Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Evidence required to supportindications for listed medicines (excluding sunscreens and disinfectants) April 2012

The TGA is seeking comment from interested parties on the draft document 'Evidence Required to Support Indications for Listed Medicines (excluding sunscreens and disinfectants)' ('the document'). The document specifies the type of evidence required to support indications made for listed (low risk) medicines and will replace the 'Guidelines for Levels and Kinds of Evidence to Support Indications and Claims for Non-Registerable Medicines, including Complementary Medicines and other Listable Medicines'.

The TGA recommends that stakeholders use this form for submitting their comments on the proposed document.

Instructions:

All submissions must be accompanied by a completed cover sheet (the second (2) page of this document).

The form for the submission of comments is prepared in MS-Word format and should be saved as such (please do not save as pdf). Please use clear language when commenting.

Additional rows can be added to the table starting on page three (3) to accommodate more comments [Click in the last cell on the last line and press <tab>].

The document should be saved with appropriate title such as adding the name of the organisation to the beginning of the file title with a date: "ORGANISATION – submission on Evidence Requirements – dd mmm 2012".

Submissions made on the response form provided here should be emailed as an attachment along with the completed coversheet to Project Manager by email to ocm@tga.gov.au

Any questions relating to submissions should be directed to the Project Manager by email to ocm@tga.gov.au or by telephone to 6232 8725.

The deadline for comments is by close of business on Friday, 25 May 2012.

Consultation submission cover sheet

This form accompanies a submission on:

The document 'Evidence Required to Support Indications for Listed Medicines (excluding sunscreens and disinfectants)'			
Name and designation:			
Company/organisation name and address:			
Phone		Email	
☐ Yes ☒ No	I would like the comments I have provided to be kept confidential: *(Please give reasons and identify specific sections of response if applicable)*		
☒ Yes ☐ No	I would like my name to be removed from all documents prior to publication and not be included within the list of submissions on the TGA website. *(Please strikethrough whichever is not applicable)*		

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

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

Business in the therapeutics industry (please tick sector):

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

☐	Sole trader	☒	Business with 360 employee(s)				
☐	Importer	☒	Manufacturer	☐	Supplier	☐	Industry organisation
☐	Government			☐	Researcher	☐	Professional body
☐	Consumer Organisation			☐	Institution *(e.g. University, hospital)*		
☐	Healthcare Practitioner - please indicate type of practice						
☐	Other (please specify):						

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Comments

Overview

Complementary medicines have been used for many thousands of years. The chemical complexity and unique nature of complementary medicines are significant as they cannot be simply compared to single drug actives – as such using a drug model to assess their benefit can be very misleading. Drug models have been designed and created around single pharmaceutical actives – these can be studied through various stages from test tube to human clinical trials. The knowledge regarding herbal medicines, for example, has evolved to the present day through many thousands of years of traditional knowledge and experience of use which has been passed on through many generations. Present day advances has seen the improvement in the knowledge and understanding of complementary medicines as advances in science and the documentation of experience in using these complex materials - from the growing of the plants, to the manufacturing of finished goods, and finally to their use as supplements has greatly improved.

In much of the developing world, 70–95% of the population rely on these traditional medicines for primary care (WHO 2011). In addition to this it is widely accepted that complementary medicines such as, herbal materials, contain a large number of chemical actives in much lower concentrations than single active pharmaceutical preparations. It has been found that synergy can occur between these actives which cause an effect which is greater than what would be expected if the chemical actives were to be used at similar doses in isolation. For this reason it is also known that herbal medicines generally take longer to have an effect and are generally safer than higher dose single actives. As such complementary medicines commonly adopt a patient centered model of care rather than a disease centered model of care which single pharmaceutical actives adopt. For this reason, science such as clinical studies which are of short duration and test for specific biomarkers may not be applicable to herbal actives as they may require a much longer duration of study to establish an effect. In addition clinically significant effects may not be detected on very specific biomarkers. This is a prime example of why there may be many variations in clinical study outcomes for complementary medicines which use similar ingredients – and this is the very reason why using the simplistic model of conducting a literature search to assess the efficacy of a complementary medicine can be misleading.

Of additional concern is the lack of knowledge, expertise, resources and experience of the TGA proposing these changes and ultimately assessing and determining levels of evidence required for complementary medicines. Using a disease centred, ‘cure’ model of detection does not seem to be relevant for complementary medicines which have a unique mode of action and unique end targets and are used to support general health and well-being. As complementary medicines work in a much more complex and unique manner to single isolated actives – adopting a very disease specific clinical trial, for example, may not be an adequate way to assess a complementary medicine’s benefit. This in depth knowledge of complementary medicines may not be known by all so called ‘experts’ who may only have knowledge of how to conduct literature reviews. As such this vital information may be missed which is very concerning.

