



Australian Government

Department of Health

Therapeutic Goods Administration

Consultation: Reforms to the regulatory framework for complementary medicines

Assessment pathways

February 2017

TGA Health Safety
Regulation



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1. Purpose and scope

The purpose of this consultation is to provide an opportunity for consumers, health professionals and sponsors to have input into the development of a range of reforms to improve the regulation of complementary medicines in Australia.

Specifically, we are seeking feedback on the following:

- The development of a three-tiered risk-based framework for the regulation of complementary medicines. This will introduce a new product assessment pathway sitting between the existing listed medicine (low risk) and registered medicine (high risk) pathways.
- The development of a list of permitted indications which must be used by the lowest risk complementary medicines.
- Allowing sponsors to claim that their medicine has been assessed by the TGA for efficacy where that medicine has undergone pre-market evaluation by the TGA.
- Mechanisms to incentivise innovation for the complementary medicines sector.

The proposed reforms will implement Recommendations 38, 39, 45 and 50 of the [Review of Medicines and Medical Devices Regulation](#) (MMDR review), each of which was supported by Government. Of the 19 recommendations relating to complementary medicines, these (which largely relate to bringing products to market) will have the most significant impact in reshaping the complementary medicines regulatory framework. Other MMDR recommendations relating to complementary medicines will be the subject of further consultation throughout 2017.

Following this consultation, and government endorsement of the proposed actions, we will work with stakeholders to develop business processes and guidance documents to support the implementation of these reforms.

Principles guiding the reforms

We are applying the following principles to guide the development of complementary medicine reforms:

1. Health professional and consumer confidence in TGA regulation of complementary medicines must be maintained.
2. The level of regulation and assessment by the TGA will be commensurate with the risk of a medicine.
3. There will be transparency for consumers and healthcare professionals as to the level of assessment by the TGA for complementary medicines entered on the ARTG.
4. The TGA will provide clear guidance for applicants on the process and requirements for each pathway.
5. The reforms should provide incentives to the industry to improve the evidence base for complementary medicines.
6. The reforms should encourage and support improved rates of compliance.
7. The processing and evaluation of applications made through the new pathway will be cost-recovered.

2. Background

Review of Medicines and Medical Devices Regulation

The Expert Panel (the Panel) conducting the [Review of Medicines and Medical Devices Regulation](#) (MMDR review) made 19 recommendations to improve the regulatory framework for complementary medicines manufactured, supplied and/or exported from Australia.

Government has agreed that there should be three pathways by which sponsors can seek entry on the ARTG for complementary medicines (Recommendation 39). The Panel recommended that these pathways be established on the basis of a hierarchy of evidence as a graded response to the risk profile of complementary medicines and the associated indications that can be made¹.

The establishment of three assessment pathways for complementary medicines also impacts on other decisions of government, including:

- the establishment of a list of permitted indications (Recommendation 38)
- the publication of a claim that the medicine has been assessed by the TGA for efficacy (Recommendation 45)
- introduction of mechanisms to improve the competitiveness of the Australian complementary medicines industry (Recommendation 50).

On 15 September 2016, the Australian Government released its [Response to the Review of Medicines and Medical Devices Regulation](#)². Consultation with stakeholders will ensure that implementation of these reforms achieves a balance between ensuring adequate consumer protections and minimising regulatory burden on industry.

Context for change

The Australian regulatory regime for therapeutic goods regulates products according to risk. All medicines (prescription, over-the-counter and complementary medicines) currently fall into two categories:

- medicines that must be registered on the ARTG following TGA evaluation
- medicines that must be listed on the ARTG on the basis of a sponsor's self-declaration of compliance with relevant regulatory requirements.

There are, however, inherent differences between complementary medicines and other higher risk medicines. Complementary medicines can encompass a wide range of products primarily used for health maintenance and health enhancement, that have varying sources of evidence supporting their efficacy, including some medicines with a history of use based on cultural and traditional values. A critical issue in the use of listed complementary medicines is to ensure that

¹ Expert Panel, Review of Medicines and Medical Devices Regulation: Report to the Minister for Health on the Regulatory Framework for Medicines and Medical Devices (31 July 2015), p 28 i, available at: <http://www.health.gov.au/internet/main/publishing.nsf/Content/Expert-Review-of-Medicines-and-Medical-Devices-Regulation>.

² Commonwealth of Australia (Department of Health), Australian Government Response to the Review of Medicines and Medical Devices Regulation (September 2016) available at: <https://www.tga.gov.au/mmdr#austgovt>.

they are suitable for self-selection by consumers and that the information provided with the medicine supports consumer health decisions.

The review's recommendations relating to complementary medicines arose from the observation that Australia's regulatory framework for these products does not appropriately align regulatory protections with risks.



The Panel did not consider the regulation of all low risk products in making recommendations relating to complementary medicines regulation. A range of products, including sunscreens, are not complementary medicines, but are currently listed on the ARTG. They are not being considered directly in this consultation but will be addressed in a separate consultation along with homeopathic products and other complementary medicines such as low dose vitamins and minerals.

Objectives of the reforms

The objectives of the reforms to the complementary medicines regulatory framework are to:

- provide additional flexibility to allow sponsors to access higher level indications than are currently appropriate for listed medicines
- encourage industry to improve the standard of evidence regarding the efficacy of complementary medicines
- avoid consumers being misled by the indications on the medicine label and reduce the rate of non-compliant indications being included on the ARTG
- increase transparency for health professionals and consumers about the evidence bases for health claims, and thereby improve confidence in products
- provide a market advantage to support innovation and improve the evidence base for complementary medicines.

Introduction of the **new pathway** will bridge the significant gap that exists for industry between the evidence requirements, costs and timeframes for the existing listed and registered medicines pathways. This will allow greater consumer access to a wider range of evidence-based remedies to self-manage their health.

Allowing sponsors to claim that **evidence of efficacy** has been assessed for products that have undergone pre-market assessment will assist consumers to make more informed healthcare decisions.

The introduction of a list of **permitted indications** will ensure that complementary medicines that are not subject to pre-market efficacy review are appropriately limited in the indications that can be made. Only permitting low level indications to be made for low risk medicines that are entered on the ARTG via sponsor self-assessment will provide greater protection for consumers on the safety, quality and efficacy of products available on the market. Evidence will continue to be required to be held by sponsors of these products. This may be reviewed as part of a strengthened post-market compliance program.

3. Assessment pathways for complementary medicines

Overview

The three pathways by which sponsors may seek entry onto the ARTG for a complementary medicine will include the following:

- Medicines will continue to be included on the ARTG following self-assessment and certification by the sponsor of the safety, quality and efficacy of the product. This is essentially the **current listing pathway** except that we will provide a list of permitted indications for sponsors to enter their product indications on the ARTG (see section 4: [Implementing a list of permitted indications](#)). We will also be increasing our post-market compliance monitoring for these products.
- Medicines could be included on the ARTG following sponsor self-assessment and certification of the safety and quality of the product, coupled with TGA assessment of the efficacy evidence supporting the proposed indications. This **new pathway** will allow sponsors to apply for indications that fall outside the permitted indications list but in all other respects the medicines meet the current eligibility criteria for listed medicines (e.g. contain only permitted ingredients).
- Medicines will continue to be included in the ARTG after a full assessment of the safety, quality and efficacy of the product by the TGA. This retains the **current registration pathway** and is commensurate with the higher level indications made or ingredients used in these products.

The classification of a medicine will continue to be based on a number of factors and their relative risk to consumers if a product fails to comply with the regulatory requirements, including:

- the intrinsic risk of the product (e.g. the toxicity of its ingredients)
- the risks associated with the quality of the product (e.g. requirements for sterility)³
- the risks associated with the intended use(s) (indications) of the product (e.g. whether incorrect use could lead to the consumer delaying necessary medical treatment).

The regulatory requirements, levels of assessment, timeframes and fees to enter a product on the ARTG, increase with an increasing degree of risk.

An overview of the requirements for each pathway is provided in **Table 1**.

In summary, the **new pathway** will be available for complementary medicines that:

- contain only permitted ingredients and meet the requirements associated with their use in listed medicines⁴

³ Note that, consistent with the current listing framework; irrespective of formulation or intended purpose, if a medicine is required to be sterile, it cannot be assessed through the new pathway, see Therapeutic Goods Regulations 1990 Schedule 4 Item 3(c)(ii).

⁴ The ingredients that are permitted for use in listed medicines and requirements associated with their use are specified in the Therapeutic Goods (Permissible Ingredients) Determination.

- are produced under GMP⁵
- make indications that fall outside the list of permitted indications but which are still appropriate for listed medicinal products ('intermediate level' indications)
- have acceptable scientific evidence to support the proposed indications, which will be assessed prior to marketing by the TGA.

The Government endorsed the recommendations that for such products sponsors should be able to claim that the product's efficacy has been assessed for the approved indication(s) (see section 5: [Claiming evidence of efficacy](#)).

⁵ Medicinal products supplied in Australia have to meet the PIC/S Guide to Good Manufacturing Practice (GMP), published by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S), see Manufacturing principles for medicinal products (April 2013) available at: <https://www.tga.gov.au/publication/manufacturing-principles-medicinal-products>.

