchers blinded?	
Potential confounders	Were potential confounders considered?	
Statistical analysis	Between group statistical comparison performed? Was it appropriate? Did it account for confounders? Was an intention to treat analysis included?	
TOTAL SCORE		

Observational studies (e.g. cohort and case-control studies)

Item	Parameter	Yes (1) or No (0)
Inclusion/exclusion criteria	Inclusion and exclusion criteria reported?	
Sample size	Power calculation performed? Attrition reported?* Reasons for attrition given?*	
Exposure	Was the methodology used to measure the exposure reported? Was the exposure assessed more than once?	
Blinding	Were the researchers blinded to the exposure status?	
Baseline comparison	Were the subjects in different exposure groups compared at baseline?	
Health outcome	Was the methodology used to measure the health outcome reported? Was the health outcome verified (e.g. through assessment of medical records, confirmation by a health practitioner)?	
Potential confounders	Were potential confounders considered?	

DRAFT

Item	Parameter	Yes (1) or No (0)
Statistical analysis	Between group statistical comparison performed? Was it appropriate? Did it account for confounders?	
Study limitations	Were the limitations of the study discussed?	
TOTAL SCORE		

*If attrition reported and no dropouts occurred please select 'Yes' for both 'Attrition reported' and 'Reasons for attrition given'.

Total number of high quality studies (quality score 8-15)	
Total number of lower quality studies (quality score 0-7)	

5. OUTCOMES OF RELEVANT EVIDENCE (Section 2.2.2.5)

Experimental studies

Reference	Quality score	Design	Sample size	Study duration	Substance	Dose	Health outcome	Effect size*	Stat sig	Clin sig†

*Include nature of measure and magnitude of effect observed
†Insert Y(d>0.5), J (<d=0.5 but justifiable), N (d<0.5 not justifiable). If J, justification MUST be provided in Section 6.

Observational studies

Reference	Quality score	Design	Sample size	Study duration	Substance	Dose	Health outcome	Effect size*	Stat sig	Clin sig†

*Include nature of measure (e.g. hazard ratio, relative risk, odds ratio) and magnitude of effect observed

†Insert Y(d>0.5), J (<d=0.5 but justifiable), N (d<0.5 not justifiable). If J, justification MUST be provided in Section 6.

Total number of statistically significant positive studies	
Total number of statistically and clinically significant positive studies	

Nº High quality studies (Quality Score 8-16)		**Nº Lower quality studies (Quality Score 0-7)**	
Nº (%) SS*	**Nº (%) not-SS***	**Nº (%) SS***	**Nº (%) not-SS***

*SS = Statistically Significant positive outcome

Estimate of Clinical Impact			
Very large (d>8)	**Large ((d=0.5-0.79)**	**Medium (d<0.5 justified)**	**Small (d<0.5 not justified)**

This consultation closed on 25 May 2012.

6. BALANCE OF EVIDENCE (Section 2.2.2.6)

Element	A (excellent)	B (good)	C (satisfactory)	D (poor)
Relevance	Average relevance Score 10-12	Average relevance Score 7-9	Average Relevance Score 4-6	N/A
Evidence base	· at least one level I study, OR · three level II studies with a low risk of bias	· one or two level 2 studies, OR · a systematic review, OR · at least three level III studies with a low risk of bias	· One or two level III studies with a low risk of bias · one or two level I or II studies with a moderate risk of bias	· Level 4 studies, OR · level 1-3 studies, OR · systematic review with a high risk of bias
Consistency	All high quality studies show SS positive effect	Most high quality studies show SS positive effect	High quality studies equivocal, lower quality studies mostly consistent with respect to a SS positive effect	Inconsistent (equivocal)
Clinical impact	Very large (d>0.8)	Large (d= 0.5-0.79)	Medium (d<0.5 justified)	Small (d<0.5 not justified)

SS=statistically significant

Additional comments (Justification re effect size):

DRAFT

This consultation closed on 25 May 2012.

Final grade of recommendation

Grade of recommendation	Description	Listable indication recommended
A	Body of evidence strongly supports listable indication	
B	Body of evidence broadly supports listable indication	
C	Body of evidence supports listable indication with qualification	
D	Body of evidence inconclusive	
E	Body of evidence does not support listable indication	

DRAFT

Appendix 3: Expert report (traditional)

1. EXPERT DETAILS

Name:

Qualifications:

Experience:

2. RECOMMENDATION

Listable indication	
Ingredient details	Ingredient: Route of Administration: Dose: Other details:
Paradigm	
Recommendation	
Signature	

DRAFT

3. IDENTIFICATION OF RELEVANT EVIDENCE

Search date:

Sources

National formularies
SUBTOTAL

National pharmacopoeia
SUBTOTAL

Textbooks	Primary references
SUBTOTAL	

DRAFT

Original historical references
SUBTOTAL

Summary (duplicates removed)

Source	Type	Relevance				Included
		Medicine	Indication	Population	Context	

Average Relevance Score of included studies (4-12)	

