Consultation submission cover sheet

This form accompanies a submission on:

The document 'Evidence Required to Support Indications for Listed Medicines (excluding sunscreens and disinfectants)'			
Name and designation:	Rachel Di Leva, Head of Regulatory and Science		
Company/organisation name and address:	Swisse Vitamins Pty Ltd		
Phone	03 9418 6708	Email	RachelD@swisse.com
☐ Yes ☒ No	I would like the comments I have provided to be kept confidential: *(Please give reasons and identify specific sections of response if applicable)*		
☐ Yes ☒ No	I would like my name to be removed from all documents prior to publication and not be included within the list of submissions on the TGA website. *(Please strikethrough whichever is not applicable)*		

It would help in the analysis of stakeholder comments if you provide the information requested below.

I am, or I represent, a: (*tick all that apply*)

Business in the therapeutics industry (please tick sector):

☐ Prescription Medicines	☐ OTC Medicines
☒ Complementary Medicines	☐ Medical Devices
☐ Blood/Tissues	☐ Other

☐ Sole trader	☐ Business with employee(s)		
☐ Importer	☐ Manufacturer	☐ Supplier	☐ Industry organisation
☐ Government		☐ Researcher	☐ Professional body
☐ Consumer Organisation		☐ Institution *(e.g. University, hospital)*	

☐ Healthcare Practitioner - please indicate type of practice

☒ Other (please specify): Sponsor

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The Choice of the Australian Olympic Team

Project Officer
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
ocm@tga.gov.au

22nd October 2012

Dear Sir/Madam

Re: Submission on the draft guideline: Evidence required to support indications for Listed medicines (excluding sunscreens and disinfectants).

Swisse Vitamins thanks you for the opportunity to provide comment on the government's consultation document *'Evidence Required to Support Indications for Listed Medicines (excluding sunscreens and disinfectants)*'.

Swisse Vitamins is a market leading, privately owned Australian company, delivering premium quality natural health and wellbeing products to Australians for over 50 years. Swisse Vitamins presently markets 160 SKUs, majority of which are Listed Complementary Medicines.

Overview of Swisse Vitamins' Response

Swisse Vitamins is fully supportive of reforms that would enhance the regulatory framework for complementary medicines to maintain credibility and public confidence in these products.

Swisse Vitamins strongly recommends that consideration be given to:

- A revised section A (Attachment 1)
- A detailed analysis of the guidance, prepared by the peak industry associations ASMI and CHC, which Swisse Vitamins contributed to (Attachment 2);
- Additions to the SEE list (Attachment 3)
- Comments in relation to weight loss (Attachment 4)

The Blueprint Reports Informal Working Group on Complementary Medicines (CM IWG) Recommendation 3 was to Update '*Guidelines for levels and kinds of evidence'* and include '*Guidelines for levels and kinds of evidence*' in regulation. This recommendation received in principle support from government with further consultation to be undertaken.

Swisse Vitamins propose a simple, clear and concise legislative entry to underpin the requirement to hold appropriate evidence to support indications for Listed medicines. The legislative entry should refer to the principles of the evidence requirements (Part A) and these should be as clear and concise as possible. Swisse Vitamins propose rewording of Part A as per Attachment 1 to this submission. This legislative entry should deal with guidance to support appropriate evidence for Listed medicines by reference, e.g. that the evidence held meet the standards specified, and be provided in a form described in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM), (currently under review).

Swisse Vitamins welcomes the removal of the requirement for an Expert, as outlined in the original consultation document. However, as many of the requirements outlined in the first draft remain virtually unchanged. For example, the templates require listing the relevant qualifications and experience of the report's author to demonstrate appropriate skills for critical appraisal of the evidence. This has the potential to introduce bias. Once again we stress that the quality of the material submitted is the issue, not the author. Swisse Vitamins is reiterating its previous strong position for change and review, particularly, that COAG principles of Best Practice Regulation be applied as the basis for addressing a perceived 'regulatory failure'.

We also appreciate the additional option of using Sources of Established Evidence (SEE). However we do not understand why so many of the previously accepted sources, and so many of those proposed by Swisse Vitamins and Industry in the previous consultation, were removed from / are not included on list of accepted SEEs. There is also no mechanism suggested for adding SEEs, or for self-certifying the quality of SEEs.

Swisse Vitamins also remain concerned about a number of issues previously raised, which remain in the revised draft. The draft guideline is more than an update; it increases the requirements substantially.

Once again we offer a revised version of the draft. This is very preliminary due to the short consultation period, and needs a great deal more work. Swisse Vitamins remains committed to working with its industry associations and the TGA to achieve a robust, workable and reasonable guideline.

Swisse Vitamins' Key Issues and Recommendation

1. Consultation Process

The consultation document was released on 27th August and the consultation period closed on 22nd October (i.e. a review period of only 40 working days). At the same time, we have also been spending a considerable amount of time and effort working on the Coded Indications project, the BPR and the ARGCM update.

This is wholly inadequate to prepare a meaningful response to the 97-page consultation document. A meaningful response requires a thorough review of the proposal, an accurate identification of all the issues, consultation with the wider business, and the synthesis of a response, which accurately reflects the views of Swisse Vitamins and the broader complementary medicines industry.

On this point Swisse Vitamins notes that the consultation document is extremely detailed, deals with a complex topic and proposes significant changes. Consequently, our response is incomplete and cannot be said to accurately identify all the issues.

2. Guiding Principles to Address Regulatory Failure

Swisse Vitamins supports the COAG Principles of Best Practice Regulation and is disappointed that the principles have still not been applied to this proposal.

In our assessment of this consultation our concerns remain in relation to the following COAG principles:

- A range of policy options have not been considered and costed (principle 2)
- The proposed changes have not been shown to provide the greatest net benefit for the community (principle 3)
- Competition will be restricted without the benefits of the proposed change having been shown to outweigh the costs and without the proposed change being shown to be the only option available (principle 4)
- Effective guidance has not been provided (principle 5)
- Mechanisms have not been proposed to monitor the proposals for relevance and effectiveness (principle 6)
- Effective consultation has not been incorporated (principle 7)
- Actions have not been shown to be effective and are not proportional to the issue (principle 8).

We encourage the TGA to adopt a risk-based approach to this issue. Listable complementary medicines are at the lower end of the risk continuum and any regulatory intervention should be consistent with that level of risk.

Swisse Vitamins encourages the TGA to consider all options before making such important changes. If a regulatory intervention is warranted then it should be the minimum effective regulation commensurate with the risk.

Additionally, the TGA should not seek to develop requirements specific to Australia and should instead seek to harmonise with appropriate international jurisdictions and standards.

2.1 **Disproportionate response:** The requirements laid out in this proposal are excessively onerous, overly complex and impractical, and appear to be equivalent to or higher than those for registered over-the-counter medicines. We consider them inappropriate for listed medicines which are low-risk by definition and which are permitted to carry only low-risk indications.

2.2 **Ineffective response**: Without increased and effective enforcement activity, the proposal will have little or no effect on non-compliant sponsors. In contrast it will have a major adverse impact on those sponsors, such as Swisse Vitamins, who do comply with the requirements. Effective monitoring, enforcement and sanctions should therefore accompany any new guidelines.

2.3 **Harmonisation:** The requirements of the proposed guideline appear to be at variance with those of comparable regulators such as Health Canada. The Baume report (1991) recommended that Australia reflect global practices rather than set up a distinctly different set of Australian regulations.

If respected authorities such as governments, WHO and the Cochrane collaboration have already produced well-constructed and robust assessments and systematic reviews, it would seem unnecessary for sponsors or the TGA to repeat the process over and over again. This is of particular concern in the absence of any compelling argument that an Australian system needs to be more demanding than other comparable systems.

Any new guidelines should therefore align more closely with other comparable jurisdictions and standards.

2.4 **Principles-based guidance**: Swisse Vitamins suggests the requirements for evidence held by sponsors to support indications for Listed medicines be principles based and as concise as possible. Guidance regarding the fulfillment of the requirements should be included in the revision of and related appendixes to the ARGCM. Guidance material should also state clearly that alternative methods are acceptable provided that the legislated requirements are met.

This approach would give legislative underpinning to the evidence requirements and the guidance document would provide an interpretation on listing compliance. This would also allow guidance to be readily amended and updated, in consultation with industry, as necessary.

3. Aims of Reforms

The stated aims of this proposal are to improve compliance with regulatory requirements by providing greater clarity and certainty for sponsors. Any guidance document should also be user-friendly and practical. However, instead of improving the clarity of existing requirements, the proposal is overly complex and prescribes inappropriate and much more onerous requirements. In certain cases it is impossible to meet these requirements.

3.1 **Lack of clarity - Inappropriate and ineffective response:** The overall readability of the document is not user friendly and is overly complex. It contains unnecessary and confusing repetition and is internally inconsistent.

4. Context within the broader TGA Blueprint for reforms

4.1 **Lack of context:** Swisse Vitamins is aware that the TGA is working on a number of reforms affecting complementary medicines, including the Coded Indications project, labelling, transparency and advertising. As these have yet to be circulated for consultation, industry has been forced to consider the draft evidence guideline in isolation from these critical components of the full reform package. This renders it impossible for Swisse Vitamins to assess the real-world impact of the full package and to deliver to the TGA a fully informed response.

The current regulatory reform projects, including labelling, coded indications and evidence requirements need to be coordinated so that sponsors can incorporate all necessary changes at the same time.

4.2 **The Evidence Report:** The removal of the independent expert requirement is underpinned by the fact that the format and content of the evidence report is the key factor, not who writes the report. Therefore, Swisse Vitamins does not support the requirement of listing the designation, relevant qualifications and experience of the report's author. The importance here is that the indications, labelling and claims are all consistent with the evidence and that the evidence may be from either an SEE or from an appropriately conducted review. Swisse Vitamins strongly supports that where evidence is obtained via a review, that evidence should be robust and representative of the body of evidence

4.3 **Inappropriate reporting requirements:** A number of the requirements for a review of scientific evidence are difficult or impossible to satisfy. Many requirements, e.g. power calculations, are not uniformly reported; their absence could have the effect of disqualifying a large body of previously acceptable evidence.

In particular, the requirement to mathematically calculate the clinical significance of every relevant study, even when this has not been reported in the research paper, is unreasonable. For no apparent reason, the guideline demands the addition of a numerical d-value, itself theoretical, untested and rarely provided by researchers. Sponsors are advised to track down the researchers, obtain the original data, and perform these calculations. However the sponsor who does this – at vast trouble and expense – could then be accused of altering or fabricating data.

As well, the requirement that trials must be conducted on subjects representative of the Australian population is difficult to justify. How is this to be determined – against the racial and cultural mix of Perth vs Sydney, for example? And who will be the arbiter? Prescription medicines trialled in Europe, or Hong Kong, or South America, are then supplied throughout the world. This requirement is excessive and should be deleted.

4.4 **Complex algorithms:** the requirements to prepare complex algorithms are not required for registered medicines and are excessive and inappropriate for low-risk medicines. These should be removed and the templates and algorithms simplified.

4.5 **RDIs:** Although Swisse Vitamins and the broader complementary medicines industry requested TGA to add a section clarifying the requirements for the dosage of essential nutrients with respect to RDIs/RDAs/AIs, we were surprised to find that the draft requirements are double those currently stated in the TGAC. The draft guideline now includes a substantial increase to the percentage of RDI, adequate intake or nutrient reference value for that vitamins/minerals/nutrients, from 25% to at least 50%, in relation to statements supporting supplementation. This proposed change would have an unsubstantiated and unjustified impact on existing products in Industry.

Swisse Vitamins recommends that requirements of the current guideline be maintained to assist consistency and transparency. Please see suggested wording as per Attachment 2.

4.6 **Herbal extracts:** Table 1 of Part A, section 3.1 states that, in order for an SEE to support an indication for an ingredient, the method of preparation of the ingredient must be comparable or identical. The same section requires that an ingredient, which is an extract, must be produced with the same conditions, solvents and extract ratios as

referenced in the SEE. This requirement is excessive and should be replaced with *comparable or identical,* and reference to the herbal equivalence guidance document.

4.7 **Advisory Statements**: There is no place for advisory statements in a guideline for evidence. Rather, these should be included in RASML (Required Advisory Statements for Medicines Labels).

4.8 **Sources of Established Evidence (SEE):** Swisse Vitamins is concerned that the list of SEE is not adequate to support the current proposal. The sources outlined in the SEE have differed in both revisions, with no explanation of the methodology used for the selection or rejection of sources. There has been a lack of transparency regarding the publication and subsequent withdrawal of the July 2012 version (V 1.0b TRIM R12/940495), where the SEE differed considerably from the current proposal. The list of accepted references in Appendix 1, excludes a very large number of high-quality sources originally accepted by TGA, as well as those put forward by industry. No justification has been provided. Swisse Vitamins is concerned that we would be forced to prepare full evidence reports, at very considerable expense, for products currently supported by evidence in those texts.

Swisse Vitamins therefore proposes the expanded list of sources of evidence, which updates that previously provided in May 2012 (see Attachment 3).

Furthermore, the list of SEE should be included as an appendix to the ARGCM, to allow for efficient review and addition. Rather than restricting sponsors to texts only on the list, Swisse Vitamins recommends that there be a reference appendix that includes a "quality" check list, this would provide transparency and guidance on what the TGA deems to be required in a reference to allow it to be considered an acceptable SEE reference.

Also, a clear process for the addition of SEE to the list is essential. Swisse Vitamins propose that a sponsor should be able to propose an SEE text and gain provisional acceptance. Justification of inclusion should be required to take into account the principle requirements outlined in part A (Attachment 1) and any guiding points outlined in the ARGCM.

4.9 **Special categories – weight loss:** The guideline contains extra and arbitrary requirements over and above those for other types of Listable indications. There should be one standard only: the evidence must be of sufficient quality, and should match the indication, ingredient and target population.