Table 1: Eligibility criteria and the regulatory requirements for the three assessment pathways

	Listed Medicines	New Pathway	Registered Medicines
Risk Level	Lowest level of risk based on their ingredients, indications, the way they are presented and administered, and the potential harm associated with their use.	Low level risk based on their ingredients, the way they are presented and administered, and the potential harm associated with their use. Make intermediate level indications.	Higher level risk based on their ingredients and the level of indications.
Ingredients	Must draw exclusively from the permitted ingredients list. Ingredients must not be included (or meet the criteria for inclusion) in a schedule to the Poisons Standard.	Must draw exclusively from the permitted ingredients list. Ingredients must not be included (or meet the criteria for inclusion) in a schedule to the Poisons Standard.	Includes those ingredients included (or meet the criteria for inclusion) in a schedule to the Poisons Standard, other than Schedule, 4, 8 or 9.
Indications	Low level indications drawn exclusively from the permitted indications list.	Intermediate level indications that exceed the permitted indications list but are not high level indications.	High level indications, ineligible for listing or the new pathway.
Product quality	Must comply with applicable standards. Non-sterile medicines only.	Must comply with applicable standards. Non-sterile medicines only.	Must comply with applicable standards. May include sterile medicines.
Manufacturing quality	Must meet the PIC/S Guide to GMP.	Must meet the PIC/S Guide to GMP.	Must meet the PIC/S Guide to GMP.
Application procedure	Self-certification.	Self-certification supplemented with premarket assessment of efficacy.	Full premarket assessment.
Level of pre-market assessment	Approval initiated by electronic application lodgement facility based on information provided by the applicant. No evaluation of the quality, safety or efficacy of the finished product prior to the approval.	Approval by delegate of the Secretary. Assessment of the efficacy of the finished product and label prior to the approval. No evaluation of the quality or, safety prior to the approval.	Approval by delegate of the Secretary. Assessment of the quality, safety, efficacy of the finished product and label prior to the approval.

Listed Medicines		New Pathway	Registered Medicines
Evidence requirements	Low level of evidence held by the sponsor to support indications and claims.	Evidence submitted by sponsor to support associated indications and claims.	Evidence submitted by sponsor to support associated indications, claims and safety and quality of the finished product.
Presentation	Presentation cannot state or imply that the medicine has effectiveness or has been assessed by the TGA.	Sponsor able to use a ' claimer ' on the label and other promotional material to indicate that product has been independently assessed.	Sponsor able to use a ' claimer ' on the label and other promotional material to indicate that product has been independently assessed.
Incentives for innovation	2 years market exclusivity for new ingredients.	2 years market exclusivity for new ingredients; and / or 3 years data protection or market exclusivity for new formulation / indication combinations.	5 years data protection for new active ingredients.
Conditions of approval	Consistent with current conditions of listing. Additional conditions relating to the use of permitted indications to be considered.	Consistent with current conditions of listing. Additional conditions relating to efficacy evidence and use of label claimer to be considered.	Consistent with current conditions of registration. Additional conditions relating to use of label claimer to be considered.
Post-market compliance	Product may be selected for random or targeted review to confirm applicant certifications correct. Compliance review to include evidence review.	Product may be selected for random or targeted review to confirm applicant certifications correct. Efficacy evidence would not be routinely re-assessed post-market.	Product may be selected for post-market review; for example if there are safety concerns.

Note: The reforms discussed in this consultation paper are shaded in grey.

Establishing a risk-based hierarchy for therapeutic indications

It is proposed that a three-tiered risk-based hierarchy of indications will be developed to ensure a graded response to the risk profile of complementary medicines⁶. The risk factors relevant to establishing a hierarchy of indications include, for example:

- whether the indications relate to the treatment of a healthy person, or persons suffering from a disease, ailment or condition
- whether the indication relates to treatment of a particular target population such as young children
- whether the indication relates to a disease or condition that is potentially serious and as a result the consumer may delay seeking medical treatment.

On the basis of these risk factors, it is proposed that indications would be categorised into three levels of risk: **low**, **intermediate** and **high**, corresponding to the listing pathway, the new pathway and the registration pathway respectively.

Eligibility criteria for each pathway will be specified in legislation so that sponsors can readily identify the appropriate assessment pathway for their medicine.

Low level indications

Low risk indications are consistent with what is appropriate for **listed complementary medicines** under the current framework and would include both specific and non-specific indications based on a tradition of use and scientific evidence⁷.

Low level indications pose the lowest risk to consumers and it is appropriate that medicines carrying such indications are not individually evaluated by the TGA before the medicine is included on the ARTG. Consistent with the risk-based framework, they will include indications for self-diagnosable, self-manageable and self-limiting conditions where a delay in medical treatment would not be detrimental to the consumer.

Low level indications refer to general health maintenance, enhancement, prevention of dietary deficiency or those that imply a benefit for a non-serious form of a disease or condition. **Table 5** provides examples of low level indications.

The criteria for low level indications will determine whether an indication is appropriate for inclusion in the permitted indications list (for more detail see **section 4: [Criteria for permitted indications](#)**).

Intermediate level indications

Medicines included in the **new pathway** may include **intermediate level indications** that exceed the criteria for low level indications but are not high level indications.

⁶ Expert Panel, p. 28.

⁷ The indications proposed by the sponsor of the listed medicine must not be for the treatment of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 to the Therapeutic Goods Advertising Code: see Therapeutic Goods Regulations 1990, Schedule 4, Item 3(d).

Intermediate level indications will include references to prevention or alleviation of non-serious forms of a disease, condition, ailment, defect or injury. Although the diseases captured by these therapeutic uses will generally be naturally self-limiting, self-diagnosable and/or self-manageable, medicines carrying these indications may present higher risk to consumers than low level indications.

Intermediate indications are generally more definitive, relate to more serious health conditions and incorrect use might, for example, lead to a delay in seeking medical treatment and adverse consequences for the consumer. Allowing such medicines to be supplied without being individually assessed for efficacy would undermine the TGA's risk-based regulatory framework.

It is also proposed that indications that refer to a **restricted representation**⁸ will be intermediate level indications. There are limited circumstances where it would be in the public interest for a low risk medicine (which had not been individually evaluated for efficacy) to refer to a restricted representation on the medicine label. In deciding whether to grant approval to use a restricted representation, the Secretary must take into account the public interest criteria specified in Part 2 of Appendix 6 of the Therapeutic Goods Advertising Code 2015, including 'whether the reference would be likely to result in consumers not seeking timely professional advice where appropriate' and 'whether the reference would be likely ... to have a negative impact on public health.'

For the public interest criteria to be satisfied there would have to be demonstrated evidence for the efficacy of the medicine and the indications which refer to the restricted representation. Consistent with the risk-based framework, it is therefore appropriate that the efficacy of indications which amount to restricted representations continues to be pre-market assessed by the TGA.

The proposed approach for establishing efficacy for existing listed medicines with a restricted representation approval is described below.

High level indications

Consistent with current requirements for **registered complementary medicines, high level indications** are those that refer to the treatment, cure or prevention of a serious form of a disease, disorder or condition, for example: 'For the treatment of iron deficiency anaemia'.

Medicines that have high level indications must be suitable for non-prescription use and they will not be able to refer to a prohibited representation.

Compared to intermediate level indications, the diseases captured by this category may not naturally resolve within a timely manner, may have undesirable effects that may persist or worsen if effective treatment is not pursued in a timely manner. Pursuant to a risk-based approach, medicines with high level indications that require the intervention of a healthcare practitioner must be individually assessed for safety, quality and efficacy before being supplied in Australia.

⁸ A restricted representation is any reference (even by implication) to a serious disease, condition, ailment or defect specified in Table 1 of Part 2 of Appendix 6 of the Therapeutic Goods Advertising Code 2015.

Proposal one: A risk based Approach for therapeutic indications

Listed Medicines	New Pathway	Registered Medicines
<p>Low level indications drawn exclusively from permitted indications list.</p> <p>A low level indication may refer to:</p> <ul style="list-style-type: none"> health enhancement health maintenance prevention of dietary deficiency <p>a disease, ailment, defect or injury other than a serious form of those diseases.</p> <p>A low level indication must not:</p> <ul style="list-style-type: none"> refer to, or imply, the prevention, alleviation, or cure of any form of a disease, ailment, defect or injury contain a prohibited representation contain a restricted representation have been specified in a non-permitted indications list. 	<p>Intermediate level indications that exceed the permitted indications list but are not high level indications.</p> <p>Intermediate level indications may refer to:</p> <ul style="list-style-type: none"> a serious disease (i.e. restricted representations); or the prevention or alleviation of a disease, ailment, defect or injury other than a serious form of those diseases. <p>Intermediate level indications may include those indications specified in a non-permitted indications list.</p> <p>An intermediate level indication must not:</p> <ul style="list-style-type: none"> refer to the prevention, diagnosis, cure or alleviation of a serious form of disease, disorder or condition contain a prohibited representation. 	<p>High level indications.</p> <p>A high level indication may refer to the prevention, alleviation, cure or management of a serious form of a disease, ailment, defect or injury (i.e. restricted representations).</p> <p>A high level indication must not:</p> <ul style="list-style-type: none"> contain a prohibited representation.

Products not suitable for the new pathway

The Panel noted that the **new pathway** is intended for complementary medicines that make intermediate indications that fall outside the list of permitted indications but which are still appropriate for listed medicinal products⁹ and which are supported by appropriate scientific evidence. The intended purpose of the new pathway is not to assess complementary medicines that only make low level indications (i.e. that are included or meet the criteria for inclusion in the permitted indications list). Only products supported by high quality scientific evidence (not evidence of a tradition of use only) will be accepted for assessment through the new pathway.