DRAFT

Guidance for assessing relevance (Section 2.2.3.3)

	Excellent (3)	Good (2)	Satisfactory (1)	Poor (0)
Relevance to medicine	Identical ingredient, dose and formulation	Consistent with ingredient, dose and formulation	Consistent with ingredient and dose	Not consistent with dose and ingredient
Relevance to target population (excluding ethocultural factors)	Population studied is identical to the target population	Population studied is similar to the target population	Some differences between study and target populations but 'clinically sensible' to apply evidence to the target population	Major differences or differences of uncertain clinical significance exist between reference and target populations
Relevance to health benefit	Indication in reference source is identical to listable indication	Indication in reference source is clearly equivalent to listable indication	Indication in reference source is equivalent (taking into account historical and cultural trends) to listable indication	Indication in reference may be interpreted as different to listable indication
Relevant to context	Clearly identified within the relevant healing paradigm	Identified (with some interpretation) with the relevant healing paradigm	Consistent with (in terms of time and location) the relevant healing paradigm	Not consistent with the relevant healing paradigm

Summary of reported health benefits

Reference	Indication (direct quote)

4. QUALITY OF EVIDENCE

Item	Yes (2), Partial/requires interpretation (1) or No (0)
Paradigm defined	
Ingredient described	
Preparation described	
Dose documented	

This consultation closed on 25 May 2012.

Item	Yes (2), Partial/requires interpretation (1) or No (0)
Route of administration	
Target population defined	
Health benefit described	
	0-14

Average Quality Score of included studies (0-14)	

5. BALANCE OF EVIDENCE

Element	A (excellent)	B (good)	C (satisfactory)	D (poor)
Level	Included in TGA approved national pharmacopoeia, national formulary or monograph	Included in non-TGA approved national pharmacopoeia, national formulary or monograph	>3 historical references spanning at least 75 years	Not included in national pharmacopoeia and national formulary and in fewer than three historical references
Relevance	Average relevance score 10-12	Average relevance score 7-9	Average relevance score 4-6	N/A
Quality	Average quality score 11-14	Average quality score 8-10	Average quality score 5-7	Average quality score <5

Grade of Recommendation	Description	Listable indication recommended
A	Body of evidence strongly supports listable indication	
B	Body of evidence broadly supports listable indication	
C	Body of evidence supports listable indication with qualification	
D	Body of evidence inconclusive	
E	Body of evidence does not support listable indication	

DRAFT

This consultation closed on 25 May 2012.

Appendix 4: Glossary

Blinding

Blinding (also called masking) is a procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignment(s). Blinding is used so that neither the patients' nor staff's expectations about the medicine or treatment under investigation can influence the outcome.

Case study

In depth description of the factors related to a disease, disorder or condition in a specific individual.

Case-control study

A study that starts with identification of people with the disease, disorder or condition of interest (the cases) and a suitable control group without the disease or outcome (the controls). The relationship of an attribute (medicine, treatment, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and in the controls. For example, to determine whether thalidomide caused birth defects, a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Clinical significance

The assessment of clinical significance is usually based on the size of the effect observed, the quality of the study that yielded the data, and the probability that the effect is a true one. Clinical significance is not the same as statistical significance; a finding in a study may demonstrate a statistical difference in an attribute under review but this may have no impact clinically.

Clinical trial/clinical study (synonym: intervention study)

A planned study in humans designed to discover or verify:

- the clinical, pharmacological and/or other pharmacodynamic effects of a medicine or treatment and/or
- to identify any adverse reactions to a medicine or treatment and/or
- to study absorption, distribution, metabolism and excretion of a medicine or treatment, with the object of ascertaining its safety and/or efficacy.

Clinically reasonable:

No known clinical, biological, psychological, social or ethnocultural factors are likely to preclude the extrapolation of the results of a study from the study population to the target population for a medicine. The evaluation of clinical reasonableness relies on an informed judgment rather than statistical methods. For example, it may be clinically reasonable to apply some clinical results in adults to children, or some clinical results in a mildly obese population to an overweight population.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)

An observational study in which a defined group of people (the cohort) are followed over time. The outcomes in subsets of the cohort are compared, for example to examine people who were exposed or not exposed, or exposed at different levels, to a particular intervention or other factor of interest. A cohort can be assembled in the present and followed into the future (this would be a prospective study or a 'concurrent cohort study'), or the cohort could be identified from past records and followed from the time of those records to the present (this would be a retrospective study or a 'historical cohort study'). Because random allocation is not used, matching or statistical adjustment at the analysis stage must be used to minimise the influence of possible confounders.

This consultation closed on 25 May 2012.

Condition

A simplified description for a disorder, which is a derangement or abnormality of function.

Control

In clinical trials comparing two or more interventions, a control is a person in the comparison group who does not receive the medicine or treatment under evaluation. Instead that person receives a *placebo*, no intervention, usual care or another form of care. In case-control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, to control means to adjust for, or take into account, extraneous influences or observations.

