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	[redacted]
Company/organisation name and address	Australian Self Medication Industry (ASMI)
Contact phone number	(02) 9923 9406
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.	☒ Yes ☐ No

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 ☒ Complementary medicines ☒ OTC medicines

☐ Medical devices ☐ Blood, tissues, biological ☐ Other

☐ Sole trader ☐ Business with employees

☐ Importer ☐ Manufacturer ☐ Supplier ☒ Industry organisation

☐ Government ☐ Researcher ☐ Professional body

☐ Consumer organisation ☐ Institution (e.g. university, hospital)

☐ Regulatory affairs consultant ☐ Laboratory professional

☐ Health professional – *please indicate type of practice*:

☐ Other - *please specify*:

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

Comments

An assessment of how the proposed change will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.
See attached.
Whether or not you support the revised Evidence Requirements. If not supported, please provide reasons why.
See attached.
Any additional information on issues not asked in the above questions. If your comments relate to specific parts of the document please provide the page number and reference.
See attached

If you would like to be kept informed about TGA activities, please subscribe to one of the TGA's email lists <http://www.tga.gov.au/newsroom/subscribe.htm>.

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The Project Officer
Office of Complementary Medicines
Therapeutic Goods Administration

By email to: ocm@tga.gov.au

24 October 2012.

Dear Sir/Madam

Invitation to comment – Evidence required to support indications for listed medicines

The Australian Self Medication Industry (ASMI) thanks you for the opportunity to provide comment on the Therapeutic Goods Administration's proposal to update the 'Guidelines for levels and kinds of evidence to support indications and claims'.

1. About ASMI

The Australian Self-Medication Industry (ASMI) is the industry body for the Australian self care industry representing consumer healthcare products including over-the-counter medicines and complementary medicines. ASMI represents companies involved in the manufacture, distribution, import and export of non-prescription consumer healthcare products. We estimate that our members' combined turnover is about $3bn per year.

ASMI's mission is to promote better health through responsible self-care. This means ensuring that safe and effective self-care products are readily available to all Australians at a reasonable cost. ASMI works to encourage responsible use by consumers and an increasing role for cost-effective self-medication products as part of the broad national health strategy.

2. Overview of ASMI's Response

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

ASMI's position can be summarised as follows:

- The guidelines should reflect a risk-based approach commensurate with the issues to be addressed.
- The legislative underpinning of the guidelines should not include details of the mechanisms or requirements.
- There should be a clear separation of principles and processes.
- Compliance with the principles should be mandatory, while the processes (e.g for preparing an evidence report) should be the presented as guidance only. Sponsors may choose to use the process described in the guideline, but they should be able to use suitable alternatives.
- The overarching aim is that the sponsor must hold adequate substantiation for any claims made about their product.
- There should be an ongoing review and assessment of any revised guidelines post-implementation.

In practical terms, ASMI suggests the following changes to the proposed guidelines:

- That section A should be revised to reflect the relevant principles only.
- That section B should be revised to contain guidance in relation to those principles only.
- That the SEE lists be expanded.

A revised copy of the guidelines (together with detailed comments) has been included as Attachment 1 to this submission.

3. Introduction

We appreciate that TGA has removed the requirement for independent experts, however the templates still 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 qualifications of the author.

We also appreciate the additional option of using sources of established evidence. However we do not understand why so few of the previously accepted sources, and so few of those proposed by industry, remain on the list of accepted SEEs. In addition to suggesting an expanded SEE list, we suggest that a mechanism be included for adding SEEs.

We remain concerned about a number of issues industry previously raised, and which remain in the revised draft. This draft guideline is more than an update, it increases the requirements substantially.

We have attached a revised version of the consultation document which outlines our concerns and suggestions. We wish to make it clear that this revised version should be considered as a preliminary draft only and suggest that the complexity of the guideline means that further refinement will be essential. ASMI remains committed to working with TGA to achieve a robust, workable and appropriate guideline.

4. ASMI's key issues

4.1 Consultation process

We must state at the outset that our response is of a preliminary nature.