⁹ Expert Panel, p. 29, Recommendation Thirty Nine, Option 2E.

To be accepted through the new pathway, products must have **at least one** indication that is an intermediate level indication. These products could also include low level 'secondary' indications from the permitted indications list that are supported by appropriate evidence. The evidence for these low level indications will be evaluated pre-market along with the related primary intermediate indication.

A sponsor could also turn a low level (permitted) indication into an intermediate level indication by making it more definitive in nature. The product could then be assessed through the new pathway. For example, a product might have an indication 'may help manage symptoms of common cold' which could become more definitive to be 'improves symptoms of common cold such as sore throat and runny nose within two days'.

Examples of the types of medicines for which applications will be accepted for evaluation through the new pathway are provided in **Attachment 1**.

This proposal will also provide industry with incentives to increase the evidence base of complementary medicines.

Proposal two: Products excluded from the new pathway

We propose that the following products will **not** be accepted for evaluation through the new pathway:

- Products that **only** have 'standard' permitted indications.
- Products that have indications based **solely** on evidence of traditional use, unless they also provide adequate scientific evidence supporting the indications.

The new pathway is also not proposed to be a provisional approval pathway pending the outcome of clinical trials (i.e. evidence of efficacy is required at the time of application to TGA).



A risk-based hierarchy for therapeutic indications

- 3.1 Do you agree with the proposed indication hierarchy and the criteria proposed to distinguish the three medicine pathways?
- 3.2 Do you envisage any difficulties with criteria used to include or exclude products from the new pathway?
- 3.3 What other considerations may need to be taken into account in implementing the new pathway?

Approaches to establishing efficacy

Many listed complementary medicine products have indications based on published studies on the separate ingredients in a formulation. Given their low risk nature, it is appropriate that efficacy of listed medicines can be established without product-specific evidence. However, the Panel proposed that the evidence for the indications assessed via the new pathway should relate to the finished product, and we propose that the pathway is to be applied to products rather than ingredients.

The efficacy of registered complementary medicines can currently be established through two methods:

- direct clinical data on the finished product; or
- a dossier of data showing that the proposed product delivers appropriate bioavailability of active ingredients that have been established to be efficacious.

We propose that medicines evaluated through the new pathway will require an ‘intermediate’ evidence package to enter their products on the ARTG. The sponsor will self-assess the product’s safety and quality (recognising that listed medicines may only be made from pre-approved ingredients with suitable safety and quality characteristics) and will be required to submit a high quality efficacy package for pre-market assessment.

This approach will enable sponsors to access the new pathway for new products, including those that are equivalent to established formulations, or existing listed products with well characterised active ingredients. This will facilitate expansion of the evidence base for complementary medicines and increase consumer access to evidence-based products.

Proposal three: Approaches to establishing efficacy

The existing approaches to establish efficacy for listed and registered complementary medicines will be retained for low and high level indications respectively. We propose that efficacy data on the finished product will be required for products to be eligible to be included on the ARTG via the new pathway at a similar standard that applies to registered complementary medicines.

Sponsors must comply with either of the following approaches to establishing efficacy:

Method 1: Clinical data on the finished product that supports the specific indication.

OR

Method 2: A data package containing:

1. evidence for efficacy of all ingredients; and
2. evidence for efficacy of the product formulation, established through bioequivalence data to existing products [consisting of evidence of release via dissolution data and absorption of the active ingredient via bioavailability data]¹⁰ or, in some instances, comparative dissolution (against established data) demonstrating release of the active ingredient with appropriate scientific justification;
3. justification of the combination of ingredients (including potential interactions).

Note: Method 2 can **only** be used for products that are composed of defined chemical entities such as vitamins, amino acids and minerals (i.e. herbs and herbal extracts, animal products, and probiotics are ineligible for inclusion via Method 2).

Refer to **Attachment 1** for case studies of products and evidence packages suitable for evaluation via the new pathway.

¹⁰ See: Guidance 15: Biopharmaceutical Studies (2 April 2015), available at: <<https://www.tga.gov.au/guidance-15-biopharmaceutical-studies>>.

Existing restricted representation approvals

Existing listed medicines that have approval to state indications that refer to restricted representations will need to transition to the **new pathway** in order to continue making these indications. Refer to section 7: [Transitional arrangements](#) below for more information.

Indications that are restricted representations will only be approved if they satisfy the public interest criteria. Consistent with a risk-based approach, evidence relating to the efficacy of the finished product must be provided to ensure that the public interest criteria are met.

Method 2 (outlined in **Proposal three** above) will allow sponsors of existing listed products that refer to restricted representations to meet the requirements for the new pathway, including the public interest criteria. This method will ensure that evidence relating to the finished product is assessed but will minimise the burden on industry having to undertake new product-specific studies. Under this method, sponsors could demonstrate efficacy for their medicine, for example, through comparative dissolution data against established bioavailability supplemented with a justification for the efficacy of all ingredients. This could include reference to the existing restricted representation approval. Examples of how the proposed approaches to establishing efficacy will apply to existing restricted representation approvals are provided in **Attachment 1**.

These requirements will be outlined in detail in TGA evidence guidelines.



Approaches to establishing efficacy

- 3.4 Do you agree with the proposed methods to establish efficacy for products included via the new pathway?
- 3.5 Is the proposed approach to establish efficacy for current listed products that have a restricted representation exemption appropriate?

Evidence requirements

The Government supported the Panel's recommendation that the three assessment pathways should be established on the basis of a hierarchy of evidence as part of a graded response to the risk profile of complementary medicines and the associated indications that can be made¹¹. To enhance public confidence in complementary medicines and the regulatory framework, the minimum standard of efficacy evidence for products assessed via the new pathway will be higher than the level required to be held by sponsors to support non-efficacy assessed medicines.

Sponsors must meet these minimum evidence requirements:

- to correctly certify that they hold appropriate evidence to support the product indications (listed medicines)
- for an application to be accepted for evaluation through a pre-market assessment process (new pathway or existing registered medicines pathway).

Failure to meet these requirements will be a basis to reject an application and / or cancel a medicine from the ARTG.

¹¹ Expert Panel, p.28.

Consistent with current arrangements, additional evidence may be required to support advertising claims to ensure that they are truthful, factual and not misleading. Therefore, pre-market assessment of products via the new pathway will involve an assessment of the medicine presentation, including the product label.

Proposal four: Evidence requirements

The existing evidence requirements for listed and registered complementary medicines will be retained to establish efficacy for low and high level indications respectively (see **Tables 2** and **3**).

We propose that sponsors seeking to include complementary medicines on the ARTG via the new pathway meet the minimum evidence requirements outlined below (**Tables 2** and **3**).

Tables 2 and **3** provide the current as well as the proposed minimum number and types of studies required for the three proposed assessment pathways for complementary medicines. It is possible that some categories of evidence may be better than others (for example a high quality, well conducted, replicable clinical trial that is consistent with the scientific body of evidence, may be better than a systematic review). The tables are proposed only as a guide for sponsors. Sponsors will need to provide justification where they choose not to follow the requirements. The overall evidence dossier requirements for medicines evaluated through the new pathway are outlined in detail in **Table 4**.

Table 2: Proposed categories of evidence

Category A	Category B	Category C	Category D
Traditional Reference text	Non-systematic, generalised reviews - including databases	Observational studies e.g. cohort and case control studies	Double blind randomised controlled trials (including cross-over trials)
Herbal Monograph	Publicised international Regulatory Authority Articles	Comparative studies (non-control).	Systematic reviews
Herbal Pharmacopoeia	Evidence based reference text - scientific		
Materia Medica	Scientific Monographs		
Publicised International Regulatory Authority Articles – Traditional only	Pharmacopoeias		

Table 3: Proposed minimum literature requirements

Listed Medicines			New pathway	Registered medicines
Indication	Traditional	Low Level scientific	Intermediate Level Indications	High level Indications
Evidence Category (required evidence)	Minimum of two independent sources from Category A OR A minimum of one from Category B	Minimum of two independent sources from Category B Plus (where required) A minimum of one from Category C	Primary indication Minimum of one from Category D OR Minimum of 2 independent sources from Category B, AND a minimum of one from Category C	Primary indication Minimum of one from Category D
Evidence Category (supplementary evidence)	Minimum 1 from Category A to support indications (where relevant)	Minimum of 1 from Category B to support specific indications (where relevant)	Secondary (low level) indications One from Category D OR Minimum of 2 independent sources from Category B, AND a minimum of one from Category C	Secondary indications One from Category D OR Minimum of 2 independent sources from Category B, AND a minimum of one from Category C

Summary of efficacy evidence requirements for the new pathway

Consistent with Method 1 and 2 (see **Proposal three** above) the evidence dossier requirements for the new pathway are provided in **Table 4**.

Note that all secondary low level indications drawn from the permitted indications list should also be supported by evidence appropriate for listed medicines outlined in **Tables 2** and **3** (i.e. supplementary evidence).

Table 4: Evidence dossier requirements for the new pathway

Data type	Method 1	Method 2
Primary indication	A minimum of one randomised controlled clinical trial (including cross-over trial) or systematic review on the product .	A minimum of one randomised controlled clinical trial (including cross-over trial) or systematic review on each active ingredient .
Body of scientific information	Full literature search report on the product or formulation .	Full literature search report on all active ingredients and formulation .
Non-clinical data	NA	Dissolution data and bioequivalence data on the product ¹² .
Formulation	NA	Justification of the use of the particular combination of ingredients, including potential interactions.
Quality	Evidence of GMP.	Evidence of GMP.