Controlled clinical trial

Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. While not all controlled studies are randomised, all randomised trials are controlled.

Crossover trial

This is a research design in which participants receive a number of treatments in sequence. Generally, this means that all participants have an equal chance during the trial of experiencing both treatment and placebo dosages without direct knowledge, instead of either placebo or the treatment. Participants may be transferred directly from one treatment to another or may have a washout period in between test treatments. This type of trial can be randomised so that all participants do not get the alternative treatments in the same order.

Disease

Any deviation or interruption of the normal structure or function of any part, organ or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose aetiology, pathology and prognosis may be known or unknown.

Disorder

A derangement or abnormality of function.

Double blind

Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given during the course of the trial.

Efficacy

A relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

General Australian population

The general Australian population is anthropologically diverse and characterised by socio-cultural heterogeneity.

Historical records

Original written or oral accounts that document use of an ingredient or formulation for a specific therapeutic purpose within a defined healing paradigm and/or region.

Illness

Term used to describe a state other than health and may include a medical condition, disease, defect or disorder.

Indication

Indication, in relation to therapeutic goods, means the specific therapeutic purpose or use of the goods. The therapeutic use of a listed medicine indicated for weight loss may refer to use in, or in connection with, alleviating a state of overweight, i.e. a reduction in body weight. Statements relating to traditional use for weight loss are considered indications as a therapeutic benefit may be inferred.

This consultation closed on 25 May 2012.

Health Profession

Includes the following disciplines: medicine, dentistry (dentists, dental therapists, dental prosthetists, dental hygienists), pharmacy, chiropractic, nursing and midwifery, optometry, osteopathy, physiotherapy, podiatry, psychology, Chinese medicine, medical radiation practice, occupational therapy, Aboriginal and Torres Strait Islander health practice, homoeopathy, herbalism and naturopathy.

p-value

The probability (ranging from zero to one) that the results observed in a study (or results more extreme) could have occurred by chance. In a meta-analysis the p-value for the overall effect assesses the overall statistical significance of the difference between the intervention groups, while the p-value for the heterogeneity statistic assesses the statistical significance of differences between the effects observed in each study.

Participant/trial participant

An individual who participates in a clinical trial, either as a recipient of the medicine or treatment, or as a control.

Peer review

Review and appraisal of the item of evidence by an independent expert in a relevant field. Where the item of evidence has not been published in a peer reviewed journal, the sponsor must hold, along with the item of evidence, an expert appraisal of the evidence. Any potential conflicts of interest must be declared in the appraisal.

Placebo

An inactive substance or treatment that supposedly has no treatment value. It is given to participants in clinical trials as a control against which to compare the effects of the test substance. In practice, placebos may also have positive or negative effects on trial participants.

Population studies

Investigations of a disease or condition using participants from a defined population. A population is a closely distributed grouping from a single community that is characterised by both genetic and cultural continuity through several generations.

Protocol

All clinical trials are based on a protocol, which describes in advance who may participate in a trial, the length of a trial and the schedule of tests, procedures, medications and dosages.

Randomisation

The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomised controlled trial (RCT)

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.

Statistical power

The probability that the null hypothesis will be rejected if it is indeed false. In studies of the effectiveness of healthcare interventions, power is a measure of the certainty of avoiding a false negative conclusion that an intervention is not effective when in truth it is effective. The power of a study is determined by how large it is (the number of participants), the number of events (e.g. strokes) or the degree of variation in a continuous outcome (such as weight), how small an effect one believes is important (i.e. the smallest difference in outcomes between the intervention and the control groups that is considered to be important), and how certain one wants to be of avoiding a false positive conclusion (i.e. the cut-off that is used for statistical significance).

This consultation closed on 25 May 2012.

Statistical significance

The probability that an event or difference is real or occurred by chance alone. It does not indicate whether the difference is small or large, important or trivial. The level of statistical significance depends on the number of patients studied or observations made, as well as the magnitude of difference observed. Statistical significance observed in a clinical trial does not necessarily imply clinical significance.

Symptom

Any subjective evidence of disease or of a patient's condition, that is, such evidence as perceived by the patient.

Systematic review

An 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. Cochrane Reviews are examples of such systematic reviews. In a systematic analysis, only those trials that meet a number of pre-set conditions in relation to research design (e.g. sample size, randomisation) are included in the final meta-analysis.

Traditional use

for a designated active ingredient, means use of the designated active ingredient that:

(a) is well documented, or otherwise established, according to the accumulated experience of many traditional health care practitioners over an extended period of time (at least 75 years); and

(b) accords with well-established procedures of preparation, application and dosage.

Washout period

The stage in a cross-over trial where treatment is withdrawn before a second treatment is given. This is usually necessary to counteract the possibility that the first substance can continue to affect the participant for some time after it is withdrawn.

DRAFT

Therapeutic Goods Administration

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