In addition, the added requirement for 6 months' duration for a weight loss trial is troubling. The Canadian and European government guidelines specify 12 weeks is adequate to support weight loss. We see no justification for arbitrary, unique and higher standards for Australia.

Swisse Vitamins therefore cannot support the parameters proposed by the TGA in relation to weight loss and stress that it should be the responsibility of the person reviewing the evidence that the evidence for a product supports the specific weight claim for the product. Additional comments can be found in Attachment 4.

4.10 **Special categories – biomarkers:** As above, the evidence should match. We cannot support the table on page 37 in its current form. The ranges specified, as a percentage beyond the normal range, are so restrictive that they cannot allow for the generation of evidence to support indications for listed medicines. Even considering the continuum between health and disease, researchers are unwilling to invest time and money in research on healthy populations.

Alternate approaches should be considered in this regard that taken into account the proposed Food Health Claims reforms and the increasing un-level playing field the complementary medicines industry faces. Swisse Vitamins is keen to continue exploring options around this area to ensure the sustainability of this industry.

5. Transitional Arrangements

Appropriate transitional arrangements are critical for industry to ensure minimum disruption to business. A transition period of a minimum 5 years is therefore required for reform of this type of magnitude, and impact on industry. This period will allow all of industry to review and re-list their product ranges. The current regulatory reform projects, including Labelling and Coded Indications, need to be coordinated with that of the evidence requirements so that Sponsors can incorporate all necessary changes at the same time.

Once agreement has been reached on the details of the reform package industry would be in a better position to assess the impact of changes and the time required to transition to new arrangements.

6. Alternative model

Within the limited time available ASMI and CHC, together with Swisse Vitamins, have developed the outline of an alternative guideline (Attachment 2). Please note that this draft is incomplete due to the inappropriate time provided, and so requires further work.

This alternative approach is for a simple, clear and concise legislative entry to underpin the requirement that the sponsor hold appropriate evidence to support all indications and therapeutic claims for a medicine.

The legislative entry would deal with the guidance documents by reference only: that is, that the evidence held must meet the standards specified, and be provided in an acceptable format, as laid out in the current version of the ARGCM. This approach would give legislative underpinning to the evidence requirements while allowing the guidance document to be amended and updated as necessary, in consultation with stakeholders.

We have provided draft models of the standards of evidence appropriate to different types of claims and indications; model templates; and a model guidance section for incorporation into the ARGCM. Due to the time constraints, it must be again stressed that these are incomplete, preliminary and untested drafts.

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Conclusion

Swisse Vitamins thanks you again for the opportunity to make this submission. Swisse Vitamins will continue to work proactively in providing feedback to the TGA on key guidance documents, including the priority update of the ARGCM and appropriate Evidence Guidelines for Listed Medicines. Swisse Vitamins encourages a closer examination of the intersection between evidence based-industry focused research and robust policy development to achieve lasting outcomes that will provide for improved population health.

We look forward to further discussions in the near future.

Regards

Rachel Di Leva
Head of Regulatory and Science
Swisse Vitamins

Attachment 1

Revised section A

Evidence requirements for listed medicines

As part of the certification made in submitting an application for listing a medicine in the ARTG, a sponsor must certify that the applicant holds evidence to support all indications made in regard to the medicine.

This **may** be done through either:

- by the identification of evidence linking an indication to an ingredient, group of ingredients or product as described in an authoritative source of information recognised by the TGA as a Source of Established Evidence (SEE) as described in Section (TBA per ARGCM review), OR

- by a thorough review and assessment of the available literature(Evidence Report), based on the principles outlined in Part A, as described in Section (TBA per ARGCM review).

These approaches apply to both scientific and traditional indications.

Part A

Interpretation
An **indication**, in relation to therapeutic goods, must describe the specific therapeutic use(s) of the goods. Indications refer to a particular health benefit and are structured to include a nominated action or effect (such as reduces, prevents, improves, maintains, stimulates, or treats) on a defined target (such as a biological factor or process, a health state or a clinical condition). Additional qualifying terms may be included to provide information relating to the context of therapeutic use or the specific qualities of the action or effect or target. Indications are classified into 'scientific indications' or 'traditional indications' according to the type of supporting evidence.

Scientific indication - based on evidence from a range of sources, including (but not limited to) clinical studies, pharmacopoeias, textbooks, peer-reviewed published articles.

Traditional indication – based on collected knowledge and experience of a traditional system of medicine. Evidence of traditional use can only be used to support indications that refer to a health benefit in the context of the traditional heath paradigm.

Substantiation of claims based on Listed indications

As part of the certification made in submitting an application for listing a medicine in the ARTG, a sponsor must certify that the applicant holds adequate substantiation for each of the claims[1] made in regard to the medicine.

Scientific indications
Adequate substantiation, includes (but is not limited to), tests, analyses, research, studies, or other evidence, taking into consideration each of the following:

- The meaning of the claim(s) being made;
- The relationship of the evidence to the claim;

- [1] Note: The TGA have indicated they will provide a legal interpretation of 'claim' in the indications document. Review required, when this is published.

- The quality of the evidence; and
- The balance and range of the evidence.

Traditional indications
Adequate substantiation, includes (but is not limited to), traditional monographs, textbooks, materiae medicae of relevance to establishing a tradition of use and traditional indications taking into consideration each of

- The meaning of the claim(s) being made;
- The relationship of the evidence to the claim;
- The quality of the evidence; and
- The balance of the evidence.

Attachment 2

Detailed Analysis of Guidance on Evidence Required to Support Indications for Listed Medicines

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Evidence required to support indications for listed medicines

(excluding sunscreens and disinfectants)

Version 2.0, August 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and 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 <www.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.

Version history

Version	Description of change	Author	Effective date
V1.0	Original Publication	TGA	March 2012
V1.0 b	TRIM R12/940495	TGA	July 2012
V2.0	Reviewed following feedback from consultation process	TGA	August 2012

Emma Burchell 22/10/12 7:37 AM
Comment [1]: Lack of transparency around the publication and withdrawal of this document which differed from V2.0

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Appendix 5: Glossary

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Executive summary

This document outlines the requirements for evidence held by sponsors to support indications for listed medicines (Part A) and provides guidance as to how these requirements can be achieved (Part B).

The *Therapeutic Goods Act 1989* (the Act) requires therapeutic goods that are imported or manufactured for supply in Australia be included in the Australian Register of Therapeutic Goods (ARTG), unless they are specifically exempted from this requirement by Schedule 5 (or 5A) of the Therapeutic Goods Regulations 1990 (the Regulations). The Therapeutic Goods Administration (TGA) adopts a risk-based approach to the regulation of medicines such that higher risk medicines are subjected to a high degree of pre-market scrutiny and must be registered on the ARTG, whilst some lower risk medicines may be listed on the ARTG following a self-certification process by sponsors.

Part 1 to Schedule 4 of the Regulations outlines those therapeutic goods, including complementary medicines, which are required to be included in the part of the ARTG for listed goods. For a medicine to be listed in the ARTG, an applicant must certify that they hold evidence to support each indication made relating to the medicine. It is also a condition of listing 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 evidence to the TGA.

The Government has announced that, once updated in consultation with stakeholders, the requirements will be included in the legislation 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 Part A of this document.

The document is divided into 2 main sections:

1. Part A sets out what is required for an assessment of evidence supporting indications, this may be achieved in one of two ways; through the use of Sources of Established Evidence (SEE) recognised by the TGA, or through a comprehensive and objective review of the available evidence that is relevant to the proposed indication (Evidence Report), Part A includes the essential steps required to be undertaken during the consideration of a SEE, and during the development of an Evidence Report.

2. Part B provides guidance regarding the use of SEE and the fulfillment of the requirements of the Evidence Report. This includes guidance about literature searching, and the assessment of the level, relevance, quality, outcomes and overall balance of currently available evidence. In order to facilitate the review of evidence used to support indications, templates that relate to the use of SEE and the development of an Evidence Report have been provided in Appendices 2-4.

The document recognises that evidence used to support indications for listed medicines is often retrieved from the available literature rather than sponsor-initiated clinical trials specifically conducted with a proposed product. As such, a large portion of this document provides direction and guidance regarding the assessment of the relevance of scientific and evidence of traditional use to a proposed indication.

Evidence provided to the TGA during any evidence based listing compliance review should be provided in the form prescribed by this document with all relevant publications appended. A sponsor may provide evidence, in relation to an indication, in a form 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.

Emma Burchell 22/10/12 7:37 AM
Comment [2]: 'must' is used interchangeably refer to page 12

Emma Burchell 19/10/12 2:23 PM
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Overview

The regulation of complementary medicines

Emma Burchell 22/10/12 7:37 AM
Comment [3]: Information on the Regulation of complementary medicines should be referred to Complementary medicine regulation basics on the TGA website and relevant sections of the ARGCM

The Act requires therapeutic goods that are imported or manufactured for supply in Australia be included in the ARTG, unless they are specifically exempted from this requirement by Schedule 5 (or 5A) of the Therapeutic Goods Regulations 1990 (the Regulations).

Part 1 to Schedule 4 of the Regulations outlines those therapeutic goods, including complementary medicines, which are required to be included in the part of the ARTG for listed goods. At the time of submitting an application for listing a medicine, a sponsor must certify that the medicine that is the subject of the application meets the requirements of Section 26A(2)(a)–(k) inclusive and, if applicable, subsection 26A(3) of the Act. In certifying under Section 26A(2)(a)–(k) of the Act, the sponsor makes a legally binding statement that, *inter alia*, the applicant holds evidence to support any indication that the applicant makes relating to the medicine.

Listed medicines are low risk medicines. In determining risk, the TGA takes into account a number of factors. These include:

- the toxicity of the ingredients (itself a complex of factors)
- the dosage form of the medicine
- whether the medicine is indicated for a serious form of a disease, condition or disorder
- whether the use of the medicine is likely to result in significant side effects, including interactions with other medicines, food or other factors; and
- whether there might be significant adverse effects from prolonged use or inappropriate self medication.

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 Act

This document is designed to help sponsors of listed complementary medicines determine whether the evidence they hold is appropriate and sufficient to meet their obligations under Section 26A(2)(j) of the Act.

Listed medicines – indications

Emma Burchell 22/10/12 7:37 AM
Comment [4]: Principles on indications considered appropriate should be included in the Coded Indications document

In principle, indications considered appropriate for listed medicines are those that can be safely and effectively used without the intervention of a healthcare practitioner and includes indications referring to health maintenance, health enhancement and for the management of non-serious, self-limiting, diseases, disorders or conditions. Listed medicines must not refer to, or imply that they are intended to manage a serious form of illness. When determining if an indication is appropriate for a listed medicine, it is important to consider whether delayed contact with a healthcare practitioner due to attempted self-medication, could lead to an increased health risk to the consumer.

All indications must be capable of substantiation – that is, evidence held by the sponsor must adequately demonstrate all indications made for the product are true, valid and not misleading. For multi-component listed products, evidence for the indications can be based on the evidence for the product itself, or on evidence for an individual ingredient or component in an ingredient.

Medicinal products submitted for inclusion in that part of the ARTG for listed goods are made via the eBusiness Services electronic listing facility (ELF). Listed medicines are not subject to pre-market evaluation for efficacy at the time of Listing. Listed medicines may be supplied only if they contain ingredients approved by the TGA for use in low risk medicines. To be consistent with low-risk, some ingredients are subject to certain restrictions or conditions of use. This includes requirements for advisory or warning statements on product labels, limits on plant part and/or preparations, quantitative limits, mode of administration or other ingredient-related restriction. Listed medicines are subject to a range of post market activities (see **post-market regulatory activities)**.

A sponsor listing a medicine on the ARTG must certify that evidence is held to support all indications included on the ARTG. 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 evidence to the TGA. All listed medicines must be manufactured according to Good Manufacturing Practice (GMP) to ensure adequate quality.

Post-market regulatory activities

Emma Burchell 22/10/12 7:37 AM
Comment [5]: Information here should be referenced to the TGA website Post-market regulatory activity

To help maintain consumer confidence in the quality, safety and effectiveness of medicines supplied in Australia, an important feature of the TGA's risk management approach to both listed and registered complementary medicines is a range of post-market regulatory activities.

The essential elements of the TGA's risk-based approach include:

- targeted and random desk-based compliance reviews of listed products
- monitoring of adverse reactions to complementary medicines
- targeted and random laboratory testing of products and ingredients
- targeted and random surveillance in the market place
- an effective, responsive and timely recalls procedure
- audit of GMP; and
- controls for the advertising of therapeutic goods.

Purpose of this document

This document provides requirements and guidance for sponsors of listed medicines to help ensure that the evidence they are required to hold under therapeutic goods legislation is appropriate and sufficient to substantiate all therapeutic indications included in the ARTG for their products.

Part A of this document puts forward the key requirements for evidence held to support indications for listed medicines. Part B of this document provides guidance material. Guidance documents are administrative instruments and therefore allow for flexibility. Alternate approaches to those described in Part B of this document may be acceptable provided they are consistent with the documents underlying principles.

Emma Burchell 22/10/12 7:37 AM
Comment [6]: Maintain – this should also capture the Listed medicine indications information going into the coded indications document.

This document should be read in conjunction with therapeutic goods legislation and other relevant guidance documents.

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Comment [7]: May and must are used in the document

Evidence requirements may be met in one of two ways:

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Comment [8]: This statement is referenced in proposed industry wording Attachment 1. Appendix to be reviewed as per ARGCM update.

1. Through the identification of an indication-ingredient or indication-formulation combination described in a source recognised by the TGA as a SEE. Sources of Established

Evidence for both Scientific and Traditional Indications are included in Appendix 1 and a checklist for assessing proposed indications against a SEE is included Appendix 2.