All studies should be compliant with International Council for Harmonisation (ICH), and European Medicines Agency (EMA) guidelines adopted by the TGA at the time of application. This includes adopted guidelines on clinical trials, Good Clinical Practice (GCP), ethical certification, non-clinical studies and bioequivalence, as outlined in Part D of the Australian Regulatory Guidelines for Complementary Medicines (ARGCM). Literature searches should likewise meet the criteria specified in the ARGCM.

All evidence will be subject to minimum requirements for relevance, quality and consistency. These requirements are currently specified in the Evidence Guidelines for listed medicines¹³, which will be updated accordingly.



Evidence requirements

- 3.6 Are the evidence requirements appropriate for the new pathway?
- 3.7 Do the proposed levels of assessment align with the proposed risk-based hierarchy?
- 3.8 What other considerations may need to be taken into account in implementing the new pathway?

¹² See: Guidance 15: Biopharmaceutical Studies (2 April 2015), available at: <https://www.tga.gov.au/guidance-15-biopharmaceutical-studies>.

¹³ Guidelines on the evidence required to support indications for listed complementary medicines (July 2014), available at: <https://www.tga.gov.au/publication/evidence-guidelines>.

4. Implementing a list of permitted indications

Overview

The Government has decided that the TGA should establish a list of permitted indications, from which sponsors must exclusively draw, to include listed medicines in the ARTG.

Currently, when applying to list a medicine on the ARTG sponsors have access to a 'free-text field' in the Electronic Listing Facility (ELF). The 'free-text field' allows sponsors to enter whatever indications they choose, noting that they must hold evidence to support all indications that are made. This has resulted in significant rates of non-compliant indications being included in listed medicine entries on the ARTG.

The Panel considered that removal of the free text field will prevent sponsors from inadvertent non-compliance¹⁴.

The TGA will prepare a legislative instrument comprising a consolidated list of all permitted indications. This list will include indications that are appropriately structured and compliant with regulatory requirements.

Sponsors will be required to select indications from the permitted indications list (see options for implementation below) when entering their medicine on the ARTG and will **not** be able to include their own indication via a free text field. Sponsors will have to certify that the indications for their medicine are from the permitted indications list **and** that they hold supporting evidence.

Criteria for permitted indications

Only low level indications will be suitable for inclusion in the permitted indications list, based on the following proposed criteria:

- The indication must meet the definition of a therapeutic indication (i.e. must describe a therapeutic use for the goods)¹⁵.
- The indication must be a low level indication (see **section 3: [Establishing a risk-based hierarchy for therapeutic indications](#)**).
- The indication must be capable of complying with the Therapeutic Goods Advertising Code when included on the product label or promotional materials. For example, the indication must not: mislead, or be likely to mislead consumers, contain any implication that the medicine is infallible, unfailing, magical, miraculous, or that it is a certain, guaranteed or sure cure; or contain any claim, statement or implication that it is effective in all cases of the condition.
- The indication must be consistent with the relevant treatment paradigm (scientific or a tradition of use).

These criteria will ensure that only indications appropriate for listed medicines and that are compliant with the regulatory requirements will be accepted for inclusion on the permitted

¹⁴ Expert Panel, p. 26.

¹⁵ All other statements and claims relating to a medicine (for example, '25% more' or 'new and improved formula') are not indications and will not be able to be included in the permitted indications list.

indications list. Products containing higher level indications will require an approval through a pre-market assessment process (i.e. the new pathway or registration).

We will draw extensively on the work previously undertaken to implement a permitted indications list to develop a comprehensive list of traditional and scientific indications that meet the proposed criteria. We will consult with stakeholders before finalising this list.

Sponsors will be able to apply for new indications to be added to the permitted indications list. Applications will be assessed by the TGA to determine whether the indication meets the eligibility criteria. Indications will not be evaluated per se, and there will be no requirement to submit supporting data. We propose to update this list on a quarterly basis, or as needed. A mechanism will also be developed to allow indications to be removed from the list where there is scientific evidence that supports their removal.

Indications suitable for inclusion in the permitted indications list

Indications that meet the proposed criteria for low level indications set out in **Proposal two** will be suitable for inclusion in the permitted indications list (see **Table 5** for examples).

A low level indication, and therefore a permitted indication, may refer to:

- health enhancement
- health maintenance
- prevention of dietary deficiency
- a disease, ailment, defect or injury **other** than a serious form of those diseases.

These criteria will ensure that indications accepted for inclusion in the permitted indications list are appropriate for low risk medicines that are not evaluated pre-market. The proposed criteria will not reduce the ability of sponsors to use indications which are currently appropriate for listed medicines. Further, as the permitted indications list will include all indications that are appropriately structured and compliant with the eligibility criteria, it is unlikely that the list will affect currently compliant sponsors.

Certain indications of listed medicines that are currently available for supply may not meet the criteria proposed above. For example, biomarker indications¹⁶ that relate to a disease that is potentially serious and may result in the consumer delaying appropriate medical treatment such as, 'may assist in effective management of reducing cholesterol levels'. These indications could however, be reworded such that they satisfy the above criteria. We will consult with stakeholders to develop a comprehensive list of traditional and scientific indications that meet the proposed criteria.

¹⁶A biomarker is a measurable biological parameter that is predictive of the risk of a serious disease when present at an abnormal level in the human body. For example, blood glucose and cholesterol.

Table 5: Indications appropriate for inclusion in the permitted indications list

A low level indication may refer to:	What this means	Examples
Health enhancement	Beneficial effects of substances on the physiological / psychological state of the body, above and beyond normal growth, development and functions of the body.	<ul style="list-style-type: none"> • May increase energy / reduce fatigue • Helps stimulate digestive function • May enhance mental alertness
Health maintenance	Normal physiological effects of substances in growth, development and normal functions of the body.	<ul style="list-style-type: none"> • Helps maintain healthy digestive function • Helps maintain healthy hair, skin and nails • May support healthy lung function • Assists with normal liver function • Helps support healthy connective tissue / joints
Prevention of dietary deficiency	Prevention of mild dietary deficiency (i.e. not prevention of diseases resulting from severe deficiency).	<ul style="list-style-type: none"> • When taken regularly, may prevent vitamin D/calcium deficiency • Helps reduce the risk of iodine deficiency • Helps prevent dietary vitamin B12 deficiency
A disease, ailment, defect or injury other than a serious form (other than a reference to the prevention, alleviation of disease)	<p>Those low risk conditions that are non-serious and self-manageable.</p> <p>May be related to reduction in risk / frequency / duration, relief, management or improvement in quality of life; without resolution of the underlying non-serious disease, ailment, defect, condition or injury.</p>	<ul style="list-style-type: none"> • Helps reduce the severity of common cold symptoms • For the management of mild dermatitis symptoms • Helps relieve muscle aches and pains • May relieve post-menopausal/PMS symptoms • Helps reduce the frequency of common cold sore outbreaks • Helps ease chesty coughs

Note: The examples provided in this table are a guide only and will be reviewed against the finalised criteria for permitted indications to determine their suitability for inclusion in the permitted indications list.

Indications not suitable for inclusion in the permitted indications list

Indications that meet the proposed criteria for intermediate or high level indications set out in **Proposal two** are not suitable for medicines that are not pre-market assessed (see **Table 6** for examples).

A low level indication, and therefore a permitted indication, must not:

- refer to, or imply, the prevention, alleviation, or cure of any form of a disease, ailment, defect or injury
- contain a prohibited representation¹⁷
- contain a restricted representation
- have been specified in a non-permitted indications list.

It is proposed that the TGA will also specify certain indications that will not be included in the permitted indications list through the making of a non-permitted indications list (see **Table 6** for examples). This will allow TGA to exclude particular indications of concern from the permitted indications list that may otherwise meet the eligibility criteria.

If a sponsor proposes to use an indication specified in the non-permitted indications list, they could only do so through the new pathway or the registration pathway (unless it contained a prohibited representation). A decision to include an indication in the non-permitted indications list will only be made following detailed stakeholder consultation.

Table 6: Indications not suitable for inclusion in the permitted indications list

A low level indication may refer to:	What this means	Examples
Refer to, or imply, the treatment, prevention, alleviation or cure of any form of a disease, ailment, defect or injury	Treatment, prevention, alleviation and cure have a more definitive meaning which are not suitable for permitted indications as they may lead to a delay in seeking medical treatment and adverse consequences for the patient.	<ul style="list-style-type: none"> • Prevents indigestion • Treats dehydration • Treats cold sores • Alleviates Irritable Bowel Syndrome
Contain a prohibited representation	Any reference regarding the treatment, cure or prevention of the following diseases: <ul style="list-style-type: none"> • Neoplastic • Sexually Transmitted Diseases • HIV AIDS and/or HCV • Mental illness 	Any reference to: <ul style="list-style-type: none"> • depression / anxiety / low mood • cancer • genital warts / prevention of the transmission of herpes virus

¹⁷A prohibited representation is any reference regarding the treatment, cure or prevention of any of the diseases specified in Part 1 of Appendix 6 of the Therapeutic Goods Advertising Code.