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 our members have also been spending a considerable amount of time and effort working on the Coded Indications project, the OTC BPR project and the ARGCM update.

As a result of these concurrent TGA projects the time given has been inadequate to prepare a meaningful response to the 94 page consultation document. A meaningful response requires a thorough review of the proposal, an accurate identification of all the issues, consultation with our members, the collation of industry feedback and the synthesis of a response which accurately reflects the views of industry.

On this point we note that the consultation document is extremely detailed, deals with a complex topic and proposes significant changes.

While our response is complete as far as the suggested approach to be taken, we suggest that further work is required to finalise the guideline details. ASMI remains committed to working with the TGA to finalise these details.

4.2 Guiding principles to address regulatory failure

ASMI endorses the COAG Principles of Best Practice Regulation and is disappointed that the principles have not been applied to this proposal.

In our assessment of this consultation 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.

ASMI 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.

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.

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 who do comply with the requirements. In response to this excessive regulatory burden, smaller Australian sponsors may be forced to close down because of increased costs, other sponsors may be tempted to move products offshore, for online purchase, or de-list products and present them as foods. Any new guidelines should be accompanied by increased and effective monitoring, enforcement and sanctions.

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 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 align more closely with other comparable jurisdictions and standards.

Principles-based guidance: the legislated requirement should be principles-based, concise and straightforward. Guidance material should stand outside legislation to allow amendment and updating as required. Guidance material should also state clearly that alternative methods are acceptable provided that the legislated requirements are met. We suggest that the guidance material be incorporated into the ARGCM (as an appendix).

4.3 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.

The overall readability of the document is not user friendly and is overly complex. It contains unnecessary and confusing repetition and is internally inconsistent.

4.4 Context within the broader TGA Blueprint for reforms

We are aware that the TGA is currently working on a number of reforms affecting complementary medicines, including the Coded Indications project, labelling, transparency and advertising. As these projects have yet to be finalised, 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 industry 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.

4.5 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. Without justification, 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. This is an unreasonable and excessive requirement for a low-risk medicine.

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? Many medicines trialled in Europe, or Hong Kong, or South America, are then supplied throughout the world. This requirement is excessive and should be deleted.

4.6 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. Industry has put some work into redrafting these however much more remains to be done.

4.7 RDIs

Although 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 specified. No justification has been provided for this change.

4.8 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 then 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 made to the herbal equivalence guidance document.

4.9 Advisory Statements

Advisory statements have been included in the draft guidelines. There is no place for advisory statements in a guideline for evidence. Rather, these should be included in RASML.

4.10 Sources of Established Evidence

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 for limiting the lists in this way. Our concern is that sponsors of products currently supported by the evidence in those texts would be forced to prepare full evidence reports, at very considerable expense. There is no mechanism proposed for adding other high-quality sources to the list.

Our proposed list of additional SEEs is provided in Attachment 2.

4.11 Special categories – weight loss

The guideline contains extra and apparently arbitrary requirements over and above those for other types of Listable indications. ASMI suggests that there should be no additional requirements for specific categories or cohorts unless justified. The starting point is that the evidence must support the indication and the indication must be listable. Any additional requirement in relation to specific categories needs to be justified.

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 as adequate to support weight loss. We see no justification for arbitrary, unique and higher standards for Australia.

4.12 Special categories – biomarkers

As above, the starting point is that the evidence must support the indication and the indication must be listable. Any additional requirement in relation to specific categories needs to be justified.

5. Impact on industry

In our previous submission on this matter we provided preliminary information on the effects on industry, to be considered in the Regulatory Impact Statement.

We are unable to provide further details until the precise nature of the reforms become clearer.

Despite this, we wish to draw the TGA's attention to a significant financial impact on those sponsors whose evidence has been found to be compliant following a section 31 review. The evidence will not be in the format prescribed in the proposed guideline, but will have been determined to have been acceptable to the TGA. Should such sponsors then have to re-format and/or repeat their reviews then they will incur unnecessary expense.

6. Transitional arrangements

Appropriate transitional arrangements are critical for industry to ensure minimum disruption to business. While it is premature to consider the details of transition arrangements in the absence of an agreed reform package we anticipate that, given the magnitude and complexity of reforms in this area, that a minimum of 5 years would be an appropriate transition period.