2. Through a thorough review of the scientific literature (and any relevant unpublished studies) and/or traditional literature, based on the criteria outlined in Part A of this document. In order to facilitate the review of evidence used to support indications that have not been incorporated into a SEE, Evidence Report templates are provided in Appendices 3 and 4 to assist sponsors with the review of evidence. Evidence provided to the TGA during any evidence based listing compliance review must be provided in the form of a completed Evidence Report with all relevant publications appended. The evidence base will then be reviewed by the TGA. An Evidence Report provided in a format that complies with the requirements of this document, does not guarantee that the TGA will be satisfied the totality of evidence supports the relevant indication.

Part A: Requirements

1. Listable indications

An indication, in relation to therapeutic goods, must describe the specific therapeutic use(s) of the goods. Indications refer to a particular health benefit and are structured to include a nominated **action or effect** (such as reduces, prevents, improves, maintains, stimulates, or treats) on a defined **target** (such as a biological factor or process, a health state or a clinical condition). Additional qualifying terms may be included to provide information relating to the context of therapeutic use or the specific qualities of the action or effect or target.

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 accordance with the Therapeutic Goods Regulations 1990, the indications for listed medicines must not refer to the treatment of a serious disease, condition, ailment or defect (as defined in Parts 1 and 2 of the Therapeutic Goods Advertising Code).

2. Types of listable indications

Indications are classified into 'scientific indications' or 'traditional indications' according to the type of supporting evidence. The evidence requirements for scientific and traditional indications are described in Section 3.

Scientific and traditional indications are fundamentally different; scientific indications are efficacy based, while traditional indications refer to a tradition of use within a particular 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. Therefore, evidence of traditional use can only be used to support indications that refer to the traditional use of a medicine or ingredient for a health benefit in the context of the traditional paradigm.

Terms used in traditional listable indications must be comprehensible to consumers and consistent with those referenced in the evidence of traditional use 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 forms of health disorders or conditions, such as 'useful for chronic inflammation' or 'used as a healing aid for urinary disorders'.

In cases where the traditional terminology may be unclear to consumers, the information should (also) be communicated using appropriate conventional terminology.

Emma Burchell 22/10/12 7:37 AM
Comment [9]: See alternate industry proposal at Attachment 1.

Emma Burchell 22/10/12 7:37 AM
Comment [10]: Principles on indications should be included in the Coded Indications document

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Comment [11]: Clarity required on the levels of claims and wording allowed

Emma Burchell 22/10/12 8:48 AM
Comment [12]: Clarity required on the levels of claims and wording allowed

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Comment [13]: Principles on indications should be included in the Coded Indications document

Emma Burchell 22/10/12 8:50 AM
Comment [14]: •liver chi stagnation in TCM for example may have no direct western terminology equivalent

In order to reduce the possibility that traditional indications are misinterpreted by consumers to imply efficacy, traditional indications must indicate that the health benefit is based exclusively on long-term use and experience.

Evidence requirements for listed medicines

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Comment [15]:
ATTACHMENT 1 - Industry recommendation to replaces current Part A.

As part of the certification made in submitting an application for listing a medicine in the ARTG, a sponsor must certify that the applicant holds evidence to support all indications made in regard to the medicine.

This **may** be done through either:

- by the identification of evidence linking an indication to an ingredient, group of ingredients or product as described in an authoritative source of information recognised by the TGA as a Source of Established Evidence (SEE) as described in Section (TBA per ARGCM review), OR
- by a thorough review and assessment of the available literature(Evidence Report), based on the principles outlined in Part A, as described in Section (TBA per ARGCM review).

These approaches apply to both scientific and traditional indications.

Part A

Interpretation

An **indication**, in relation to therapeutic goods, must describe the specific therapeutic use(s) of the goods. Indications refer to a particular health benefit and are structured to include a nominated action or effect (such as reduces, prevents, improves, maintains, stimulates, or treats) on a defined target (such as a biological factor or process, a health state or a clinical condition). Additional qualifying terms may be included to provide information relating to the context of therapeutic use or the specific qualities of the action or effect or target. Indications are classified into 'scientific indications' or 'traditional indications' according to the type of supporting evidence.

Scientific indication - based on evidence from a range of sources, including (but not limited to) clinical studies, pharmacopoeias, textbooks, peer-reviewed published articles.

Traditional indication – based on collected knowledge and experience of a traditional system of medicine. Evidence of traditional use can only be used to support indications that refer to a health benefit in the context of the traditional heath paradigm.

Substantiation

As part of the certification made in submitting an application for listing a medicine in the ARTG, a sponsor must certify that the applicant holds adequate substantiation for each of the claims made in regard to the medicine.

Scientific indications

Adequate substantiation, includes (but is not limited to), tests, analyses, research, studies, or other evidence, taking into consideration each of the following:

- The meaning of the claim(s) being made;
- The relationship of the evidence to the claim;
- The quality of the evidence; and
- The balance and range of the evidence.

Traditional indications

Adequate substantiation, includes (but is not limited to), traditional monographs, textbooks, materiae medicae of relevance to establishing a tradition of use and traditional indications taking into consideration each of

- The meaning of the claim(s) being made;
- The relationship of the evidence to the claim;
- The quality of the evidence; and
- The balance of the evidence.

Part B. Guidance material

These guidelines demonstrate a method accepted by the TGA for fulfilling the evidence required to support indications for listed medicines.

1. Evidence requirements for listed medicines

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As part of the certification made in submitting an application for listing a medicine in the ARTG, a sponsor must certify that the applicant holds evidence to support all indications made in regard to the medicine. 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 Act.

This **must** may be done through either:

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Comment [16]: Inconsistent with the term . 'may' used on page 6 and 27.
See alternate industry proposal at Attachment 1.

- by the identification of evidence linking an indication to an ingredient, group of ingredients or product as described in an authoritative source of information recognised by the TGA as a SEE as described in Section 3.1, OR
- by a thorough review and assessment of the available literature (Evidence Report) as outlined in Section (TBA) of this document.

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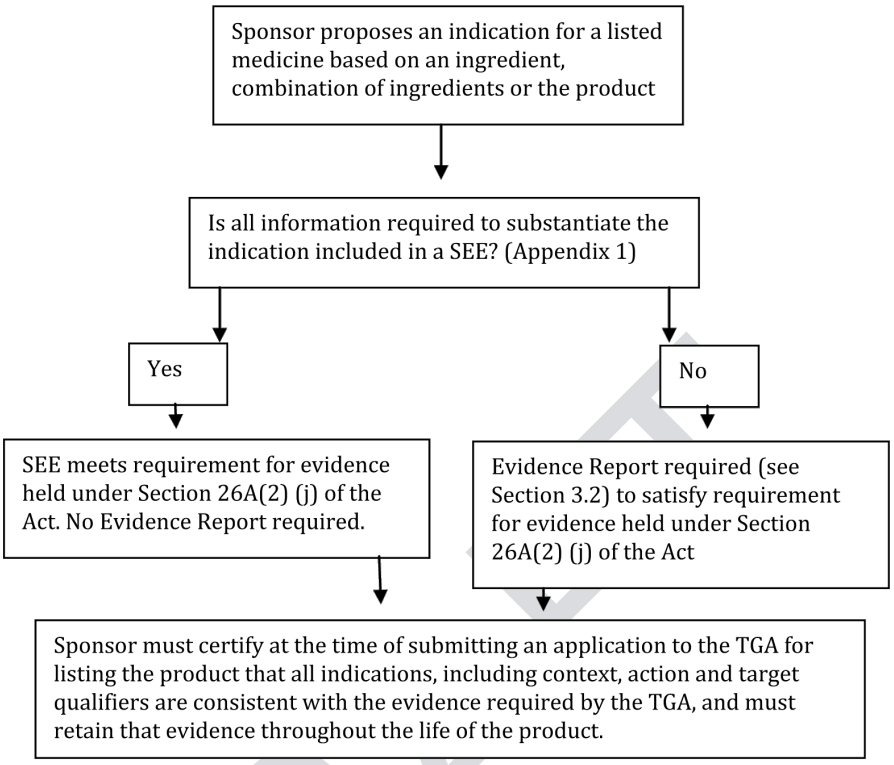
These approaches apply to both scientific and traditional indications and are shown schematically below.



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1.1. Meeting evidence requirements through sources of established evidence (SEE)

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Some indications for ingredients and products are underpinned by an established and valid body of knowledge. Where evidence linking an ingredient or product to an indication has been documented in a source recognized by the TGA, the review may be considered to be appropriate to meet the requirements of Section 26A(2) (j) of the Act. It is essential that the information included in the SEE is complete and relevant to the proposed product and its indication/s.

1.1.1 Sources of established evidence

Appendix 1 lists a range of SEEs that are generally considered to be sources of established evidence that may be used to substantiate scientific and traditional indications and a history of use for ingredients and listable products. Where there are multiple editions or versions of a SEE, the latest edition/version of SEEs should be used. Where older editions/versions are referenced, they should be assessed for currency to ensure consistency with the latest version.

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Comment [17]: Please refer to Attachment 3 Expanded list of SEEs.

1.1.2 Information required from sources of established evidence

In order for an indication to be supported by evidence contained in a SEE, it is essential that the information included in the SEE is complete and relevant to the ingredient or product and the indication/s to be listed. This includes listed medicines in which the therapeutic indication, dosage and administration are based on traditional knowledge but the dosage forms have been modified to modern dosage forms, e.g. capsules or tablets, for the ease of use and increased therapeutic compliance. The following Table provides the criteria in a SEE to link an active ingredient(s) or product to an indication(s) for listed medicines.

1.1.3 Including indications sourced from SEE in the ARTG

Only indications that meet the definition of therapeutic use are to be included on the ARTG.

The therapeutic indication, including any relevant contextual information (such as the traditional medicine paradigm for traditional indications, or any restrictions or contraindications related to use) must be **identical in intent** with that included in the SEE (including any traditional terminology). In cases where the traditional terminology may be unclear to consumers, the information should also be communicated using appropriate conventional terminology.

1.1.4 Indications supported by sources of established evidence

Where an indication associated with an ingredient, group of ingredients or product is consistent with the information contained within a SEE recognized by the TGA as described in Table 1, the SEE is considered to be appropriate to meet the requirements of Section 26A(2) (j) of the Act.

It is the responsibility of sponsors to determine if the information and evidence cited in the SEE is valid, relevant and sufficient to justify all indications for the specific complementary medicine product to be listed.

A SEE Assessment Template is included in Appendix 2 and must be completed for every indication that is supported by a SEE. The template is a tool developed to help sponsors ensure that the SEE is valid for the product to be listed on the ARTG. The template should be used in conjunction with the criteria described in Section (TBA).

Where it is not possible to meet the criteria described in Table 1, an Evidence Report must be prepared

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

- the proposed indication must be appropriate for a listed medicine as described in Section 1
- the indication must be linked to a defined and sufficiently characterised ingredient, group of ingredients or product; and
- the indication and all qualifiers must be consistent with the evidence (as described in Part B Guidance Material), be clear to consumers in terms of the expected health benefit and not be misleading.

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Deleted: provided the requirements in the following table are fulfilled.

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Comment [18]: should

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Comment [19]: should

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Comment [20]: Principles on indications should be included in the Coded Indications document.

Documents linked through disclaimer – "this document should be read in conjunction with therapeutic goods legislation and other relevant guidance documents being X, Y, Z.

Table 1 Criteria in a SEE required to link an active ingredient(s) or product to an indication(s) for listed medicines.

Information included in a SEE	Requirements for listed medicine
Therapeutic use/s clearly described including any relevant context, qualifier and risk information (such as the traditional medicine paradigm for traditional indications, directions of use, target populations, restrictions or contraindications related to use).	The wording of the indication is **identical in intent** with that included in the SEE (including any traditional terminology). Different words with the same intent (i.e. a medical synonym) may be used to describe the indication included in the ARTG. In cases where the traditional terminology may be unclear to consumers, the information should (also) be communicated using appropriate conventional terminology.
Each active ingredient has been clearly identified and characterised. For herbal ingredients, the Latin binomial (scientific) name together with the plant part for each herbal ingredient.	Ingredient (including plant part for herbal preparations) is **identical,** comparable, or not significantly different from that described in the SEE. Comparability may need to be demonstrated by using appropriate analytical data such as chemical/chromatographic fingerprinting or based on chemical 'marker' content.
Where relevant, the method of preparation for each active ingredient or product is described.	**Where** relevant, the method of preparation is the same, comparable or consistent to that described in the SEE For extracts, the method of preparation must be the same, comparable or consistent with that described in the SEE (e.g. extraction conditions and solvent, extract ratio).
Dosing details (dose or dosage range, dose frequency, and duration of use) are clearly described.	Dosing details are **within the ranges** specified in the SEE.
Route of administration is clearly described or implicit.	The intended route of administration for the listed medicine is the **same** as that specified in the SEE.
Product risk information cautions, warnings, and contraindications associated with use.	Any cautions, warnings, and contraindications associated with use are taken into account.

It is the sponsors' responsibility to ensure that all these requirements are met for each individual indication.

In some traditional medicine paradigms, risk information (cautions, warnings, and contraindications) may be communicated in language that is specific to that healing paradigm or

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Comment [21]: Remove from Part A and incorporate in Part B guidance as an appendix to the ARGCM, currently under review .

The same table is included on 13 and 29, where it should only be required in guidance.

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Deleted: It is the responsibility of sponsors to determine if the information and evidence cited in the SEE is valid, relevant and sufficient to justify all indications for the specific complementary medicine product to be listed. .

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culture. In such cases, the risk information can be expressed using a qualifier. For example, Ganjiang (Rhizoma Zingiberis) is indicated for cough due to lung-cold, but not for dry cough due to lung-heat.

Meeting evidence requirements through anevidence report

Where evidence from a SEE is not available to support the requirements of Section 26A(2) (j) of the Act (an applicant for listing a medicine in the ARTG must hold evidence to support any indication made), a sponsor must base their certification on an objective, comprehensive and systematic review of the evidence linking the product (or an ingredient) to the indication (the Evidence Report).