A low level indication may refer to:	What this means	Examples
Contain a restricted representation	<p>Any reference (even by implication) to a serious disease, condition, ailment or defect specified in Table 1 of Part 2 of Appendix 6 of the Therapeutic Goods Advertising Code</p> <p>Serious, in this context means those diseases, conditions, ailments or defects that are:</p> <ul style="list-style-type: none"> • Generally accepted not to be appropriate to be diagnosed and/or treated without consulting a suitably qualified healthcare professional, and/or • Generally accepted to be beyond the ability of the average consumer to evaluate accurately and to treat safely without regular supervision by a qualified healthcare professional 	<ul style="list-style-type: none"> • Reduces risk of atherosclerosis • Reduces elevated blood glucose (referring to diabetes and or unhealthy biomarkers) • Helps naturally decrease high blood pressure • Alleviates arthritis symptoms, such as inflammation and pain • Reduces symptoms of reflux • Beneficial for anaphylaxis
Have been specified in a non-permitted indications list	<p>Those indications that the TGA will have determined to be unsuitable for inclusion in the permitted indications list e.g. on public health grounds.</p>	<p>Indications referring to areas of public health importance, for example:</p> <ul style="list-style-type: none"> • certain biomarkers that are predictive of a serious disease, e.g. diabetes, cardiovascular disease • smoking cessation • obesity • vulnerable populations (e.g. 4 week old infants)

Proposal five: Criteria for permitted indications

We propose that the criteria for low level indications will determine whether an indication is appropriate for inclusion in the permitted indications list as outlined above (**Tables 5 and 6**).



Criteria for permitted indications

- 4.1 Are the proposed criteria for inclusion of an indication on the permitted indications list appropriate?
- 4.2 What other considerations should be taken into account in implementing the permitted indications list?

Mechanisms to allow market differentiation of products

In implementing a list of permitted indications, there needs to be a balance between two competing principles:

- Allowing too much flexibility may result in continued high levels of non-compliant indications and therefore do little to improve consumer protections.
- If there is insufficient flexibility, sponsors may not have adequate market differentiation or be able to align indications with the evidence held for their medicine.

Sponsors may vary the wording of the permitted indications on the product label, provided the intent and meaning is not changed. Where more than one indication is required, they may be combined to form simple sentences where appropriate, provided that the intent and meaning is not changed and that any additional requirements are also met.

This approach would help contain the size of the permitted indications list and give flexibility to sponsors without undermining consumer protections.

Structure of a permitted indication

The current Evidence Guidelines for listed medicines state that an indication is made up of the components listed in **Figure 1** (see **Table 7** for examples). The mandatory core components of an indication are the traditional context (if applicable), action and target. These mandatory components can be qualified with action qualifiers, target qualifiers and indication qualifiers to further specify the therapeutic use of the goods. The use of specific indication qualifiers requires sponsors to hold commensurately more specific evidence for their medicine. On the other hand, if qualifiers are not used, sponsors would need to hold more general and broad evidence to match the indication

Figure 1: Indication structure and components

An indication is comprised of the following components:

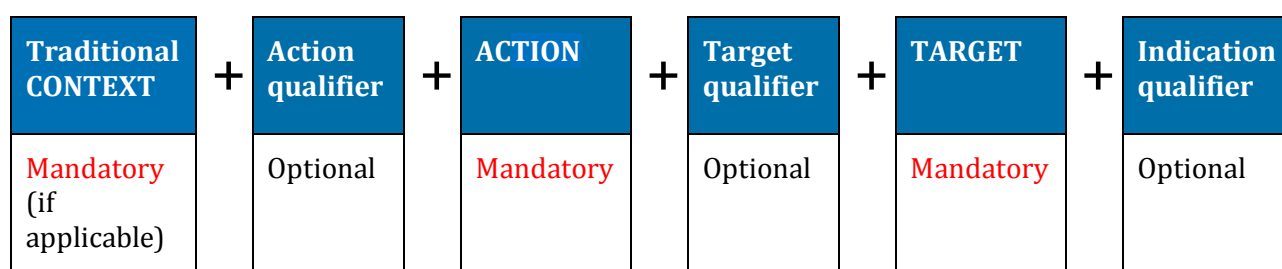


Table 7: Examples of components of an indication

Indications component	Explanation	Examples
ACTION	<p>The:</p> <ul style="list-style-type: none"> Action Effect Mechanism Benefit 	<ul style="list-style-type: none"> Reduce(s) Relieve(s) Prevent(s) Improve(s) Stimulate(s) Maintain(s) Enhance(s) Increase(s) Support(s) Combat(s) Ease(s)
ACTION QUALIFIER	Terms that ensure the action is suitable for the level of evidence the sponsor holds. They often specify effectiveness.	<ul style="list-style-type: none"> May help / to help / helps Assists with / may assist / assist to For the temporary relief of
TARGET	<p>Either a:</p> <ul style="list-style-type: none"> physiological / psychological factor or process; or disease, ailment, condition, defect or injury. 	<ul style="list-style-type: none"> Thermogenesis Inflammation General health and well being Normal growth and development Headache Excess mucous Healthy eyes Muscle cramps and spasms
TARGET QUALIFIER	<p>Terms that ensure:</p> <ul style="list-style-type: none"> the target is suitable for the evidence the sponsor holds; and/or the indication is not referring to a restricted representation (e.g. mild osteoarthritis). 	<ul style="list-style-type: none"> Mild Symptoms of Healthy/Normal Occasional Uncomplicated Moderate Excess Everyday
INDICATION QUALIFIER	<p>Additional terms that may provide information relating to the evidence held by the sponsor.</p> <p>This includes terms that specify a healthy target population and times of use.</p>	<ul style="list-style-type: none"> In the elderly In sports athletes In pregnant women In normal healthy individuals During times of stress After strenuous exercise

The existing indication structure: standardises permitted indications; clarifies the necessary components of an indication for applicants; and clarifies whether a proposed new indication duplicates an existing indication. This structure will be used to ensure that permitted indications are structured consistently.

In line with the risk based framework for medicines, sponsors of listed medicines are required to hold evidence that demonstrates that the product is effective. As the TGA has not confirmed the efficacy through pre-market evaluation, indications should reflect this lack of certainty. In certain circumstances mandatory indication qualifiers may be necessary to:

- convey that a low level indication is non-definitive (i.e. to distinguish listed medicines from medicines that have undergone pre-market efficacy assessment under the new pathway or registration); or
- to identify the context of therapeutic use and the evidence base (i.e. to identify indications that are supported by evidence of a tradition of use).

Qualifiers must be included as part of the ARTG entry **before** they can be included on product labels. See options provided below. If qualifiers are included as part of an indication on the ARTG, and that indication is also included on advertising material, then the qualifiers must also be used with the indications on the advertising material.

Options for implementation of the permitted indications list

Three options for implementation of the permitted indications list are proposed for consultation. In selecting indications for inclusion on the ARTG, applicants could draw permitted indications from:

- a prescriptive list
- core permitted indications which can be modified with pre-approved qualifiers
- pre-approved indication components to build a unique indication.

Option 1: Develop a comprehensive prescriptive list of permitted indications

Under this option sponsors would be required to draw from a comprehensive prescriptive list of permitted indications that are based on the current indication structure (see **Figure 1**). The wording of permitted indications could be modified on the product label provided the intent/meaning was not changed. Where a sponsor had differing evidence and wished to modify a permitted indication through the inclusion of a different indication qualifier, they would need to apply for the inclusion of an entirely new indication if it was not already on the list. This option is likely to lead to a large and unwieldy permitted indications list.

Option 2: Core permitted indications which can be modified with pre-approved qualifiers

Under this option, 'core' permitted indications (consisting of a: traditional context if applicable, action and target - see **Figure 1** above) will be specified in a legislative instrument. All applicants for listed medicines will be required to select permitted indications when entering their indications for inclusion on the ARTG. Applicants could modify the core indication to align with the supporting evidence held by optionally selecting pre-approved qualifiers from a drop-down list (see **Figures 2** and **2.1**). Specific indication qualifiers would be approved through

administrative measures rather than being legislative in nature. This would ensure that indication qualifiers are still included on the ARTG but the TGA would not need to update the permitted indications list to include new qualifiers.