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.

7. Alternative model

Within the limited time available ASMI and CHC have reviewed the proposed guideline and developed some alternative guidelines with the assistance of representatives from both associations. Although there still needs to be more work to finalise the details, the revised guideline presented in Attachment 1 represents the combined feedback from the members of both associations.

Our 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 relevant guidelines. 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.

8. <u>Suggested way forward</u>

ASMI remains committed to work with the TGA to develop solutions which will achieve the stated aims of the reforms.

We thank you again for the opportunity to make comments on this draft guideline and look forward to further discussions in the near future.

Yours sincerely,

[redacted]

Attachments

<u>Attachment 1</u> Detailed comments from Industry on the draft guideline

<u>Attachment 2</u> Industry's proposed list of additional SEE's

Attachment 1

Detailed comments from Industry on the Draft Guideline

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Evidence required to support indications for listed medicines

(excluding sunscreens and disinfectants)

Proposed Revised Version – ASMI October 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>.

Version history

V1.0	Original Publication	TGA	March 2012
V2.0	Reviewed following feedback from consultation process	TGA	August 2012

Contents

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.

Comment [redacted] This is a guideline. Use of the term MUST is inappropriate.

Overview

The regulation of complementary medicines

Listed medicines – indications

Post-market regulatory activities

Comment [redacted] Does not belong in this document

Comment [redacted] : See above

Comment [redacted] See above

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.

This document should be read in conjunction with therapeutic goods legislation, the requirements for coded indications, and other relevant guidance documents.

Evidence requirements may be met in one of two ways:

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

Comment [redacted] Does not belong in this document

2. Types of listable indications

Comment [redacted] See above

3. 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 **must** 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 SEE as described in **Part B.** OR
- by a thorough review and assessment of the available literature (Evidence Report) as outlined in **Part B** of this document.

Comment [redacted] Update with correct section reference

These approaches apply to both scientific and traditional indications.

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.

Comment [redacted] : It is not possible to establish totality of 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 **and range** of the evidence.

Comment [redacted] As above

NOTE:

We consider that the requirements should be principles-based only and that all guidance material and detail be spelt out in Part B. The material previously included here is either reproduced in Part B or irrelevant to an evidence guideline.

Part B. Guidance material

These guidelines demonstrate one method accepted by the TGA for fulfilling the requirements of Part A. Other methods may be acceptable provided they fulfil all the requirements.

1. Listable indications

Comment [redacted] : Put this in the coded indications documentation. Make clear that applicants may need to use both documents in conjunction.

3. Evidence guidelines 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. 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.

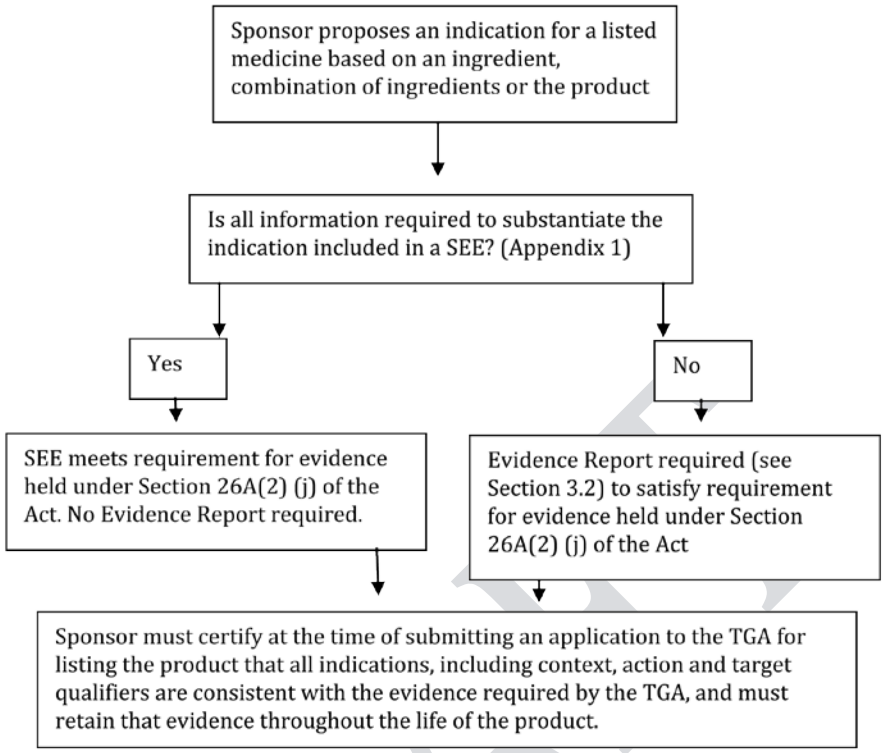
Sponsors should not only focus on individual statements or phrases, but also on what expected effect or benefit is being promoted when all of the statements being made for the product are considered together. Although it is important that individual statements be substantiated, it is equally important to substantiate the overall "message" contained when the claims are considered together.