Lastly the World Health Assembly resolution 62.13, passed in May 2009 by the WHO Member States urges national governments to respect, preserve and widely communicate traditional medicine knowledge while formulating national policies and regulations to promote appropriate, safe, and effective use; to further develop traditional medicine based on research and innovation, and to consider the inclusion of traditional medicine into their national health systems. WHA 62.13 also urges Member States to cooperate with each other and to share knowledge while working to strengthen communication between conventional and traditional practitioners (WHO 2011).

It does seem that the draft document in question does not work to further develop traditional medicine research and innovation and does not consider the inclusion of traditional medicine into the national health system. On the contrary it seems to try to place complementary medicine into the specific conforms of allopathic medicine – which as would be expected, utilises very specific approaches which are not in line with the complementary medicine, patient cantered model of care. Couple this with the fact that TGA staff have limited experience and knowledge of the complementary medicines being assessed - we are very concerned that the end consumer will not benefit from this reform, as the information generated from the expert reports may not be accurate or a true reflection of the potential benefit to the consumer's general health and wellbeing – which is the intended use of the complementary medicines.

Comment on impact:
As the current draft stands – resources and expert personal would need to be increased at a significant cost to our organisation. In addition innovation would reduce significantly as resources and time spent on innovation would shift to completing expert reports. Lastly current product production and new product production will be significantly reduced.

Comment on implementation:
Significant time should be allowed for adjustment - up to 2 years depending on what changes are implemented as significant changes would require enormous amounts of work for the industry as a whole.

Specific document comments.

Page no./Reference	Issue	Comment
5/Overview	The subtext for which a listed medicine is characterised, namely as a low risk medicine, has not been altered from current guidelines; the proposed guideline however does alter the way in which evidence to support a listed medicine is assessed and presented. This creates a situation whereby the level of evidence required to support certain claims is above and beyond that which would be deemed relevant to a low risk medicine.	The TGA has considered listed medicines to be of low risk (ARGCM Part II, 6.1.1) and to only contain ingredients that have been assessed by the TGA to be of low risk and must be manufactured under GMP. In the current guideline the claims/indications being made by a listed complementary medicine can only be general or medium level. Listed medicines are defined in Section 1 of the document and range in Health Indications including, health maintenance and health enhancement to Illness Indications such as, but not limited to, management of illness and cure of illness. In this way the TGA have moved away from their previous model whereby indications and claims were grouped as general, medium or high level and are proposed to be considered equal in terms of required evidence to support a claim. Given the very broad terms for which a listed medicine may be appropriately indicated this lack of characterisation will inevitably restrict the use of commonly available and safe ingredients to consumers. As an example, any indication previously considered to be general, such as a health maintenance claim, will now require the same rigour of evidence to be presented as a claim to cure or treat, which was previously considered a high level claim. By this reasoning a claim that Vitamin C may assist with the maintenance of immune function will require a full literature review and compilation of an expert report to validate this claim. In this way the level of evidence and analysis required is beyond the scope of the types of indications allowed to be made, or that are intended to be made on listed products. In essence, the current characterisation of a listed medicine allows a sponsor to make structure function claims based on known biological activities of a compound, whereas the proposed guideline requires detailed literature review to assess the claims that have previously been sufficiently substantiated by rigorous scientific data such as that compiled in relevant monographs or textbook format, for example, that Vitamin C may enhance the function of the immune system.