Figure 2: Option for modifying a core permitted indication

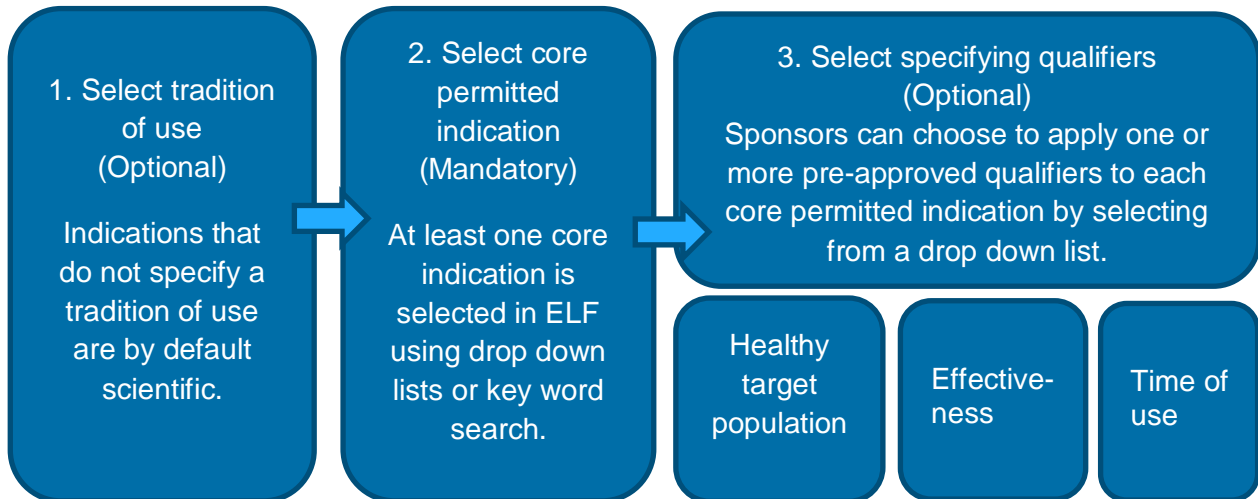
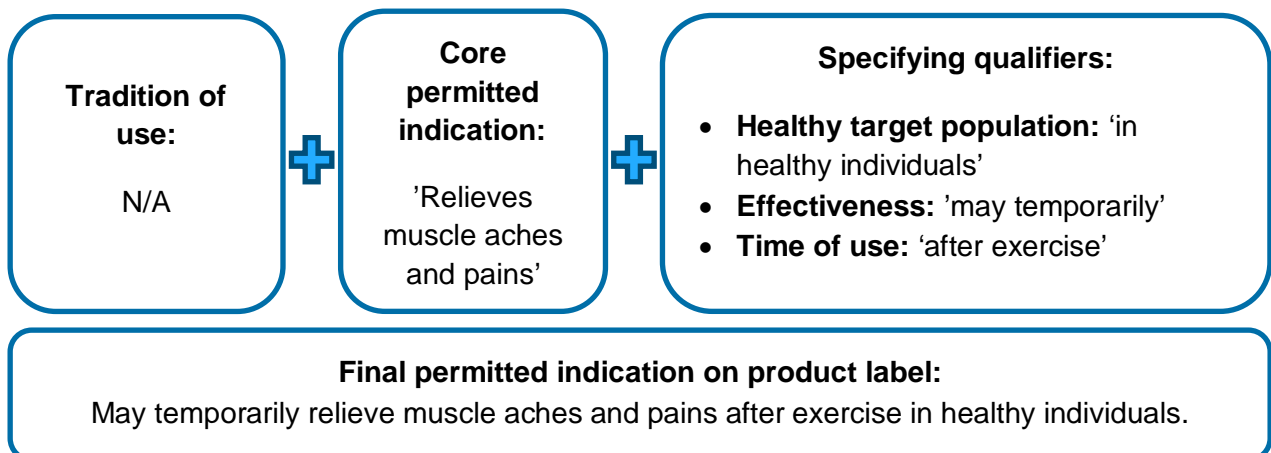


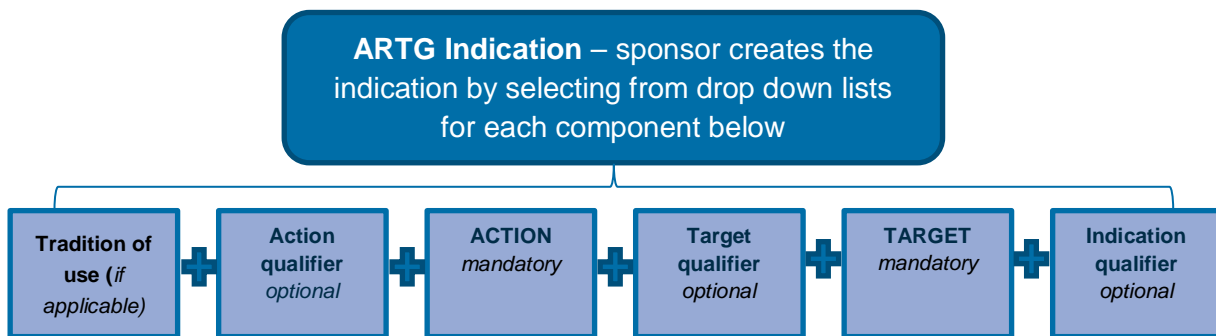
Figure 2.1: Example indication



Option 3: Build a unique indication from pre-approved indication components

Under this option sponsors could combine specific pre-approved indication components (see **Figure 1**) to form a tailored indication. Drop down lists would be available within ELF for each indication component (see **Figure 3**).

To create an indication a sponsor would be required to select a tradition of use (if applicable) an action and a target (see **Figure 3.1**). The use of indication qualifiers would be optional.

Figure 3: Building a unique indication from pre-approved indication components**Figure 3.1: Example indications**

Tradition of use	Action qualifier	ACTION	Target qualifier	TARGET	Indication qualifier
Traditionally used in Western herbal medicine	To help	Stimulate	Healthy	Digestion	-
-	May help	Relieve	Symptoms of	Eye strain	Associated with prolonged computer use

Final permitted indications on product label:

1. This product has been traditionally used in Western herbal medicine to help stimulate healthy digestion.
2. May help relieve symptoms of eye strain associated with prolonged computer use.

Proposal six: Implementation of permitted indications

We believe that **Option 2** may strike the best balance between ensuring that all indications in the permitted indications list comply with the regulatory requirements and allow industry sufficient flexibility to differentiate their products in the market by aligning indications with the evidence held for their medicine. This option would also help contain the size of the permitted indications list.

Under this option, the TGA would develop a comprehensive list of traditional and scientific 'core' indications and specifying qualifiers for further consultation with stakeholders.



Implementation of the permitted indications list

- 4.3 Is Option 2 for selecting indications for inclusion on the ARTG and on product labels and promotional material suitable to address the objectives for permitted indications?
- 4.4 What other considerations should be taken into account in implementing the permitted indications list?

Additional requirements for the use of permitted indications

As well as specifying permitted indications, the list will also include requirements in relation to some indications. The purpose of imposing a requirement for a permitted indication is to ensure that the indication is suitable for use in medicines that have not been pre-market assessed. The requirements may specify circumstances when the indication can or cannot be used or specify conditions that must be met. These requirements will be consistent with the current regulatory framework.

For example, a requirement might:

- specify a target population for which the indication is not suitable, such as children
- require a label warning statement, such as: where an indication refers to the signs and symptoms of a disease, there may be a requirement to include a label warning statement, with words to the effect of: 'If symptoms persist consult your healthcare practitioner'.

5. Claiming evidence of efficacy

Overview

The Panel recommended that following pre-market efficacy assessment by the TGA, sponsors should be able to claim that the product's efficacy has been assessed for the approved indication(s) (use a 'claimer'). In supporting this recommendation, the Government identified the need to carefully consider the design and use of these statements.

Use of a claimer will allow complementary medicines that have had their efficacy assessed to differentiate themselves in the market. It may also improve consumer awareness of the different levels of assessment of complementary medicines undertaken by the TGA and encourage use of the new assessment pathway for products carrying intermediate level indications.

Criteria for use of 'claimers'

In implementing the ability for sponsors to claim that the efficacy of their product has been assessed, the following criteria are proposed:

- A claimer will be approved for:
 - complementary medicines evaluated by the TGA via the new pathway

- registered complementary medicines that have undergone pre-market evaluation.
- A claimer must not imply superiority of the product over other medicines that have been pre-market assessed such as other listed or registered (OTC and prescription) medicines (for which claimers are not permitted).
- A claimer will not be approved for:
 - medicines that have been included on the ARTG via sponsor self-certification and have not been evaluated by the TGA through a pre-market assessment process
 - ‘grandfathered’ registered medicines (medicines that were available in the marketplace when the ARTG was established and were entered on the ARTG as ‘grandfathered’ products), as the efficacy of these medicines have not been evaluated by the TGA.
- A claimer must be supported by the appropriate level of evidence as outlined in the Evidence Guidelines (as revised).
- Where a claimer is used for a medicine that has multiple indications (including low level permitted indications), the evidence must support all indications made for the medicine.
- A claimer must comply with advertising requirements e.g. not be misleading.
- The claimer must not be more prominent or detract from the label information mandatorily required by the Therapeutic Goods Order No. 92 – Standard for labels of non-prescription medicines. For example, the colour, position and size of the font should not be more prominent than any required label advisory statements.
- Inclusion of a claimer on a medicine’s label or promotional material following an approval will not be mandatory.

In keeping with the intent of the Panel’s recommendations for the new pathway, low risk listed medicines that have undergone post-market evidence assessment will not be able to make claims of having been efficacy assessed¹⁸.



Criteria for the use of a claimer

- 5.1 Do the proposed criteria for the use of a claimer address the objectives for the recommendation?
- 5.2 What other considerations should be taken into account in implementing this recommendation?

Use of claimers

The Panel recommended that sponsors should be able to include a claimer on promotional materials, including the product label to recognise the considerable effort for sponsors to obtain an approval for a medicine via the new pathway. In doing so, this will also improve the transparency of the efficacy claims for consumers¹⁹. To acknowledge the higher level of

¹⁸ Expert Panel, p. 38.

¹⁹ Expert Panel, pp. 38-39.

pre-market scrutiny, it is proposed that the claimer may also be approved for registered complementary medicines. However it is not proposed that claimers be permitted for registered OTC medicines (i.e. those containing a scheduled substance) or prescription medicines.