For Evidence Reports addressing scientific indications, the Report must include a literature review of the existing body of evidence relevant to an indication. New or unpublished data may also be relevant but must be assessed within the context of the existing published body of knowledge. Evidence Reports that address traditional indications must undertake a critical review of the relevant traditional literature.

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~~).
- **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.[1] 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.
- **Expected health benefit:** the results of scientific studies must be assessed for statistical and meaningfulness (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 the terms used to refer to a health benefit in evidence held are identical or equivalent to those 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.

The Evidence Report must include the following sections:

- Sponsor details
- Product name

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

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Comment [22]: Must be comprehensible to the average consumer.

- Product Rational (see att. X)
- Indication details
- Overall product presentation
- Identification of evidence
- Relevance of evidence
- Quality of evidence
- Assessment of the expected health benefit
- Assessment of the balance of relevant evidence

The following table outlines the structure and essential features of the Evidence Report. Information regarding the assessment of evidence required to substantiate listable indications is provided in Section (TBA) and (TBA). 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. Evidence Report templates have been provided in Appendix (TBA of the ARGCM) to assist sponsors in ensuring the Evidence Report contains all necessary information. An Evidence report **must be** provided to the TGA if requested.

Section	Information included in Evidence Report for scientific indications	Information included in Evidence Report for traditional indications
Sponsor details	Sponsor name, designation, company and contact details.	Sponsor name, ~~designation~~, company and contact details.
Product details	Product name.	Product name.
Indication details	Indication/s, ingredient details route of administration, dosing details.	Indication/s, ingredient details, route of administration, dosing details.
Identification of evidence	Literature search strategy (including inclusion and exclusion criteria), literature search results, any additional non-published studies.	Sources searched: pharmacopoeias, national formularies, monographs, textbooks, historical references.
Relevance of evidence	Assessment of the relevance of retrieved results to proposed indication, proposed formulation, target population and context of use.	Assessment of relevance of retrieved results to proposed indication, proposed formulation, target population and context of use.
~~**Level of evidence**~~	~~Level of each relevant item of evidence according to NHMRC levels of evidence hierarchy.~~	

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Comment [23]: This section should be replaced with a check list (ticker box) to ensure that each of the following have been completed, provided, or justified where required.

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Comment [24]: Should not required. The content and quality of the report not who reviewed it is what matters.

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Emma Burchell 22/10/12 7:37 AM
Comment [25]: NHMRC levels of evidence should not be required, it was designed for prescription medicines and treatments guidelines.

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Section	Information included in Evidence Report for scientific indications	Information included in Evidence Report for traditional indications
Quality of evidence	Critical appraisal of each item of evidence using a published critical appraisal tool that includes as a minimum: Study design/method, participant eligibility (inclusion/exclusion criteria), randomisation and blinding of participants (for Randomised Controlled Trials (RCT)).Sample size justification/power calculations, controlling for potential confounders, study attrition (for RCT and cohort studies), statistical analyses undertaken.	Assessment of how well the paradigm, ingredient, preparation, dose, route of administration, target population and health benefit has been described in each item of evidence.
Expected health benefit	Document relevant health outcomes, assessment of statistical and clinical significance.	Document the exact phrasing of health benefit described in the sources of evidence of traditional use.
Balance of relevant evidence	Summary of body of evidence (quality, consistency and significance) utilising high quality studies (and low quality studies if balance of high quality studies is equivocal).	Summary of consistency of paradigm, ingredient, preparation, dose, route of administration, target population and health benefit across items of evidence.

In addition to the parameters described in subsequent sections, any new clinical studies conducted should be conducted according to Good Clinical Practice (GCP) guidelines[2] and, the reporting of trials conducted should adhere to the principles outlined in the CONSORT statement.[3] Sponsors should also be aware of any requirements for listed medicines outlined in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM).

3.2.1 Evidence required to support listable scientific indications

3.2.1.1 Sponsor details

The name, ~~designation~~, company and contact details of the sponsor **must** be included.

~~Any relevant qualifications and experience of the person responsible for the Report may also be included in order to establish that the person responsible for the review has clinical knowledge and the appropriate skills to critically assess the available evidence and its relevance to the proposed indication and listed medicine. For traditional indication it is also important to include information that supports knowledge of the traditional medicine from which the indication is derived.~~

3.2.1.2 Product name

[2] Note for guidance on Good Clinical Practice (CPMP/ICH/135/95). Therapeutic Goods Administration 2000. <http://www.tga.gov.au/pdf/euguide/ich13595.pdf>
[3] 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>

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Comment [23]: This section should be replaced with a check list (ticker box) to ensure that each of the following have been completed, provided, or justified where required.

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Comment [26]: These aspects should be covered off when completing the template provided at Appendix 3.

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Comment [27]: Included: 'Where reported'.

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Comment [28]: These details are already covered in the appendix 3 no further explanation required.

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Comment [29]: Remove this requirement as it is not relevant to the quality of the evidence report. Appendix 3 to be amended.

The name of the product to be listed on the ARTG **must** be documented.

3.2.1.3 Indication details

This section **must** provide the following:

A valid (see 3.2.1.9) listable indication including any appropriate contextual or qualifying terms (see Part B Section 1 Listable indications).

The characterisation of all active ingredients. For herbal ingredients, this must include the Latin binomial (scientific) name together with the plant part.

Dosage form

Route of administration

Dosing details (dose or dosage range, dose frequency, and duration of use)

These **must** all be consistent with the supportive evidence base. Careful attention should be paid to the wording of the indication/s so as to ensure they are comprehensible to consumers.

3.2.1.4 Identification of evidence

An objective, comprehensive, transparent and reproducible review of the literature that is of potential relevance to the listable indication is required.

The search of the literature **must** be documented to internationally accepted standards.[4] The search terms used databases and search interfaces used and the numbers of references retrieved **must** be documented in the report.

The search **must** utilise MEDLINE/PubMed and should involve at least one other relevant database.

The search **must** extend retrospectively for least 10 years from the present day. Non-English language literature will need to be considered if this is a source of significant scientific work. All publications appended to the final report must be in the English language, or be a certified English transcript from the native language.

Unpublished studies contribute to the evidence base for a scientific listable indication if they are relevant and fulfil the required criteria outlined below and have been reviewed by at least two independent reviewers (one of these may be the sponsor if not an author of the study). To facilitate an accurate interpretation of methodological quality, any original research **must** be appropriately documented.[5]

3.2.1.4 Identification of evidence

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 Evidence Report or which TGA may subsequently identify as of concern, and should consider synonyms and alternate spellings and terminologies.

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Comment [30]: Information on the identification of evidence condensed from Part A and Part B . This information should be guidance only and simplified to ensure a comprehensive search, evaluation and conclusions have been completed.

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Emma Burchell 22/10/12 7:37 AM
Comment [31]: The 'Must' requirements in the original Part A rely on references for systematic reviews and prescriptions level, which are not appropriate for indications for listed, low risk medicines.

[4] 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>

[5] Schulz KF, Altman DG, Moher, D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine 2010, 152 (11):726-W.293. <http://www.annals.org/content/early/2010/03/18/0003-4819-152-11-201006010-00232.full.pdf+html>

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/PubMed 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 medicinal ingredients are also components of food.

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 translated and 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 clearly documented ~~to internationally accepted standards.~~[6] ~~The databases and search interfaces used and the numbers of references retrieved must be documented in the report.~~

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 sponsor if not an author of the study). Sponsors should not rely simply on the fact that a study is published as being sufficient to support indications. However, studies that have been verified through peer review are more likely to be methodologically robust and valid. 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 should be appropriately documented.[7]

Abstracts or informal summaries of an article is less reliable, because such documents usually do not give sufficient detail as to how the research was conducted or how the data were analysed, to objectively evaluate the quality of the research data and the conclusions drawn by the authors.

3.2.1.5 Relevance of evidence identified

Only studies that have been determined to be relevant to proposed listable indications are to be included in any subsequent analysis. Table 2 lists inclusion and exclusion criteria for determining study relevance for substantiating scientific indications through an Evidence Report.

3.2.1.5 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 relevant 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 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 ingredient that is administered in a similar form and preparation as that present in the medicine. In the case of listable indications

[6] 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>

[7] 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>

Emma Burchell 22/10/12 7:37 AM
Comment [32]: "if necessary may" Access to additional databases is a cost impact to industry and can not be justified.

Emma Burchell 22/10/12 7:37 AM
Comment [33]: The CONSORT and CDC requirements are excessive for low risk listed medicines. The level is higher than that required in ARGOM.

Emma Burchell 20/10/12 11:44 AM
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Emma Burchell 22/10/12 7:37 AM
Comment [34]: Not required

Emma Burchell 20/10/12 11:51 AM
Deleted: It is recommended that the help of a librarian is sought when conducting the literature review

Emma Burchell 20/10/12 11:51 AM
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Emma Burchell 22/10/12 7:37 AM
Comment [35]: Not required in ARGOM or ICH

Emma Burchell 20/10/12 11:53 AM
Deleted: must

Emma Burchell 22/10/12 7:37 AM
Comment [36]: Part A and Part B requirements condensed here to form the basis of guidance only

Emma Burchell 22/10/12 7:37 AM
Comment [37]: Only relevant and unclear abstracts should be the trigger for the need to purchase the full article. Estimated cost, per article is $30-$60 USD.

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*.

Indications must only be linked to products or ingredients which meet acceptable standards of evidence (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 ingredients at comparable doses. This is discussed further in Section (TBA)

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.

Emma Burchell 22/10/12 8:56 AM
Comment [38]: Provisions should be made for TCM herb and an Ayurvedic herb in the same formula for example.

Emma Burchell 20/10/12 12:00 PM
Deleted: 3.4.

Emma Burchell 22/10/12 7:37 AM
Comment [39]: Recommend removing this section

The study population should be consistent with the target population. Where studies show differences in results these should be documented.

The glossary definition for Australian population recognises the diversity here and the general requirement may cause more questions than it assists.

Table 2: Assessing study relevance for scientific indications

	Excellent	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details, formulation and route of administration.	Identical active ingredient and route of administration, comparable dosing details and formulation.	Identical route of administration, comparable active ingredient, or formulation and dosing details.	Different active ingredient or route of administration.
Relevance to target population	Population studied is identical to the target population.	Population studied is comparable to the target population.	Some differences between study and target populations but 'clinically reasonable' to extrapolate 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 measure health benefit in listable indication.
Relevance to context of use	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.

Emma Burchell 22/10/12 7:37 AM
Comment [40]: Repeated on page 42. Should only form guidance.

When an indication is directed at a specific sub-group of the population, eligibility criteria will reflect the indication. 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

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 the analysis of evidence, and studies not achieving this ranking must be excluded.

3.2.1.6 Level of relevant evidence

Each relevant item of evidence must be categorised according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence for intervention studies, prognosis

or aetiology[8]. The hierarchy for prognosis or aetiology may only be used where randomised controlled trials are impractical or unavailable.

Table 3: NHMRC Levels of Evidence

Emma Burchell 22/10/12 7:37 AM
Comment [41]: Remove, not required see comments on NHMRC levels

Level	Intervention	Prognosis	Aetiology
I 4	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study	A prospective cohort study
III-1	A pseudo-randomised controlled trial(i.e. alternate allocation or some other method)	All or none	All or none
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study Interrupted time series without a parallel control group	A retrospective cohort study	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

3.2.1.7 Quality of relevant evidence

The quality of every relevant item of evidence **must** be assessed utilising a published, critical appraisal instrument that is appropriate for the type of evidence being considered. The instrument **must** include as a minimum an assessment of the following:

- characterisation of the ingredient/s
- study design/methods
- participant eligibility (inclusion/exclusion criteria)
- randomisation and blinding of participants (for Randomised Controlled Trials (RCT))

[8] National Health Medical Research Council. 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>

- sample size justification/power calculations
- controlling for potential confounders
- study attrition (for RCT and cohort studies); and
- statistical analyses undertaken.

The critical appraisal tool **must** then be used to classify each relevant item of evidence as a high or low quality study.

3.2.1.8 Assessment of the expected health benefit

The results of every relevant item of evidence **must** be considered. For each of these, any relevant outcome measure **must** be described. In addition, the presence or absence of a statistically significance effect (positive or negative) for each relevant outcome measure **must** be recorded.

For each study, the meaningfulness of the observed effect/s to consumers at an individual and/or population level (clinical significance) **must** be assessed. Guidance regarding the assessment of clinical significance is included in Section 3.2.1.8 of Part B of this document).

For indications relating to weight loss in overweight individuals (BMI 25-30 kg/m^2), clinical significance is only achieved if supporting evidence demonstrates:

- 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.

3.2.1.9 Assessment of the balance of relevant evidence

The assessment of the balance of evidence **must** consider the quality and outcomes of all relevant studies included in the report.

The consistency of the relevant outcomes observed in high quality studies **must** be assessed first. This **must** take into account both the statistical and clinical significance of the outcomes.

Only if the balance of high quality evidence is equivocal are the outcomes of lower quality studies to be included in assessing the balance of evidence.

An indication is only valid if the balance of evidence is supportive.

3.2.2 Requirements for the evidence report for traditional indications

3.2.2.1 Sponsor details

Sponsor name, designation, company and contact details **must** be recorded.

3.2.2.2 Product name

The name of the product to be listed on the ARTG **must** be documented.

3.2.2.3 Indication details

Evidence of traditional use can only be used to support indications that refer to a health benefit in the context of the traditional heath paradigm. Traditional indications must not imply efficacy.

Emma Burchell 22/10/12 9:54 AM
Comment [42]: Ensure consistency between consultation documents. traditional claims not implying efficacy is at odds with the TGA draft coded indications document

This section of the Evidence Report **must** include:

- the wording of the traditional indication, including the provision to indicate that the health effect is based on long-term use and/or experience
- the characterisation of all active ingredients. This includes ingredient name and quantity and, depending on the ingredient type, will also include, as appropriate, details of plant part, plant preparation, extract details, homoeopathic potency.
- dosage form
- route of administration; and
- dosing details (dose or dosage range, dose frequency, and duration of use).