When a medicine's claims may have more than one reasonable interpretation, consider substantiation for each interpretation. Consumer testing may be useful to determine consumer understanding of each claim, in context.

Evidence may be provided either:

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

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



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 Section 3), be clear to consumers in terms of the expected health benefit and not be misleading.

Nutrients and nutrient supplementation

a) Health benefits: Statements relating to supplementation with vitamins, minerals or other essential nutrients (e.g. 'a source of calcium' or 'magnesium supplement') 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.

Comment [redacted]: It is very concerning to find that, without any particular reasoning or alerting the industry, this new draft guideline includes substantial increases of the amounts of vitamins/minerals/ nutrients in relation to supplementation of named vitamins/ minerals (nutrients) from 25% to at least 50%.

Additionally we don't find the delineation clearly described to assist clarity and transparency. This proposed change would have a big impact on the industry especially for any existing products and their claims.

As there is no reasoning provided for the increase of the requirements, we would recommend that requirements of the current guideline are included in this proposed guideline to assist consistency and transparency plus providing a clearer wording for the requirements in the guideline. Please see suggested changes.

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.

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.

3.1 Meeting evidence requirements through sources of established evidence

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.

3.1.1 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.

3.1.2 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.

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.

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

Comment [redacted] To be updated with the correct section reference

Information included in a SEE	Requirements for listed medicines
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 with that described in the SEE. For extracts, the method of preparation must be is the **same, comparable or consistent** with that described in the SEE (e.g. extraction conditions and solvent, equivalent dry weight, ~~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.

Comment [redacted] : The equivalent dry weight and extraction process are far more important than the final extract ratio. There is no significant difference between 1 g of a 5:1 and 2g of a 10:1 extract with similar processing.

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 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.

3.1.3 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.

3.2 The evidence 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

Comment [redacted] : Must be comprehensible to non-academics

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

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.

Therefore, the Evidence Report must include the following sections:

- Sponsor details
- Product details
- **Product rationale**
- **Overall product presentation**
- Indication details
- Identification of evidence
- Relevance of evidence
- ~~Level of evidence (scientific indications only)~~
- 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 3.2.1 and 3.2.2. 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 3 to assist sponsors in ensuring the Evidence Report contains all necessary information. An Evidence report **must be** provided to the TGA if requested.

Comment [redacted] We propose addition of these to the evidence templates as in our earlier submission.

Comment [redacted] **:** NHMRC ranking is inappropriate and unnecessary.

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.~~	

Comment [redacted] We consider this all repetition and recommend replacing it with a tick-box section: EG applicant to ensure that each of the following has been completed, provided , considered or justified, as appropriate.

Comment [redacted]: This should not be required. TGA has already agreed that the quality abnd substance of the report is what counts, not who completes it.

Comment [redacted]: As above. This requirement is unnecessary as it is immediately followed by the requirement to evaluate quality of every study. In addition the NHMRC guidelines were designed for the use of prescription medicines and treatment guidelines.

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.