Under the current legislative requirements, medicine sponsors cannot imply that the TGA or any other foreign government authority has endorsed or approved the efficacy of any product. Legislative changes will be required to allow the use of a claimer for this specific category of medicine.

The use and presentation of a claimer will be approved by the TGA following pre-market assessment of the complementary medicine product. The approval will specify that the wording of the claimer in promotional material must be the same as that approved for the label.

It will not be mandatory for sponsors to use the claimer following an approval.

Proposal seven: Use of a claimer

We propose that a claimer may only be used on complementary medicine labels and / or other product promotional materials following TGA approval as part of a pre-market assessment process.



Use of a claimer

5.3 Will the use of a claimer on complementary medicines have any unintended consequences?

Presentation of claimer statements

In considering the appearance of a claimer, a balance is required between providing flexibility to industry (to obtain a market advantage) and the need for direct and clear information to enable consumers to make informed healthcare decisions. The presentation of a claimer must not detract from essential product information. It must also not imply that other pre-market assessed medicines (i.e. OTC and prescription medicines) with similar indications are less effective because those medicines do not carry a claimer.

An approved presentation for the claimer statement will be developed and will be the same for all products; no variation to the presentation of the claimer will be allowed. The approved presentation will standardise the font size, colour, location and wording of the claimer statement.

The presentation of a claimer is envisaged to be in the form of an appropriately worded statement, although stakeholder advice on alternative presentation options, such as a symbol is sought. These options are explored below. Irrespective of what option is selected, implementation of the claimer will be accompanied by a consumer education campaign.

Option 1: Claimer as a statement

Sponsors could indicate that the efficacy of their product has been assessed by including a statement on their label and/or promotional material. Examples of different statements are provided below:

- 'The efficacy of the product has been independently assessed for the approved indication'.
- 'The evidence held by the sponsor to support the indications for this medicine has been reviewed by the TGA'.
- 'Evidence has been reviewed by the TGA'.

The positioning of the statement should not detract from essential product information, so that, if included on a medicine label, the statement should be in font size no bigger than the indications or advisory statements for the medicine.

Option 2: Claimer as a visual identifier (symbol) as well as a statement

Under this option, sponsors could use a standard visual identifier (symbol) of a design determined by the TGA, as well as the statement to indicate that efficacy of their product has been assessed.

If implemented, a visual identifier must be:

- standardised and easily recognisable by consumers
- appropriately placed on the label / other promotional material so that it does not detract from essential product information.



Presentation of claimers

- 5.4 Should the claimer be presented as a visual identifier as well as a statement?
- 5.5 Do you have any views on the possible wording or design of the label claimer?
- 5.6 What other considerations should be taken into account in implementing the claimer?

6. Incentives for Innovation

Overview

The Government supported the Panel's recommendation that mechanisms to improve the competitiveness of the Australian complementary medicines industry be introduced by providing incentives for innovation. The Panel noted that encouraging greater development of evidence relating to complementary medicines would have the benefits of greater consumer

confidence in the efficacy of complementary medicines, and the improved reputation and competitiveness of the sector²⁰.

Mechanisms to incentivise innovation

In considering how to incentivise innovation for complementary medicines, the Panel made specific reference to data protection and market exclusivity but did not make a specific recommendation in favour of any particular mechanism.

Data protection is a form of secrecy that prevents access to and use of data that supported a product approval from being used for a subsequent evaluation of competitor's similar product. Another person may, however, use their own data to register their own similar product. For example, the TGA could not abridge an evaluation of a generic application based on an evaluation of an innovator product during the data protection period. Section 25A of the Act provides for a five year period of data protection for information about a new active ingredient contained in a **registered** medicine. However, it does not apply to listed therapeutic goods, which represent the majority of complementary medicines.

Market exclusivity is a form of protection that concerns a product or an ingredient, and prevents any other person from using the ingredient or obtaining an approval for the product during the exclusivity period. For example, during the period of exclusivity, the TGA would not be able to approve another application for the inclusion of a similar product (same ingredient / dose form / indications etc.) on the ARTG regardless of whether the applicant had generated their own data.

Data protection and exclusivity are not mutually exclusive and could possibly be used in combination to encourage innovation by protecting investment in developing new ingredients; new indications supported by new clinical investigations or new product formulations.

It is noted that innovations in the complementary medicines sector can also be protected by other types of intellectual property rights such as patents and trademarks.

Criteria for innovation incentives

In considering formal mechanisms to improve competitiveness in the complementary medicines sector, the following criteria are proposed:

- Incentives should only be available to novel ingredients and or products supported by high quality evidence that has undergone pre-market assessment by the TGA.
- Incentives will be implemented in a way that does not permit the incentives to be earned for marginal innovations.
- Incentives should strengthen transparency for consumers by encouraging generation of evidence based research.
- The TGA will not undertake compliance monitoring to enforce any data protection or market exclusivity periods. However, the TGA will consider use of administrative measures to help ensure that protections are maintained, for example: sponsor certification or electronic flags in databases. Sponsors will be responsible for enforcing protection mechanisms.
- An innovator may consent to the submission (or license) of a subsequent application by another person during the protection period. However, the TGA will not intervene or

²⁰ Expert Panel, pp. 45-46.

arbitrate disagreements between sponsors, manufacturers or suppliers in relation to licensing agreements.

These principles will ensure that we are fulfilling the intent of this recommendation, whilst improving evidentiary standards for complementary medicines and minimising the impact on our existing regulatory functions.

Protection for new ingredients

New ingredients approved for use in listed complementary medicines are assessed by the TGA. If the TGA is satisfied with the safety and quality of the ingredient, the substance will be approved for use as an ingredient in listed medicines. The ingredient will then be included in the Therapeutic Goods (Permissible Ingredients) Determination. Any sponsor can then use that ingredient to include a product on the ARTG through the listing pathway without having to undertake the necessary research to support the safety and quality of the ingredient.

The current process for new ingredient applications does not recognise or protect the resources invested by innovators who research and develop new ingredients to be used in complementary medicines.

Protection procedure

In line with the intent of this recommendation, it is proposed that a limited period of **market exclusivity** will be provided to successful applicants for **new** ingredients.

Under this proposal the use of a protected ingredient in a medicine within the exclusivity period would be limited to the ingredient applicant (who may or may not be a medicine sponsor) or by other persons nominated by the applicant. The approval for the use of the new ingredient in listed medicines would be published, but could not be used by other sponsors to include a product on the ARTG. At the end of the exclusivity period, the exclusive approval would then revert to a general approval and other sponsors could then use the ingredient and apply for inclusion of their medicine on the ARTG. This protection is similar to the provision for exclusive permissions for novel foods in the Australia New Zealand Food Standards Code – Standard 1.5.1 – Novel foods (the food standard).

Timeframe

It is proposed that after a new ingredient has been approved the exclusivity period will apply for a period of **2 years**. The proposed duration is intended to reflect the level of effort involved in preparing a new ingredient application for evaluation and support return on investment. The length of the exclusivity period is less than the data protection period afforded to new active ingredients included in registered medicines under section 25A of the Act to reflect the relatively lower level of research needed to meet the evidence requirements. The period of exclusivity will automatically lapse on expiry, with no provision for extension.

Additional considerations

Consideration could also be given to allowing a sponsor of another medicine to apply to the TGA for use of an ingredient during the original applicant's exclusivity period for that ingredient. Such an application would require its own supportive data. The exclusivity period for both applicants would end on expiry of the exclusivity period for the first applicant. This approach is similar to the exclusivity arrangements under the food standard. This approach would provide a 'first to market advantage' for the original applicant, while also encouraging further research into the safety and quality of new ingredients.

In order to support the exclusivity of the first applicant, it is proposed that publication of the compositional guideline²¹ will be delayed until the ingredient reverts to a general approval.

Proposal eight: Protection for new ingredients

We propose that:

- A limited period of market exclusivity will be granted to applicants for new ingredients approved for use in listed medicines.
- There would be a 2 year exclusivity period.

Protection for new ingredients



- 6.1 Is the proposed process and mechanism to provide market protection for new ingredient applicants appropriate?
- 6.2 Is the proposed 2 year period of exclusivity an appropriate period to reward the innovation and allow for a return on the investment made?
- 6.3 Should multiple applicants be able to apply for exclusive use of the same new ingredients using their own data during the exclusivity period?
- 6.4 What other considerations should be taken into account in implementing the proposed incentive for innovation?

Protection for efficacy data from clinical studies

The proposal to introduce a new assessment pathway for complementary medicines is intended to encourage further research and development. If sponsors have supporting data, implementation of a new approval pathway may allow sponsors to have exclusive use of intermediate level indications that fall outside the permissible indications list. To be eligible for intermediate level indications, sponsors would need to submit an application with appropriate evidence for each specific product.

While most complementary medicines rely on information in the public domain, some complementary medicines also rely on data from their own studies which can be much more expensive to produce. The proposed approaches to establishing efficacy (see **Proposal three** above) under the new pathway will accommodate new products with new active ingredients, generic formulations as well as new uses for well-characterised active ingredients. This may not protect the resources invested by innovators who develop new products supported by direct clinical data (**Method 1, Proposal three** above) which could be used to establish bioavailability for subsequent products (i.e. using **Method 2, Proposal three** above) because such clinical data will generally be in the public domain.

²¹ A TGA compositional guideline is a summary of descriptions, tests and appropriate acceptance criteria (which are numerical limits, ranges or other criteria) that define the characteristics and specify the composition of an ingredient permitted for use in listed medicines.