3.2.2.4 Identification of evidence

An objective, comprehensive, transparent and reproducible review of the literature that is of potential relevance to establishing a tradition of use and traditional indications is required.

The search of the literature **must** be documented to internationally accepted standards.[9] The search terms used, databases and search interfaces used and the numbers of references retrieved **must** be documented in the report.

3.2.2.5 Relevance of identified evidence of traditional use

Only items of evidence that have been determined to be relevant to proposed listable indications are to be included in any subsequent analysis. Table 4 lists inclusion and exclusion criteria for determining study relevance for substantiating traditional indications through an Evidence Report.

[9] 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>

Table 4: Assessing relevance of items of evidence for supporting traditional indications

	Excellent	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details and route of administration.	Identical active ingredient and route of administration, comparable dosing details, dose form and formulation.	Identical route of administration, comparable active ingredient or formulation dosing details and dose form.	Different active ingredient or route of administration.
Relevance to target population	Traditional population is identical to the target population.	Traditional population is comparable to the target population.	Some differences between traditional population and target populations but 'clinically reasonable' to extrapolate evidence to the target population.	Major differences or differences of uncertain clinical significance exist between traditional and target populations.
Relevance to traditional health benefit	The wording of the indication is identical to item of evidence, including, the use of traditional terminology.	The wording of the indication is identical in intent to item of evidence, including, the use of traditional terminology (traditional synonym used to describe the indication).	The wording for the indication is identical in intent to item of evidence, but using contemporary terminology (modern synonym used to describe the traditional indication).	The wording and intent for the indication is inconsistent with the item of evidence.
Relevance to traditional context	Clearly identified and used continuously within the relevant traditional paradigm over at least 75 years.	Identified within the relevant traditional paradigm but with disclarity regarding consistency of use over a period of 75 years.	Identified within the relevant traditional paradigm with some disclarity regarding characterisation of the active ingredients or formulation.	Not consistent with the relevant traditional paradigm.

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

3.2.2.6 Quality of relevant evidence

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.

The assessment of quality **must** consider how well the:

- traditional paradigm has been defined
- ingredient(s)/product has been fully characterised
- preparation has been described
- dose and dosing details have been documented
- route of administration has been specified
- target population has been defined; and
- traditional therapeutic use (indication) has been described.

3.2.2.7 Assessment of the traditional therapeutic use

The exact terms used by each piece of evidence of traditional use to describe the intended health benefit **must** be explicitly documented.

3.2.2.8 Assessment of the balance of relevant evidence

The wording of the indication, including terms used to describe the health benefit, **must** be representative of the balance of evidence. The assessment of the balance of evidence **must** consider the quality of relevant items of evidence and the terms used to describe the intended health benefit.

Part B. Guidance material

1. Listable indications

An indication, in relation to therapeutic goods, must describe the specific therapeutic use(s) of the goods. Indications refer to a particular health benefit and are structured to include a nominated **action or effect** (such as reduces, prevents, 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 the context of therapeutic use (e.g. within a particular traditional health paradigm or a particular subset of the population) or the specific qualities of the action or effect (e.g. rapid or sustained) or target (e.g. acute, severe or persistent).

Indications can generally be schematically represented in the following way:

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

Where:

- CONTEXT= contextual qualifier where appropriate
- ACTION=action, outcome or effect
- TARGET=the clinical condition, health status or biological factor
- QA=action qualifier if appropriate
- QT=target qualifier if appropriate.

Example indications:

Traditionally used in Herbal Medicine to reduce the recurrence of urinary tract infections

CONTEXT | ACTION | Q_T | TARGET

For the temporary relief of mild to moderate headache

Q_A | ACTION | Q_T | TARGET

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).

Emma Burchell 22/10/12 7:37 AM

Comment [43]: From this section onwards, all comments have been included and information condensed to the sections above it.

Industry strongly suggest these sections be further reviewed and clarified in the review of the ARGCM and relevant sections and templates relating to evidence requirements can be highlighted in appendixes.

An indication for a listed medicine:

- 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 active ingredient, combination of active ingredients or formulation
- must comply with the requirements of Schedule 4 of the Therapeutic Goods Regulations 1990; and
- must not refer to a disease, ailment, defect or condition generally accepted to be beyond the ability of the average consumer to diagnose, treat or manage without the intervention of an appropriately qualified healthcare practitioner (this includes obesity but does not include management of overweight). The serious health risks associated with obesity require intervention and management by an appropriately qualified healthcare professional. Medicines with indications that refer to obesity must be included in the ARTG as registered medicines. Indications for listed medicines, in general, must only refer to ailments or health states that are self-diagnosable, self-treatable, self-resolving and the consumer can recognise if the product is ineffective and make decisions to discontinue use, seek an alternate product or seek the advice of a healthcare professional, as appropriate.

2. Types of listable indications

Indications are categorised in a number of ways. Historically, the approach has been to recognise three categories of indications (general, medium and high)[10] that form a hierarchy based on the 'strength' of the indication made, with each requiring an increasing 'level' of evidence.

Linking the 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 study results to the population for whom the medicine is intended, and the applicability of the results to the Australian (and/or local) health care setting.[11]

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

2.1 Indications based on scientific evidence or evidence of traditional use

Indications are classified into 'scientific indications' or 'traditional indications' according to the type of supporting evidence.

Scientific and traditional indications are fundamentally different; scientific indications are efficacy based, while traditional indications are based on a tradition of use within a particular health paradigm (e.g. traditional Chinese medicine; traditional herbal medicine).

[10] Available at: http://www.tga.gov.au/pdf/cm-evidence-claims.pdf. Accessed 12 June 2012.
[11] National Health and Medical Research Council. levels of evidence and grades for recommendations for developers of guidelines. December 2009.

Scientific evidence is derived from the scientific literature and may be used to substantiate indications that refer to health benefits for the Australian population in general or for specific Australian sub-populations (e.g. children; menopausal women).

Evidence of traditional use requires documentary evidence that an ingredient or product has been used consistently over 75 years for a specific health purpose. For many products and ingredients there has been little quantifiable scientific research undertaken into their mode of action and effect.

Indications that are based on traditional use must be true, valid, not misleading and consistent with the traditional use of an ingredient, group of ingredients or product. As the evidence to substantiate traditional indications is based on a history of use rather than an assessment of efficacy, provisions must be in place to ensure that consumers are aware of the nature of the evidence supporting traditional indications to guide an informed choice.

Traditional indications are based on evidence of a history of medicinal use of the ingredients or products that exceeds 75 years.

Evidence of traditional use can only be used to support indications that refer to a health benefit in the context of the traditional heath paradigm. Traditional indications **must not** imply efficacy. To reduce the possibility that traditional indications are misinterpreted by consumers to imply efficacy, traditional indications **must** indicate that health benefit is based exclusively on long-term use and experience.

Expressing health benefit based on long term use or experience

Used traditionally in Native American medicine for the relief of coughs and colds.

Traditional Native American medicine for relief of coughs and colds.

This traditional medicine has been used by Native Americans for the relief of coughs and colds.

Terms used in traditional listable indications must be comprehensible to consumers and consistent with those referenced in the evidence of traditional use 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 forms of health disorders or conditions, such as ‘useful for chronic inflammation’ or ‘used as a healing aid for urinary disorders’

In cases where the traditional terminology may be unclear to consumers, the information should (also) be communicated using appropriate conventional terminology.

The use of appropriate contextual qualifiers and the inclusion of a statement to the effect that the health benefit is based exclusively on long-term use and experience, ensures that such information is readily available to consumers.

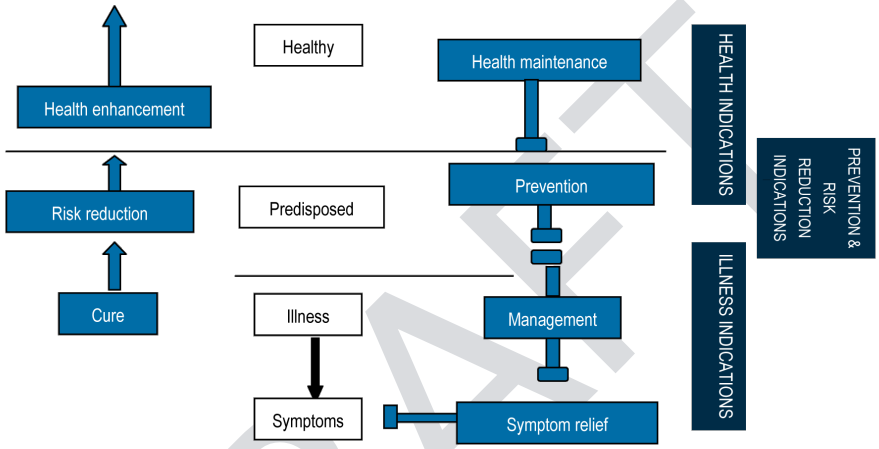
In situations where the requirements for both scientific evidence and evidence of traditional use are met for an active ingredient or product, traditional and/or scientific indications may be made. If an indication is solely supported by scientific evidence, it must not use the words ‘traditionally used’.

The guidance regarding the assessment of evidence for scientific and traditional indications is provided in Section 3.

2.2 Types of indication according to type of health benefit

Listable indications may be further classified according to type of health benefit. In broad terms, indications may target biological factors or processes, health states or clinical conditions. The following diagram provides a schematic representation of all states of health through healthy 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 can be conveniently separated into three clusters – indications targeting: a generally healthy state; risk reduction/prevention; and illness. All indications must be supported by evidence that is appropriate and valid.

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.[12] 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. condition, disease or disorder.
- 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 cluster includes the following types of indications:

- **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**: reduces the frequency, duration and/or severity of a symptom or cluster of symptoms associated with a named illness.
- **cure**: effects complete resolution of an illness and all associated morbidity.

2.3 Nutrients and nutrient supplementation

Nutrients and nutrient supplementation

a) Health benefits: Statements relating to supplementation with vitamins, minerals or other essential nutrients (e.g. 'a source of calcium') imply a health benefit (i.e. the maintenance of good health). Health benefit claims are only permitted on products if the recommended daily dose of the product provides at least 25 % of the Australian Recommended Dietary Intake (RDI), Adequate Intake (AI) or nutrient reference value for that vitamin, mineral or nutrient.

Claims should not refer to the presence of vitamins, minerals or nutrients (e.g. 'contains Zinc') unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, AI or nutrient reference value for that vitamin, mineral or nutrient, unless there is evidence to support a therapeutic effect below this level.

b) Prevention or treatment of a nutrient deficiency: If the indication refers to prevention or treatment of a nutrient / **dietary** deficiency, the nutrient must provide at least 100 percent of the RDI, AI or nutrient reference value for the relevant nutrient.

c) Specific Indications: Where vitamins, minerals or other nutrients are the subject of other indications, the dose must be consistent with the evidence to support the indication.

Emma Burchell 22/10/12 7:37 AM
Comment [44]: See specific comments in submission.

Emma Burchell 22/10/12 6:42 AM
Deleted: Statements relating to supplementation with vitamins, minerals or other essential nutrients (e.g. 'a source of calcium') imply a health benefit (i.e. the maintenance of good health). Such statements are permitted on products if the recommended daily dose of the product provides at least 25 percent of the Australian recommended dietary intake (RDI), adequate intake (AI) or nutrient reference value for that vitamin, mineral or nutrient. If the listed medicine states that it is intended to supplement a named nutrient, it must provide at least 50 percent of the RDI, AI or nutrient reference value for that nutrient. If the indication refers to prevention or treatment of a nutrient deficiency, the nutrient must provide at least 100 percent of the RDI, AI or nutrient reference value for the relevant nutrient. Where available, Australian RDI, AI or nutrient reference values published by NHMRC are to be used. If there is no Australian RDI, AI or nutrient reference value for a vitamin, mineral or other nutrient, a nationally accepted RDI, dietary reference intake or equivalent nutrient reference value of another country may be used. Where vitamins, minerals or other nutrients are the subject of other indications, the dose must be consistent with the evidence to support the indication. ... [28]

[12] An indication that is associated with well-being, wellness or to health generally, requires supporting evidence. Well-being, wellness and health are complex states and do not just refer to the absence of illness. The multiple dimensions of these states are complex and holistic. Metrics used to quantify them would need to be valid measures and take into account both objective and subjective data such as quality of life physiological, psychological, social and demographic factors.

Where available, Australian RDI, AI or nutrient reference values published by NHMRC are to be used. If there is no Australian RDI, AI or nutrient reference value for a vitamin, mineral or other nutrient, a nationally accepted RDI, dietary reference intake or equivalent nutrient reference value of another country may be used.

All indications for nutrient-containing medicines, whether implicit or explicit, must be consistent with those permitted for listed medicine (see Section xx) and, in general, must not refer to serious diseases.

Health status

The health status of the study population must be representative of the target 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.[13] Because of these factors, weight changes observed in obese individuals with a BMI >35 kg/m^2 may 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

[17] National Health and Medical Research Council 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>

Emma Burchell 22/10/12 7:37 AM
Comment [45]: Repeated information m ... [30]
Emma Burchell 22/10/12 7:37 AM
Comment [46]: Recommend complete r ... [31]
Emma Burchell 19/10/12 6:50 PM
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Emma Burchell 20/10/12 12:28 PM
Deleted: Many listed medicines target hea ... [32]
Emma Burchell 22/10/12 7:37 AM
Comment [47]: Maybe useful for review ... [33]
Emma Burchell 20/10/12 12:48 PM
Deleted: are …ay not applicable to over ... [34]
Emma Burchell 20/10/12 12:29 PM
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Deleted: <5.5mmol/L
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Deleted: 2.0-3.4mmol/L
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Deleted: Blood TAG
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Deleted: **Overweight**
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... [39]

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

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).