Comment [redacted]]: We consider this all repetition and recommend replacing it with a tick-box section: EG applicant to ensure that each of the following has been completed, provided , considered or justified, as appropriate.

Comment [M20]: Surely the template provided is adequate?

Comment [redacted] Where reported!!!! If they are not reported they cannot be entered.

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

Comment [redacted] Repetition. We recommend including a tick-box for applicants as above.

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*~~

[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>

~~*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.*~~

Comment [redacted] : It is the report which counts not the writer. These details are likely to introduce bias.

3.2.1.2 Product name

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
- 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 it is comprehensible to consumers.

3.2.1.4 Identification of evidence

Comment [redacted] This whole section could be simplified and clarified eg Search, document, evaluate and draw conclusions.

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.
- 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 **IF NECESSARY MAY** 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.

Comment [redacted]: Access to additional databases is extremely costly and normally provides little or no additional information. The expense cannot be justified in most cases.

- 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 **MAY** 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 must be documented **CLEARLY.** ~~to internationally accepted standards.~~[4] ~~The databases and~~

[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>

~~search interfaces used and the numbers of references retrieved must be documented in the report.~~

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

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.[5]

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 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 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

Comment [redacted] : The CONSORT and CDC requirements are not required by ARGOM or ICH They are excessive and inappropriate.

Comment [redacted] : The report is the issue, not who does it or who helps.

Comment [RK28]: Not required by ARGOM or ICH. Excessive and inappropriate for a listed medicine.

Comment [redacted] : CLARIFY that this reference is ONE acceptable method.

Comment [redacted] TOO WORDY. This section requires simplification and clarity.

Comment [redacted]]: This must be clear: in most cases the abstract will reveal whether or not a study is relevant. Only relevant and unclear abstracts need to trigger purchase of the complete article. Note that the cost of purchase of a full copy is from $30 - $60 per paper.

[5] 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>

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 3.4.

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**~~

~~**Health status**~~

~~**Example:**~~

~~The following table summarises the characteristics of biomarker ranges~~

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

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

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

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).

Comment [redacted]: We reject the requirement to use only studies representative of the Australian population. It is possible for this to be interpreted so tightly that only studies performed on Australians will be accepted. Is this required for registered medicines?
We agree that the study population should be consistent with the target population eg women, children under 12, older men.
Where studies show differences in results with different races etc this should be documented and stated clearly.

Comment [redacted]: We believe that there should be only one set of rules for the evidence, and no extra requirements for sub-categories or specific cohorts. The table on P 37 of the draft cannot be supported by industry in its current form. The ranges specified, as a percentage beyond the normal range, are so restrictive that they do not 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.

Comment [redacted]: There should be no additional requirements for specific categories or cohorts. The evidence must support the indication; the indication must be listable; full stop. Delete.

Comment [redacted]: CMs should be able to carry the same indications as permitted for foods by FSANZ. E.g. lowering cholesterol.

Comment [redacted]: Requires clarification: does this mean eligibility of the study population or of the consumer? And for what? Should be redrafted.

Comment [redacted]: As above. There should be no additional requirements for specific categories or cohorts unless justified. The starting point is that the evidence must support the indication and the indication must be listable. Any additional requirement in relation to specific categories has to be justified. Delete.

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.

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

Comment [redacted] : As above: The starting point is that the evidence must support the indication. Any additional requirement in relation to specific categories has to be justified. Delete.

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:

~~A reasonable timeline to achieve a significant degree of weight loss is six months.~~

Comment [redacted] : This is inconsistent with EU, Canada who specify 12 weeks. The starting point is that the evidence must support the indication. Any additional requirement in relation to specific categories has to be justified. If the study is assessed as having adequate quality it should be accepted.

Relevance of context

It is important to recognise that the body of evidence relevant to a listable indication is generally derived under conditions that are more restrictive than those experienced by consumers of listed medicines. In research studies, tight control of experimental conditions and intensive monitoring are important in controlling for confounding across treatment and placebo groups. Studies conducted in this way are ideal for estimating potential medicine **efficacy** but may overestimate medicine **effectiveness** within its target population. Studies that are less prescriptive may provide useful adjunctive information about 'real-world' medicine effectiveness. However, such studies may not accurately predict potential medicine efficacy, as the results of such studies may be subject to confounding and bias due to differences in environmental conditions, participant characteristics and compliance.