Protection procedure

In line with the intent of this recommendation, it is proposed that a limited period of **data protection** will be provided to applicants of medicines approved via the **new pathway** who provide direct clinical data on the finished product formulation to establish product efficacy (see **Method 1, Proposal three** above).

Data protection could be provided in the same manner as currently applies to registered medicines under section 25A of the Act, which is for products containing information about new active ingredients only. Other applicants could apply for approval for a medicine with an identical ingredient / indication combination during the protection period using their own efficacy data from clinical studies. Dossiers demonstrating that the proposed product delivers appropriate bioavailability of components established to be efficacious (see **Method 2, Proposal three** above) may be assessed but will not be approved during the protection period.

For products that don't qualify for data protection under this proposal, there would still be a more limited first to market advantage for sponsors that undertake high quality product-specific clinical studies as all medicines approved through the new pathway must be supported by evidence relating to the finished product.

Timeframe

It is proposed that after a new product has been approved via the new pathway, the data protection will apply for a period of 3 years. The proposed duration of the data protection period is intended to reflect the significant investment of resources to prepare clinical data on the finished product formulation. The length of data protection is less than that currently afforded to registered medicines under section 25A of the Act that are required to undertake a greater level of research (i.e. safety, quality and efficacy data) in order to meet the evidence requirements. The data protection period will automatically lapse on expiry, with no provision for extension.

Additional considerations

Under the current data protection provisions that apply to registered medicines under section 25A of the Act, protection is not provided for new uses or new formulations of existing products. Furthermore, under section 25A of the Act, data protection is only available for information that is **not** in the public domain, yet one of the principles that guide the reforms is to strengthen consumer transparency by encouraging dissemination of evidence based research.

To promote innovation in the complementary medicines sector, consideration could also be given to implementing a modified form of data protection that would allow protection for published clinical studies that refer to a specific brand named product or specific formulation, including new studies involving an existing substance with new indications. This would provide incentives to the industry to improve the evidence base for complementary medicines and encourage use of the new assessment pathway.

Proposal nine: Protection for efficacy data

We propose that:

- A limited period of data protection is granted to applicants of products with new ingredients supported by direct clinical data on the finished product formulation.
- There would be a 3 year protection period



Protection for efficacy data

- 6.5 Is the proposed process and mechanism to provide data protection for efficacy data appropriate?
- 6.6 Is the proposed 3 year data protection period for efficacy data appropriate to reward innovation and allow for a return on the investment made? Is it excessive?
- 6.7 Should protection be available for new uses of existing substances and /or be available for information that is not in the public domain?
- 6.8 What other considerations should be taken into account in implementing the proposed incentives for innovation?

7. Implementation

Legislative and regulatory amendments

To implement the recommendations, legislative amendments to the *Therapeutic Goods Act 1989* (the Act) and the Therapeutic Goods Regulations 1990 (the Regulations) will be necessary.

It is anticipated that legislative changes will be needed to:

- establish three pathways (i.e. the **new pathway**) by which sponsors may seek entry of complementary medicines onto the ARTG
- allow the Minister (through a delegate) to make a determination, by legislative instrument, of indications permitted for use in listed medicines and to determine any requirements for the use of those indications
- establish a mechanism to amend the permitted indications list
- amend the applicant certification provisions to require sponsors to certify that any indication selected for their listed medicine is either an indication from the permitted indications list, or a more specific version of one of those indications
- implement a mechanism to grant an approval for a sponsor to use a label claimer for products that have undergone a pre-market assessment process and to specify the form of a label claimer
- implement mechanisms to incentivise innovation.

The conditions of inclusion on the ARTG and cancellation provisions that currently apply to listed and registered complementary medicines will also be amended to support these changes.

Transitional arrangements

Some of the reforms proposed in this consultation will have direct implications for products currently included on the ARTG. Where this is the case, transitional arrangements will be put in

place to provide industry with sufficient time to comply with the new regulatory requirements. We will consult with stakeholders on the details of the transition once the main elements of the reforms outlined in this consultation are agreed.

We are applying the following principles to guide the development of transitional arrangements to assist industry to comply with the new requirements:

- A transition period of **three years** from the commencement of the new legislative package is planned. A three year transition period would provide sufficient time for industry to bring their medicines in line with any new requirements that might apply to their products and will align with the transition period for Therapeutic Goods Order No. 92 – Standard for labels of non-prescription medicines.
- During the transition period, sponsors of existing listed and registered medicines will need to comply with the new provisions as follows:
 - sponsors of existing listed products with low level indications will be required to transition their products to the new requirements by selecting appropriate indications exclusively from the list of permitted indications
 - existing listed products with intermediate indications, including those with an existing restricted representation approval, will be required to transition their products to the new assessment pathway or to alternatively, choose low level indications from the permitted indications list
 - there are no transition requirements for currently registered medicines.
- We will seek to minimise the regulatory burden on industry by keeping compliance costs to a minimum. For example, we anticipate that:
 - sponsors of existing listed products who apply to update their ARTG entry to select permitted indications will not be charged an application fee during the first 18 months from commencement of the new legislative package
 - sponsors will be able to retain their existing AUST L number, in line with current arrangements.



Transition arrangements

- 7.1 Do you agree with the proposed principles to support transition arrangements?
- 7.2 What other factors should we consider?

Administration

Fees and charges

Our existing processes for the assessment of new ingredients and inclusion of complementary medicines on the ARTG (including application and evaluation costs) are fully cost-recovered as fees from applicants. Post market monitoring and surveillance activities are recovered in the form of annual charges. Full cost recovery (of the **new pathway** and applications for **permitted**

indications) is proposed to be consistent with existing practices, which align with the Australian Government Cost Recovery Guidelines²².

To recover the additional costs we propose to create:

- an application fee for assessing whether a medicine meets the eligibility requirements for assessment via the new pathway
- an evaluation fee for medicines that undergo pre-market efficacy assessment via the new pathway
- an application fee for assessing whether a proposed new indication meets the criteria for inclusion on the permitted indications list.

The proposed application and assessment fees for the new pathway will be less than the registered complementary medicines fees, as only the efficacy of the product will be assessed pre-market.

Assessment timeframes

Legislative timeframes will apply to the assessment of applications submitted through the new pathway and registration pathway. Timeframes will be developed once the regulatory requirements for the new pathway are confirmed, and after the TGA has completed pilot assessments.

The timeframes for the new pathway will be significantly reduced compared to registered complementary medicines, as only the efficacy of the product will be pre-market assessed.

²² Department of Finance 2014, Australian government cost recovery guidelines, July 2014, Third edition, Department of Finance, Canberra.

Attachment 1: Case studies

The types of medicines for which applications will be received through the new pathway are described below. These products contain only ingredients permitted for use in listed medicines, and have indications that fall outside of the permitted indications list.

Table 8: Examples of products suitable for evaluation via the new pathway

Product type	Example of products
Standard product (e.g. multiple active ingredients)	Method 1: A sponsor proposes to list a product consisting of 1000 IU of Vitamin D (cholecalciferol 25 micrograms) and 1200 mg calcium indicated for reducing the risk of fractures associated with osteoporosis. The sponsor has evidence from multiple clinical trials and a systematic review of the literature indicating that daily supplementation with the product reduces the risk of fractures associated with osteoporosis.
Single ingredient active	Method 1: A product contains 300 mg elemental calcium. The sponsor wishes to use the indication 'assists in the prevention of osteoporosis when dietary intake is inadequate' (this is currently an approved restricted representation). The sponsor can provide clinical evidence to support this indication.
Single ingredient active (immediate release only) with established bioavailability	Method 2: A product contains 450 micrograms of folic acid. The sponsor wishes to use the restricted representation 'prevents neural tube defects when used during the first trimester of pregnancy'. The sponsor can provide dissolution studies indicating that the product results in appropriate release of the active, and evidence supporting the indication.
Generic²³ product	Method 2: A product contains 250 micrograms of potassium iodate and 500 micrograms of folic acid. The sponsor wishes to use the indications 'for the treatment of iodine deficiency', and 'prevention of neural tube defects when used during the first trimester of pregnancy'. The sponsor can provide dissolution studies and bioavailability data indicating that the product is bioequivalent to a pre-existing evaluated supplement.
Product making high and low level indications	Method 1: A product contains 1000 mg Omega-3-fatty acid ethyl esters. The sponsor has evidence from multiple clinical trials on the active ingredient showing an improvement in dyslipidaemia when used as a supplement to an appropriate diet. The sponsor wishes to use the following indications: <ul style="list-style-type: none"> • Reduces cholesterol levels when taken as part of a healthy diet, and • Maintains cardiovascular health.

²³ A generic product is a medicine that, in comparison to another medicine that is approved or has previously been assessed: has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the medicine; has the same pharmaceutical form; is bioequivalent; and has the same safety and efficacy properties.

Product type	Example of products
Standard product containing a well-studied single-active proprietary ingredient (PI)	Method 2: A sponsor proposes to list a product consisting of 500 mg of dimethyl sulfone and starch PI formulation, and 500 mg of ascorbic acid. The sponsor has a double blind randomised controlled trial that they consider indicates that daily supplementation of the PI results in reduction of joint discomfort. The sponsor proposes to include indications for the supplementation of ascorbic acid and also has evidence that the PI and ascorbic acid have no negative interactions.

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Reference/Publication D17-26411