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Deleted: Indication

Emma Burchell 20/10/12 12:30 PM
Deleted: Relevant population

Emma Burchell 20/10/12 12:30 PM
Deleted: For weight loss in overweight individuals when used in conjunction with a calorie or kilojoule controlled diet and physical activity (or exercise).

Emma Burchell 20/10/12 12:30 PM
Deleted: Male and female participants aged 18-65 years generally healthy population with BMI 25-34.9 kg/m^{2}sociocultural similar to the Australian population

Emma Burchell 20/10/12 12:30 PM
Deleted: Reduces pain.

Emma Burchell 20/10/12 12:30 PM
Deleted: Male and female participants aged 18-65 years generally healthy population with a range of painful (non-serious) conditions.

Emma Burchell 20/10/12 12:30 PM
Deleted: Relieves fever in children.

Emma Burchell 20/10/12 12:30 PM
Deleted: Male and female participants aged 2-18 years generally healthy population with cough associated with a range of (non-serious) conditions.

Emma Burchell 20/10/12 12:30 PM
Deleted: Calcium helps maintain healthy strong bones.

Emma Burchell 20/10/12 12:30 PM
Deleted: Male and female participants aged 18-65 years generally healthy population dietary and lifestyle pattern similar to the Australian population.

Example:

A study that assesses the effect of an ingredient on the duration of the common cold does not support evidence for an indication that describes symptomatic relief 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.

Metabolism	Body shape and composition	Weight-related	Appetite

Emma Burchell 22/10/12 11:04 AM
Comment [48]: See comments regarding weight loss.

Emma Burchell 22/10/12 11:04 AM
Deleted: The following table provides representative examples of terms related to weight loss, that cannot be substituted for weight loss in a listable indication

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Emma Burchell 22/10/12 11:04 AM
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Fat loss
Weight maintenance
Appetite suppression
... [40]

Emma Burchell 22/10/12 11:04 AM
Deleted: Fat loss
Weight maintenance
Appetite suppression
... [41]

Emma Burchell 22/10/12 11:04 AM
Deleted: Weight maintenance
Appetite suppression
... [42]

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Deleted: Appetite suppression
... [43]

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 3.2.1.8). However, inclusion of the health benefit as a secondary outcome may be acceptable provided that the observed result is shown to be statistically and clinically significant.

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

Example:

An indication relating to weight loss refers to a specific biological 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 indications 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 sponsor 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.

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 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 sponsor 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 the level of pain for several hours after an initial dose and continue for long enough to be representative of the pattern of use expected of a consumer when used to control pain associated with a non-serious, self-limiting condition.

Example:

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

Emma Burchell 22/10/12 7:37 AM
Comment [49]: Inconsistent with study results coming out of Canada, mostly of 12 week duration. EFSA suggests studies supporting weight maintenance should be of about 6 months duration. See submission for more detailed comments.

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Deleted: A reasonable timeline to achieve a significant degree of weight loss is six months. After about

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Deleted: six months, the rate of weight loss usually declines as weight plateaus, and some regain is common.[14] Studies assessing weight loss should be of at least six months duration.[15,16] 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.

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 3.2.1.8) and this should be justified in the Evidence 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	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details, formulation and route of administration.	Identical active ingredient and route of administration, Comparable dosing details and formulation.	Identical route of administration Comparable active ingredient, or formulation and dosing details.	Different active ingredient or route of administration.
Relevance to target population	Population studied is identical to the target population.	Population studied is comparable to the target population.	Some differences between study and target populations but 'clinically reasonable' to extrapolate 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 measure health benefit in listable indication.
Relevance to context of use	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.

When an indication is directed at a specific sub-group of the population, eligibility criteria will reflect the indication. 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

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.

In order to estimate the relevance of the body of evidence included in the report, 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 RS=study relevance score, RM=relevance to medicine, RP=relevance to target population, RB=relevance to health benefit, and RC=relevance to context.

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

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

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 3.2.1.9): 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 template at Appendix 3.

3.2.1.6 Level of evidence

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.

NHMRC levels of evidence

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Comment [50]: This requirement is irrelevant and inappropriate .

Studies with increased methodological rigor are able to produce evidence that more closely reflects the health benefits associated with a particular intervention. 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. This may be the case where randomised controlled trials are impractical or unethical.

Accordingly, the NHMRC has developed the following hierarchy of evidence[17]:

Level	Intervention	Prognosis	Aetiology
I 4	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies

[17] National Health and Medical Research Council 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>

Level	Intervention	Prognosis	Aetiology
II	A randomised controlled trial	A prospective cohort study	A prospective cohort study
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	All or none	All or none
III-2	A comparative study with concurrent controls: non-randomised, experimental trial; cohort study; case-control study; interrupted time series with a control group.	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: historical control study; two or more single arm study; interrupted time series; without a parallel control group.	A retrospective cohort study	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

3.2.1.7 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.

The quality of every relevant item of evidence should be assessed utilising a published, critical appraisal instrument that is appropriate for the type of evidence being considered. Appendix 3 includes examples of critical appraisal instruments for experimental and observational studies that may be used to aid with the assessment of study quality. The instrument enables the sponsor to determine a quality score (out of 18) for each study considered and requires the sponsor to tabulate the number of high quality (score 10-18) and lower quality studies (score 0-9).
Other published critical appraisal tools, such as the CONSORT statement[18] or Dalhousie critical appraisal instrument[19] may be used in place of these instruments, however the instrument used should include as a minimum an assessment of the following:

- characterisation of the ingredient or formulation used
- study design/methods

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Comment [51]: Only reported data should be entered. If it is not reported, this is reordered and forms part of assessment. the requirement to obtain original data and perform calculation (d-value on appendix) is not justified.

Emma Burchell 22/10/12 7:37 AM
Comment [52]: "Must' terms not appropriate in a guidance document.

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[18] Schulz KF, Altman DG, Moher, D. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine 2010, 152 (11):726-W.293
[19] Jurgens T, et al. **Development and evaluation of an instrument for the critical appraisal of randomized controlled trials of natural products.** BMC Complementary and Alternative Medicine 2009, **9**:11.

- participant eligibility (inclusion/exclusion criteria)
- randomisation and blinding of participants (for Randomised Controlled Trials (RCT)).
- sample size justification/power calculations
- controlling for potential confounders
- study attrition (for RCT and cohort studies)
- statistical analyses undertaken

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Comment [53]: Suggest replace with a check list (tick box) option

The critical appraisal tool **must** be used to classify each relevant item of evidence as a high or low quality study, as studies of higher methodological quality will carry more weight in an assessment of the relevant evidence base for a particular indication.

The following sections provide guidance relating to the assessment of study quality.

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 required 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 3.2.1.8. 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.[20] Sensitivity analyses provide an additional means of assessing the effect of dropouts on study results.

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.

3.2.1.8 Assessment of the expected health benefit

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 meaningful to consumers.

The results of every relevant item of evidence **must** be considered. For each of these, any relevant outcome measure **must** be described. In addition, the presence or absence of a statistically significance effect (positive or negative) for each relevant outcome measure **must** be recorded.

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

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.

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

For health indications, the effectiveness of ingredients 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 percent) 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 percent certainty. When 95 per cent confidence intervals are generated around outcome measures, the 95 percent 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

Consideration should be given to the likely significance of an observed outcome to the intended target population.

The following table provides a useful approach to the assessment of clinical significance for listed medicines.

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

For some health benefits the parameters used to determine clinical significance may be prescribed by the TGA. This is the case for indications related to weight loss.

Points to consider 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.[25] 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[26] 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.[27, 28, 29]

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[30] postulated that a mean reduction in

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Deleted: Not all statistically significant differences are clinically significant.[21,22,23] A statistically significant outcome indicates only that there is likely to be a relationship between intervention and outcome. Clinical significance is more difficult to define but is commonly considered to represent a degree of benefit that is worthwhile in real life to justify intervention, and may consider factors such as cost, side effects and inconvenience. ... [44]

Emma Burchell 22/10/12 7:37 AM
Comment [54]: Guidance only, to be reviewed as an appendix to the ARGCM. See submission for specific comments in regard to weight loss / maintenance.

Emma Burchell 20/10/12 12:53 PM
Deleted: Special requirements

25 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>

26 National Health and Medical Research Council (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>

27 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.

28 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.

29 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.

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

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.[31] 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 an ingredient 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 should demonstrate:

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- 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.

3.2.1.9 Assessing the balance of evidence

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Comment [55]: Cover in the one area.

Once the characteristics of individual studies have been assessed, the balance of the scientific evidence must be determined. The assessment of the balance of evidence **must** consider the quality and outcomes of all relevant studies included in the report 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.

The consistency of the relevant outcomes observed in high quality studies **must** be assessed first. This **must** take into account both the statistical and clinical significance of the outcomes.

Only if the balance of high quality evidence is equivocal are the outcomes of lower quality studies to be included in assessing the balance of evidence.

The following matrix provides guidance regarding the assessment of the balance of evidence. It is also provided in Section 5 of the Evidence Report template at Appendix 3.

31 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.

Element	Excellent	Good	Acceptable	Unacceptable
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) or negative effect
Clinical impact	Meaningful health benefit very likely to achieved by consumers	Meaningful health benefit likely at the individual or population level	Clinical impact uncertain- meaningful health benefit possible.	Unlikely to be meaningful

Level of Study derived from NHMRC 200932 (See Section 2.2.2.2)
*If only one study then consistency rated as N/A
+ SS= statistically significant

The sponsor can then use the information summarised in the matrix to assess support for the proposed indication. An indication is only valid if the balance of evidence is supportive. In general, scores of at least C in both statistical significance and clinical impact **are required** to infer a supportive balance of evidence.

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 product (or 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. It may be that unsupported indications become supported if favourable evidence emerges that tips the balance.

3.2.2 Assessing evidence to establish a traditional of 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 Strait Islander healing practices. Traditional medicine may also be referred to as indigenous, folk, holistic or natural medicine, and other variations.

[32] National Health and Medical Research Council. 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>

Some traditional systems of medicine are highly developed and well documented. They are based on systematised knowledge, a comprehensive methodology and 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 a 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 use. 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). 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 traditional indications for listed medicines provided that they meet the requirements of the following sections of this guideline. Substantiating indications based on a tradition of use depends on identifying evidence that supports the use of a product or ingredient within a particular paradigm over 75 years for a specific health purpose.

It may be difficult to find references that explicitly indicate that a product or ingredient has been used for at least 75 consecutive years. In such cases, a sponsor may wish to consider the following approaches to establish the historical use of the ingredient or product:

- If the reference refers to the ingredient product in the context of a particular cultural paradigm (such as the Chinese culture), and it is apparent that the cultural system has been in existence for at least 75 years, it can be assumed that the ingredient or product has been used for that particular purpose for 75 years or more.

- By referring to sales records, depending on their length and scale of activity, it may be possible to infer use of a product or ingredient for 75 years from this information.

Textbooks provide useful information in guiding the sponsor towards sources of primary evidence but are not sufficient evidence to substantiate traditional indication. Where textbooks are referenced, evidence of traditional use 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.

In the case of classical preparations described in early pharmacopoeias, *materia medica* or other classical references that were developed without access to modern analytical techniques, a comprehensive and satisfactory specification for the identification and quality of the ingredient or product is unlikely to be available. In such situations, the starting material and method of preparation must be identical to that described in the classical literature or otherwise established that the composition of the ingredient or product is comparable or not significantly different

from the classically produced ingredient or product (e.g. chemical or chromatographic fingerprint).

In instances where it is not possible to access the original reference which describes the traditional use, evidence of traditional use may be supported by contemporary references reporting the original tradition. However, contemporary references must provide sufficient information to substantiate the consistency of the identity of the ingredient, method of preparation, ingredient and dosage form and conditions of use (route of administration, dose, frequency and duration of use, target population and risk information), as far as possible, with the ingredient or product described in the original reference.

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

3.2.2.1 Sponsor details

Sponsor name, company and contact details **must** be recorded.

Emma Burchell 21/10/12 4:00 PM
Deleted: designation,

3.2.2.2 Product name

The name of the product to be listed on the ARTG **must** be documented

3.2.2.3 Indication details

Evidence of traditional use can only be used to support indications that refer to a health benefit in the context of the traditional heath paradigm. Traditional indications must not imply efficacy. This section of the Evidence Report **must** include:

- the wording of the traditional indication, including the provision to indicate that the health effect is based on long-term use and/or experience
- the characterisation of all active ingredients. This includes ingredient name and quantity and, depending on the ingredient type, will also include, as appropriate, details of plant part, plant preparation, extract details, homoeopathic potency
- dosage form
- route of administration; and
- dosing details (dose or dosage range, dose frequency, and duration of use).

3.2.2.4 Identification of evidence

Emma Burchell 22/10/12 7:37 AM
Comment [56]: Cover in the one area.

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 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 must be made 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.

Emma Burchell 22/10/12 7:37 AM
Comment [57]: See previous comment.

Emma Burchell 21/10/12 4:01 PM
Deleted: It is recommended that the help of a specialist librarian is sought, particularly when searching non-English databases when conducting the literature review

Emma Burchell 21/10/12 4:01 PM
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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.

Abstracts or informal summaries of an original document are less reliable, because these usually do not give sufficient detail of ingredients or products and/or their use within a traditional paradigm.

This literature review should involve the following steps:

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Deleted: will

- 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)
- 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; and
- documenting the search parameters and the results of the search.

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 (ingredient, 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 3.2.2.5.

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.

3.2.2.5 Relevance of evidence of traditional use

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 comprehensible to consumers and consistent with those referenced in the evidence of traditional use 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 forms of health disorders or conditions, such as 'useful for chronic inflammation' or 'used as a healing aid for urinary disorders'
- refer to serious forms of disease, disorders, or condition or signs or symptoms that may imply a serious disorder or condition (as per all listable indications).