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

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**~~

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 **may** 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[6] or Dalhousie critical appraisal instrument[7] may be used in place of these instruments, however the instrument used **may** include as a minimum an assessment of the following:

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

Comment [redacted]: See above. This requirement is irrelevant and inappropriate. Assessment of quality establishes stronger and weaker evidence.

Comment [redacted]: Only reported data should be entered. If it is not reported, this is to be recorded and forms part of the assessment. There is no justification for requiring applicants to track down researchers and obtain the original data and then perform calculations themselves.

Comment [redacted]: This has already been described. Suggest replacing with a tick – box: have each of these been considered and assessed?

Comment [redacted]: Remove all MUST terms and re[lace with may or should

[6] 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

[7] 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.

- statistical analyses undertaken

Comment [redacted] We suggest replacing this section with tick-a-box list as a tool for sponsors.

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.[8] 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

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

- clinically significant.

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 health 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.

~~**Special requirements for indications related to weight loss**~~

Comment [redacted] : Suggest a list of points to consider NOT additional requirements

3.2.1.9 Assessing the balance of evidence

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.

Comment [redacted] : Reduce repetition. Simplify.

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.

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 20099 (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.

[9] 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>

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.

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.

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

Comment [redacted] : Simplify, reduce repetition

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. ~~It is recommended that the help of a specialist librarian is sought, particularly when searching non-English databases when conducting the literature review.~~

Comment [redacted] : As above, the report is important not who compiles it or helps.

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:

- 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.

Comment [redacted] : Where available

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.

Relevance to medicine

Comment [redacted] : This is repetitious. Needs simplification and shortening.

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

When evidence supports a health benefit for one or more ingredients in the medicine (but not the medicine as a whole) indications **must** include this information:

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

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

A judgement may need to be made to determine whether the product to be listed in the ARTG is essentially the same as detailed in the supporting reference(s). Active ingredients can be considered as sufficiently identical 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.

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.

~~An average relevance score (ARS)~~

Comment [redacted]1]: Remove scoring system. Better templates will remove the need for this.

3.2.2.6 Quality of evidence of traditional use

Comment [redacted] : simplify into one section: assessment of traditional evidence

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

When supporting evidence includes independent written histories of use in the classical or traditional literature, the significance and clarity of references to any health benefit must be assessed. In some cases, references to 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.

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.

Comment [redacted]3]: requires clarification. Reword and simplify

3.3 Potential clashes between traditional and scientific evidence

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 or use vague terms such as 'has been shown to produce weight loss'. For this reason, traditional indications must refer to the tradition of use. In additional, all indications based on traditional use must include a statement to the effect that the efficacy of the product is based exclusively on long-term use and experience.

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

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~~

Comment [redacted] : does not belong in this document

Appendix 1: Sources of established evidence

Comment [redacted] This list of reference sources is wholly inadequate. Please see our list of references proposed for inclusion.

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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Heart Foundation (Australia) Guides, policies and position statements. http://www.heartfoundation.org.au/information-for-professionals/food-professionals/Pages/guides-policies-position-statement.aspx
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MedlinePlus: Drugs, Supplements & Herbal Information http://www.nlm.nih.gov/medlineplus/druginformation.html
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Therapeutic Goods Administration

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

Reference/Publication #

Attachment 2

Industry's proposed list of additional SEE's

PROPOSED ADDITIONS TO THE LIST OF SOURCES OF ESTABLISHED EVIDENCE

GENERALLY ACCEPTED SCIENTIFIC EVIDENCE SOURCES

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PROPOSED ADDITIONS TO THE LIST OF SOURCES OF ESTABLISHED EVIDENCE

GENERALLY ACCEPTED TRADITIONAL EVIDENCE

Authoritative, recognised pharmacopoeia, formulary or monographs

African Herbal Pharmacopoeia by the Association for African Medicinal Plants Standards, 2010
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