In cases where the traditional terminology may be unclear to consumers, the information should (also) be communicated using appropriate conventional terminology.

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 of traditional use for suppression of hunger and promotion of fasting are **not** acceptable justification to indicate that a product or ingredient has a traditionally been used for weight loss.

Emma Burchell 22/10/12 7:37 AM
Comment [58]: Keep in the one area. Weight loss guidance to be reviewed as an appendix to the ARGCM. See submission for specific comments in regard to weight loss / maintenance.

Relevance to 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.

Emma Burchell 22/10/12 7:37 AM
Comment [59]: Note previous comment for Table 1 Criteria in a SEE that is inconsistent with this statement.

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 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, 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;
- 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 indication is based require scientific evidence in order to substantiate their claimed action.

Example:

A sponsor wants to list a product with an indication: '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 that the ingredients have a tradition of use within the paradigm is a copy of the relevant pages from a contemporary Chinese reference that indicate one of the herbs present in the medicine was used in ancient times for symptoms 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.

Relevance to population

Evidence of traditional use may be derived from populations that do not closely resemble the general Australian population. The context of use (paradigm/region) **must** be referred to in the traditional indication and must also include wording to the effect that the health effect is based on long-term use and/or experience.

Traditional Khmer medicine used by the people of north west Cambodia for the treatment of stomach ache

In some traditional medicine paradigms may specifically exclude certain subgroups of the populations from access to a medicine (e.g. children, pregnant women). This information may be provided in language that is specific to that traditional paradigm or culture. In cases where the traditional terminology may be unclear to consumers, the information should (also) be communicated using appropriate conventional terminology.

Relevance to traditional 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 may not resemble those experienced by consumers of listed medicines as the historical and cultural context of use is removed from self-selection and self-use use by consumers in contemporary Australia.

Emma Burchell 22/10/12 7:37 AM

Comment [60]: Ensure consistency with statements. Statement included in the general factor section previously.
'Studies used to justify scientific listable indications should be conducted in populations that are reasonably representative of the general Australian population'

CHC rx: The study population should be consistent with the target population. Where studies show differences in results these should be documented.

The glossary definition for Australian population recognises the diversity here and the general requirement may cause more questions than it assists.

In order to be considered relevant to a traditional context or paradigm, use within a particular paradigm over a period of at least 75 years must be demonstrated. Ideally, the indicated use would be clearly identified and continuously applied within the relevant traditional paradigm over at least 75 years

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 evidence of traditional use 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 items of evidence from further analysis based

	Excellent	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details and route of administration.	Identical active ingredient and route of administration, comparable dosing details, dose form and formulation.	Identical route of administration, comparable active ingredient or formulation dosing details and dose form.	Different active ingredient or route of administration.
Relevance to target population	Traditional population is identical to the target population.	Traditional population is comparable to the target population.	Some differences between traditional population and target populations but 'clinically reasonable' to extrapolate evidence to the target population.	Major differences or differences of uncertain clinical significance exist between traditional and target populations.
Relevance to traditional health benefit	The wording of the indication is identical to item of evidence, including, the use of traditional terminology.	The wording of the indication is identical in intent to item of evidence, including, the use of traditional terminology (traditional synonym used to describe the indication).	The wording for the indication is identical in intent to item of evidence, but using contemporary terminology (modern synonym used to describe the traditional indication).	The wording and intent for the indication is inconsistent with the item of evidence.
Relevance to traditional context	Clearly identified and used continuously within the relevant traditional paradigm over at least 75 years.	Identified within the relevant traditional paradigm but with disclarity regarding consistency of use over a period of 75 years.	Identified within the relevant traditional paradigm with disclarity regarding consistency of use over a period of 75 years and/or disclarity regarding characterisation of the active ingredients or formulation.	Not consistent with the relevant traditional paradigm.

For traditional indications context refers to more than 75 years of medicinal use within a traditional medicine paradigm.

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

3.2.2.6 Quality of evidence of traditional use

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 the identity and characterisation and 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 (particularly, the holistic nature of many traditional medicine paradigms) 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, cannot 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 4 includes a quality checklist for evidence of traditional use that can be used by sponsors to assist in the assessment of quality for every source reviewed.

3.2.2.7 Assessment of the evidence of traditional therapeutic use

In many cases, evidence of traditional use 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 ingredient or medicine and not its 'efficacy' or 'effectiveness'.

It is important to ensure that the traditional therapeutic use of an ingredient(s) described in the supporting evidence is consistent with the proposed indication. The exact terms used by each piece of evidence of traditional use to describe the intended health benefit must be explicitly documented in Section 5 of Appendix 4.

3.2.2.8 Assessing the balance of evidence of traditional use

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 as outlined in the preceding sections.

The assessment of the balance of evidence **must** consider the quality of relevant items of evidence and the terms used to describe the intended health benefit.

Emma Burchell 22/10/12 7:46 AM
Comment [61]: Remove scoring system.

Emma Burchell 22/10/12 7:46 AM
Comment [62]: Remove

Emma Burchell 22/10/12 7:47 AM
Comment [63]: This section should be simplified and included into one section on the assessment of traditional evidence.

Emma Burchell 22/10/12 7:45 AM
Deleted: 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: ... [45]

Emma Burchell 22/10/12 7:45 AM
Deleted: score for all items of evidence and divide by the total number of included items ... [46]

Emma Burchell 22/10/12 7:45 AM
Deleted:

The wording of the indication, including terms used to describe the health benefit, **must** be representative of the balance of 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 6 of Appendix 4 and aims to assist the sponsor in the assessment of the balance of evidence of traditional use.

Element	Excellent	Good	Acceptable	Unacceptable
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 sponsor can then use the information summarised in the matrix to assess support for establishing a history of use over a period of greater than 75 years and its traditional therapeutic use in relation to the proposed indication.

3.3 Potential clashes between traditional and scientific evidence

Emma Burchell 22/10/12 7:48 AM
Comment [64]: Useful but could be simplified.

The potential exists for apparent clashes between the conclusions of traditional and scientific evidence. Ingredients 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 negate evidence that the ingredient(s) or product has been traditionally used within the traditional paradigm for a particular health effect. 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 For this reason, traditional indications must refer to the tradition of use. In additional, all indications 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.

Emma Burchell 22/10/12 7:49 AM
Deleted: or use vague terms such as 'has been shown to produce weight loss'.

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.

3.4 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 3.2.1 or Section 3.2.2. 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 within the context of the traditional paradigm 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.

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, dosing details and indication) 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 considered to be an active ingredient or excipient will have important consequences for the consideration of the evidence base. Some traditional medicines contain an ingredient that mitigates or alters the effects of the primary medicinal ingredient to prevent adverse reactions. Because they are biologically active, they are regarded as active medicinal ingredients.

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.

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

For multi-active ingredient products (i.e. two or more medicinal ingredients in a single product), to be listed based on a well-established tradition of use, a combination rationale is required unless all of the active ingredients of the product are captured in a single product monograph (established formulations – see below). In the absence of a single product monograph, the combination rationale must establish that each ingredient is within the same identified traditional paradigm (e.g. traditional Chinese medicine, traditional herbal medicine, etc) and why the combination of medicinal ingredients is not only permissible, but is logical based on the uses of ingredients within the identified system of traditional medicine.

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 the evidence sources, 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.

Combinations of scientific evidence and evidence of traditional use

Where products contain multiple ingredients where some are associated with scientific indications and others with traditional indication, the kind of evidence supporting each indication must be clearly communicated to the consumer. In cases where both scientific evidence and evidence of traditional use support an indication, both scientific and traditional indications may be made.

A combination of a non-traditional ingredient with traditional ingredients is a non-traditional combination. Similarly, cross-paradigm formulations may combine individual ingredients with traditional indications within their original traditional context. However, the resulting product is not traditional in the context of either of the original traditional paradigms. For example, an ingredient from traditional Chinese medicine may be combined with another ingredient from traditional Ayurvedic medicine. Since the new formulation is neither from traditional Chinese nor Ayurvedic medicine, the multiple ingredient product as a whole cannot claim a history of use.

3.5 Disclaimers and required advisory statements

Emma Burchell 22/10/12 7:51 AM
Comment [65]: As previously stated, this section does not belong in the document.

Emma Burchell 22/10/12 7:51 AM
Comment [66]: Not relevant to an evidence document.

Emma Burchell 22/10/12 7:51 AM
Deleted: 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: ... [47]

Emma Burchell 22/10/12 7:51 AM
Deleted: <#>'.

Emma Burchell 22/10/12 7:53 AM
Comment [67]: See att. 3 for a proposed extended list. Detail of proposed mechanism for addition to the SEE is required, rx. in the submission.

This should form a appendix to the ARGCM document.

Appendix 1: Sources of established scientific evidence

A **Source of Established Evidence** (SEE) must provide evidence for all scientific indications to be listed for the product or evidence that the product or its active ingredient has a well-established traditional of use and that the indication is consistent with its traditional use.

If the SEE is assessed in a competent way to meet the all the criteria described in Section 3.1.2 - Information required from Sources of Established Evidence, the documentation should be sufficient to meet the evidentiary requirements for listing a medicine under Section 26A(2) (j) of the Act. The documentation may be subsequently reviewed and assessed by the TGA as part of its post market activities.

Other sources of information may be used to provide evidence for scientific and traditional indications and to establish a tradition of use for active ingredients or products. However, this information must held in the form of an Evidence Report (see Section 3.2 for details).

It is recognised that some SEEs may be deficient in information necessary to fully substantiate scientific or traditional indications or a history of use for a specific ingredient or product. In such situations, contributions from more than one SEE may be linked to provide the necessary substantiation. For example, substantiation can only occur if the ingredient or product is thoroughly identified and specified. In some early SEEs, the names used to describe the same plant, animal or mineral material and their method of preparation were variable and sometimes complicated by transliteration from the original language. This is not necessarily a failing of the information source in reporting studies, but due to the cultural and technical standards operating at the time. However, in more recent literature, these names can be linked to unambiguous scientific names and standardised in their use.

Multi-ingredient traditional medicines

For multi-active ingredient products (i.e. two or more medicinal ingredients in a single product), to be listed based on a well-established tradition of use, a combination rationale is required unless all of the active ingredients of the product are captured in a single product monograph. In the absence of a single product monograph, the combination rationale must establish that each ingredient is within the same identified traditional paradigm (e.g. traditional Chinese medicine, traditional herbal medicine, etc) and why the combination of medicinal ingredients is not only permissible, but is logical based on the uses of ingredients within the identified system of traditional medicine.

Correct identification of medicinal plant species

The same medicinal material may be described using different names. Latin pharmaceutical names, as used in some *materia medica* and pharmacopoeia, must be unequivocally linked to the valid, standardised, Latin binominal and author (eg. Corydalis Rhizoma is the dried tuber of *Corydalis yanhusuo* W.T. Wang)

It is the responsibility of sponsors to determine if the information and evidence cited in the SEE listed below is valid, relevant and sufficient to justify either a scientific indication or a well-established tradition of use for the specific complementary medicine product to be listed.

Where it is not possible to meet the criteria described in Section 3.1.2, an Evidence Report must be prepared.

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Blumenthal, M., Goldberg, A, Brinckmann, J. (ed). Herbal Medicine, Expanded Commission E Monographs. American Botanical Council Austin, Texas 2000.
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Compendium of Monographs. Ottawa (ON): Natural Health Products Directorate, Health Canada. Single ingredient monographs available at: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng. Product monographs available at: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/monosReq.do?lang=eng&monotype=product.
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SOURCE
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Customary Medicinal Knowledgebase (CMKb) http://biolinfo.org/cmkb/index.php
Economic Botany Collection (EBC), Royal Botanic Gardens, Kew (UK) http://apps.kew.org/ecbot/search
Global Information Hub on Integrated Medicine (GlobinMed) (Malaysia) http://www.globinmed.com/index.php?option=com_content&view=article&id=80848&Itemid=201

SOURCE
MedlinePlus: Drugs, Supplements & Herbal Information http://www.nlm.nih.gov/medlineplus/druginformation.html
Natural & Alternative Treatments (EBSCO) https://healthlibrary.epnet.com/GetContent.aspx?token=af362d97-4f80-4453-a175-02cc6220a387&chunkiid=33802.
Natural Standard http://www.naturalstandard.com

Appendix 2: SEE assessment template

The SEE Assessment Template is a tool developed to help sponsors ensure that the SEE is valid for the indication to be listed on the ARTG. The template should be used in conjunction with the criteria described in Section 3.1.2. - Information required from Sources of Established Evidence.

The SEE Assessment Template consists of a series of questions with respect to EACH indication. Each question should be answered either **yes** or **no** based on the information in the SEE for each active ingredient or, where applicable, the product as a whole. Answering **no** to any of the questions means that the SEE is deficient and does not meet the evidence requirements to substantiate the scientific or traditional indications or a history of use for the listable product.

Information included in an SEE		
The therapeutic use/s is clearly described including any relevant context, qualifier and risk information (such as the traditional medicine paradigm for traditional indications, directions of use, sub-populations, restrictions or contraindications related to use).	☐ Yes	☐ No
The wording of the indication for inclusion in the ARTG is **identical in intent** with that included in the SEE (including, where appropriate, the use of traditional terminology) Different words with the same intent (ie a medical synonym) may be used to describe the indication included in the ARTG.	☐ Yes	☐ No
Each active ingredient or the product as a whole is clearly identified and characterised and is comparable or not significantly different from the ingredient name and quantity and as appropriate, details of plant part, plant preparation, extract details or homoeopathic potency.	☐ Yes	☐ No
For multi-active ingredient traditional products (i.e. two or more ingredients in a single product) the SEE supports the combination rationale within a single traditional health paradigm.	☐ Yes	☐ No
Where appropriate, the method of preparation (eg extraction conditions and solvent, extract ratio, chemical/chromatographic fingerprint) for each active ingredient or formulation described in the SEE is **comparable** to that of the active ingredients or product to be listed in the ARTG. Where the SEE refers to a liquid extract a corresponding dry extract would usually be acceptable. Where there is a extraction solvent used to prepare an ingredient or product is different from that given in the SEE, comparability may need to be demonstrated by using appropriate analytical data such as chemical/chromatographic fingerprinting or chemical 'marker' content.	☐ Yes	☐ No
Dosing details, as appropriate, described in the SEE (dose form, route of administration, dose or dosage range, dose frequency, and duration of use) are not significantly different from that proposed for the product listing.	☐ Yes	☐ No

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Comment [68]: Include previous recommendations for check list / tick box.

Information included in an SEE		
Any relevant product risk information cautions, warnings, and contraindications associated with use that is in the SEE have been taken into account.	☐ Yes	☐ No

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Comment [68]: Include previous recommendations for check list / tick box.

Additional Information: Append any additional information to substantiate scientific or traditional indications or a history of use. For example, data demonstrating comparability between the ingredients or product described in the SEE such chemical/chromatographic fingerprints or chemical 'marker' content.

Appendix 3: Evidence report (scientific)

1. Sponsor and product details (section 3.2.1.1-2)

Sponsor name	
Contact details	
)	
Product name	

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2. Indication details (section 3.2.1.3)

Listable indication		
Ingredient details	Ingredient	
	Route of administration	
	Dose	
	Other details	
Supported/not supported		
Signature		

3. Identification of relevant evidence (section 3.2.1.4)

Search Date	**Search terms**
Source searched	**#References**

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)								

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Guidance for assessing relevance (Section 3.2.1.5)

	Excellent	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details, formulation and route of administration	Identical active ingredient and route of administration, Comparable dosing details and formulation	Identical route of administration Comparable active ingredient, or formulation and dosing details	Different active ingredient or route of administration
Relevance to target population	Population studied is identical to the target population	Population studied is comparable to the target population	Some differences between study and target populations but 'clinically reasonable' to extrapolate 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 measure health benefit in listable indication
Relevance to context of use	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.

4. Evidence level and quality (for each included study) (sections 3.2.1.6-7)

Level of evidence:

Quality of experimental studies (e.g. randomised controlled clinical trials)

Item	Parameter	Yes (1) or No (0)	
Characterisation of the ingredient/s	Ingredient named (genus, species and plant part if herb)? Extraction/preparation described? Dose and route of administration?	☐ Yes	☐ No
Inclusion/exclusion criteria	Inclusion and exclusion criteria reported?	☐ Yes	☐ No
Sample size	Power calculation performed? Attrition reported? Reasons for attrition given?	☐ Yes	☐ No
Group allocation	Randomised? Randomisation method reported? Randomisation appropriate? Allocation concealed?	☐ Yes	☐ No
Blinding	Were subjects blinded? Were the researchers blinded?	☐ Yes	☐ No
Potential confounders	Were potential confounders considered?	☐ Yes	☐ No
Statistical analysis	Between group statistical comparison performed? Was it appropriate? Did it account for confounders? Was an intention to treat analysis included?	☐ Yes	☐ No
	TOTAL SCORE		

Quality of observational studies (e.g. cohort and case-control studies)

Item	Parameter	Yes (1) or No (0)	
Characterisation of the ingredient/s	Ingredient named (genus, species and plant part if herb)?	☐ Yes	☐ No
	Extraction/preparation described?	☐ Yes	☐ No
	Dose and route of administration?	☐ Yes	☐ No
Inclusion/exclusion criteria	Inclusion and exclusion criteria reported?	☐ Yes	☐ No
Sample size	Power calculation performed?	☐ Yes	☐ No
	Attrition reported?*	☐ Yes	☐ No
	Reasons for attrition given?*	☐ Yes	☐ No
Exposure	Was the methodology used to measure the exposure reported?	☐ Yes	☐ No
	Was the exposure assessed more than once?	☐ Yes	☐ No
Blinding	Were the researchers blinded to the exposure status?	☐ Yes	☐ No
Baseline comparison	Were the subjects in different exposure groups compared at baseline?	☐ Yes	☐ No
Health outcome	Was the methodology used to measure the health outcome reported?	☐ Yes	☐ No
	Was the health outcome verified (e.g. through assessment of medical records, confirmation by a health practitioner)?	☐ Yes	☐ No

Item	Parameter	Yes (1) or No (0)	
Potential confounders	Were potential confounders considered?	☐ Yes	☐ No
Statistical analysis	Between group statistical comparison performed?	☐ Yes	☐ No
	Was it appropriate?	☐ Yes	☐ No
	Did it account for confounders?	☐ Yes	☐ No
Study limitations	Were the limitations of the study discussed?	☐ Yes	☐ No
	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 10-18)	
Total number of lower quality studies (quality score 0-9)	

5. HEALTH BENEFIT (Section 3.2.1.9)

Experimental studies

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

*Include nature of measure and magnitude of effect observed

Observational studies

Reference	Quality score	Design	Sample size	Study duration	Ingredient	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	

High quality studies (Quality Score 8-16)		**Lower quality studies (Quality Score 0-7)**	
N° (%) SS*	**N° (%) not-SS***	**N° (%) SS***	**N° (%) not-SS***

*SS = Statistically Significant positive outcome

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

6. BALANCE OF EVIDENCE (Section 3.2.1.9)

Element	Excellent	Good	Acceptable	Unacceptable
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) or negative effect

Element	Excellent	Good	Acceptable	Unacceptable
Clinical impact	Meaningful health benefit very likely to achieved by consumers	Meaningful health benefit likely at the individual or population level	Clinical impact uncertain- meaningful health benefit possible.	Unlikely to be meaningful

SS=statistically significant

Additional comments (eg Justification re effect size):

Appendix 4: Evidence report (traditional)

1. Sponsor and product details (section 3.2.1.1-2)

Sponsor name	
Contact details	
)	
Product Name	

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2. Indication details (section 3.2.1.3)

Listable indication		
Ingredient details	Ingredient	
	Route of administration	
	Dose	
	Other details	
Supported/not supported		
Signature		

3. Identification of relevant evidence (section 3.2.2.4-5)

Search date	

Sources

National formularies	
SUBTOTAL	

National pharmacopoeia	
SUBTOTAL	

Textbooks	**Primary references**
SUBTOTAL	
Original historical references	

Textbooks	Primary references
SUBTOTAL	

Summary (duplicates removed)

Source	Type	Relevance				Included
		Medicine	Population	Indication	Context	
Average Relevance Score of included studies (4-12)						

Guidance for assessing relevance

	Excellent	Good	Satisfactory	Unsatisfactory
Relevance to medicine	Identical active ingredient, dosing details and route of administration	Identical active ingredient and route of administration, Comparable dosing details, dose form and formulation	Identical route of administration Comparable active ingredient or formulation dosing details and dose form	Different active ingredient or route of administration
Relevance to target population	Traditional population is identical to the target population	Traditional population is comparable to the target population	Some differences between traditional population and target populations but 'clinically reasonable' to extrapolate evidence to the target population	Major differences or differences of uncertain clinical significance exist between traditional and target populations
Relevance to traditional health benefit	The wording of the indication is identical to item of evidence, including, the use of traditional terminology.	The wording of the indication is identical in intent to item of evidence, including, the use of traditional terminology (traditional synonym used to describe the indication).	The wording for the indication is identical in intent to item of evidence, but using contemporary terminology (modern synonym used to describe the traditional indication).	The wording and intent for the indication is inconsistent with the item of evidence.
Relevance to traditional context	Clearly identified and used continuously within the relevant traditional paradigm over at least 75 years	Identified within the relevant traditional paradigm but with disclarity regarding consistency of use over a period of 75 years	Identified within the relevant traditional paradigm with some disclarity regarding characterisation of the active ingredients or formulation	Not consistent with the relevant traditional paradigm

4. Quality of evidence (Section 3.2.2.6)

Item	Yes (2), Partial/requires interpretation (1) or No (0)
Paradigm defined	
Ingredient described	
Preparation described	
Dose documented	
Route of administration	
Target population defined	
Health benefit described	
Average Quality Score of included studies (0-14)	

5. Traditional therapeutic use (Section 3.2.2.7)

Reference	Indication (direct quote)

6. Balance of evidence (Section 3.2.2.8)

Element	Excellent	Good	Acceptable	Unacceptable
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

Element	Excellent	Good	Acceptable	Unacceptable
				<5

Appendix 5: 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

Clinical significance refers to the meaningfulness of an observed health effect to consumers. 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 not result in an outcome that is meaningful to consumers.

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.

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.

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

R**eview** 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 ingredient 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 ingredient. 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).

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 ingredient can continue to affect the participant for some time after it is withdrawn.

Therapeutic Goods Administration

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Attachment 3:
Additions to the SEE List

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Attachment 4:

Comments in relation to weight loss

Comments in relation to Weight Loss

While it acknowledges the benefits of weight loss, this draft sets the criteria for scientific assessment at high levels making it unlikely that any existing research on listable complementary medicines would be acceptable to the TGA as supporting evidence for a weight loss indication.

We recommend that the following three parameters proposed in the TGA draft be deleted and that it should be the responsibility of the person reviewing the evidence that the evidence for a product supports the specific weight claim for the product.

1) *"Studies relevant to weight loss indications must be of at least 6 months duration"*

- Appendix 1 of the TGA draft lists sources of established scientific evidence that are acceptable to the TGA. This includes the Compendium of Monographs of the Natural Health Products Directorate, Health Canada. This Compendium includes a monograph for Green Tea Extracts:
  http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_greentea-thevert-eng.php

  This monograph supports the following statement of purpose for a specific green tea extract that contains caffeine and is high in catechins: "To be used with a program of reduced intake of dietary calories and increased physical activity (if possible) to help in weight management."

  All the studies used to support this statement were of less than 6 months duration and all showed a reduction in body weight – most were 12 week duration. One study (Westerterp – Plantegna) demonstrated weight maintenance after weight loss in some groups - one month of very low energy diet followed by 3 months on a weight maintenance diet.

- Refer to "EFSA Guidance on scientific requirements for health claims related to appetite ratings, weight management, and blood glucose concentrations":
  http://www.efsa.europa.eu/en/efsajournal/doc/2604.pdf
  Clause 4.1 says a reduction in body weight is considered a beneficial physiological effect for adults with excess body weight if body fat is reduced. It also says that evidence for a sustained effect with continuous consumption of the food/constituent over, for example, about 12 weeks, should be provided.
  Clause 4.2 discusses weight regain after significant weight loss (i.e. weight maintenance). It suggests studies supporting weight maintenance should be of about 6 months duration.

While ongoing weight maintenance after weight loss is an ideal situation, it is important to note that EFSA regard weight loss (supported by 12 week trials) to be of beneficial physiological effect. Therefore, we suggest that the TGA draft remove the requirement for a minimum 6 month study.

- Comment: The Canadian monograph and EFSA scientific opinion show that beneficial effects can be demonstrated in weight loss studies of less than 6 months duration. The cost of a 12 week weight loss study is in the vicinity of $2 million. A 6 month study would cost considerably more and is beyond the financial capabilities of the complementary medicines industry. We are not aware of any complementary medicine weight loss product / ingredient with a 6 month clinical trial. By enforcing a 6 month minimum study period, the TGA would effectively preclude nearly all existing products from sale and inhibit any new research, even if shorter studies showed worthwhile benefits. The only weight loss products likely to be listed would be those that are supported by SEE sources that, as shown above, are likely to rely on studies of less than 6 months duration.

2) *50 per cent of the participants in the treatment group must have achieved a loss of at least 5 per cent of initial body weight.*

Recent genetic research has shown significant variability in a population in the relationship between an individual's genes and the way that their diet affects their weight and their ability to control their weight within the ideal range. Because of genetic variability in study participants, it is possible that many people, even though they would not represent more than 50 per cent of an Australian study population, would benefit from a particular complementary medicine designed for weight loss. As it is not currently practical to do large scale genetic testing in Australia, many people who could benefit from a weight loss supplement would be denied access to it if this 50% requirement was implemented.

http://www.inherenthealth.com/media/4759/wm_scientific%20summary.pdf

3) *A mean overall loss of at least 5 per cent initial body weight in the treatment group, which is at least 3 per cent greater (for RCT) or 5 per cent greater (for non-RCT) than that of the placebo / control group.*

There may be many people who are moderately overweight (e.g. BMI of 27) who would be quite satisfied if a listed medicine, in conjunction with appropriate diet and exercise, enabled them to lose just a few kilograms. Also, page 50 of the draft supports that a reduction of one kg/m2 across a population could make significant impacts on the prevalence of obesity and overweight.

Therefore, mandating a mean overall weight loss of 5 per cent would result in some products not being available to satisfy some consumers. It could also increase the number of overweight people in the population and increase health burdens on the community.

CONCLUSION

High dropout rates, different diets and exercise programs and adherence to these programs as well as genetic differences can complicate interpretations of weight loss clinical trials.

It is shown above that other jurisdictions reach different conclusions to those proposed in the TGA draft. As listed medicines are low risk products, we propose that the parameters set by the TGA be deleted in favour of the reviewer being responsible for determining the specific indications that the evidence can support.

Weight loss indications should be quite specific so that the consumer has a clear understanding of what the evidence supports. Therefore, the TGA's Coded Indications project should provide flexibility for adding new indications to ensure that consumers are fully informed about the efficacy of products they purchase.

For example, two different indications for different products with different evidence may be:

- Supports moderate weight loss in overweight people when taken in conjunction with an appropriate diet and exercise program for 3 months.
- Supports weight loss and maintaining reduced weight of overweight people when taken in conjunction with our recommended diet and exercise program for 4 months.

Satiety, increase in lean body mass and other similar measures should be permitted as indications provided they can be supported by SEE documents or by a scientific evidence report, but as highlighted in many reports, they should not be used to imply a weight loss claim.