		Thesuggestion that such a claim then requires collation of an expert report to substantiate the function of a compound questions the very integrity of such scientific knowledge. This then raises the question as to the relevance of the expert report when the evidence has been previously reviewed and is generally accepted within the scientific community. Take, for example, the use of a positive review published by the Cochrane Review. Is the expert then required to repeat the review and draw one'sown conclusions? It is a concern that the TGA is moving away from its previous model where the higher the level of claim being made needs to have higher levels of evidence to be able to substantiate the claim/indication. The requirement for the level of evidence to maintain general wellbeing or nutritional support to be similar to that to cure or treat a specific disease or condition does not match with the relevant risk associated with such claims.
7/1.3	"Level of evidence of a study must be considered alongside a number of other factors such as the quality of the study, how well the study is reported, the consistency of its findings to those from other studies, the clinical impact of the studies.	Listable medicines cannot be classified or considered as prescription medicines pertaining to clinical impact. For listable medicines efficacy data and medicinal effects are drawn from the available literature. Clinical impact data of herbal ingredients, for example, is not always available in the literature.Available literature and historical knowledge of the medicine as evidence should be sufficient.
7/1.3	" applicability of the results to the Australian population"	This is a very vague statement, if the study was performed overseas how will webe able to consider that data for listing for the Australian population, especially with the many cultural backgrounds that exist with the modern society that we now are.
7/1.3	"Requiring different types of indications to be backed by different levels of evidence of evidence creates a situation that is potentially confusing and misleading to consumers, and one that does not provide an incentive for sponsors to market products backed by strong supportive evidence."	The current guidelines already have requirements for indications to be balanced, relevant and of sufficient quality. The level of evidence in a general level claim may be lower but this does not mean that it is of any less balanced, relevant or of lower quality. The proposed guidelines do not distinguish between level of evidence determined to be of level, 'a', 'b', or 'c' in strength and so, contrary to the statement provided in the proposed document, does not create any more transparency and therefore does not assist the consumer in making more informed decisions, nor does it reduce confusion. It could also be argued that by making the changes as drafted it may create potential confusion and misleading of the consumer based on all

		indications/claims being treated equally irrespective of the claim.
7/1.3	Indications may be better classified according to type of supporting evidence and the type of health benefits expected, this approach maximises transparency and ensure that consumer are able to make informed choices about the product they decide to buy.	The data used to support indications is not generally available to the general public so how this maximises transparency to the consumer is not clear. Consumers are already in a position to make informed choices about the products they can buy through their current access to a healthcare professional.
9/2	In order for a listable indication to be supported by evidence, the following criteria MUST be fulfilled: … It needs to be clear in terms of the biological/clinical factor affected and the expected benefit. It must be linked to a defined and sufficiently characterised ingredient or group of ingredients.	In relation to plant materials the range of evidence currently available may not have elucidated as to the specific chemical factors likely to produce a biological effect however this is not to say the effects are not evident. An example of this would be the clinical effectiveness of St Johns Wort in mood disorders in which there is sufficient evidence to support this claim however it is not clear as to the exact physiological mechanism of action or ingredient group responsible for the effect. Using such a simplistic model for a complex ingredient such as a herbal component is not realistic or adequate.
9/2.1.1.1	**2.1.1.1 Characteristics and qualifications of an 'expert'** The author of the expert report required for support a listable scientific indication must have both clinical and critical appraisal skills. A scientific expert will have completed, as a minimum, the following: a. a tertiary degree (of at least three years duration) in a health profession; **and** b. at least one of the following i. a course in critical appraisal or biostatistics from a tertiary institution (this could include a short course or a component of a masters); or ii. a PhD in a scientific or health related discipline; or	Whilst we agree an "expert" should hold appropriate qualifications to conduct a review of literaturefor high level claims, the TGA is not taking into account experience or relevant qualification into the ingredient being studied. In this instance the requirement for the level of qualification is going well beyond the scope of the desired outcome of listed medicines. Additionally the cost that would be incurred by sponsors to compile such expert reports for each ingredient in each product would no doubt render the product financially unviable. It is also important to note that by these standards many naturopaths working in the industry with many years' experience and an extensive knowledge of these ingredients would not fall under the definition of an expert, whereas their counterparts may have no knowledge of the ingredients for which they are assessing.For listed products the requirements for the "expert" should be in line with the requirements for those of the "approved person" in regards to release for supply.

	iii. a specialist medical qualification.	

10/2.1.1.2	Expert report	The current guidelines and the ARGCM only have a requirement for an expert report for registered medicines. As no change to the level of risk has been determined for listed medicines there is no acceptable reason to increase this requirement to such low risk medicines. Not only would there be difficulty in the industry of qualifying to be considered an expert the cost of providing a report would be considered great for the level of risk involved. If the evidence was to be subject to a review by the TGA would the TGA itself have access to appropriately independent experts to provide a timely review without increasing the cost of any process to cover for this requirement.For listed products the requirements for the "expert" should be in line with the requirements for those of the "approved person" in regards to release for supply.
11/2.1.2.1	**2.1.2.1 Characteristics and qualifications of an 'expert'** The author of the expert report required for support a traditional listable indication must have clinical skills, detailed knowledge of the relevant healing paradigm, and the ability to critically asses the relevant literature. An expert in the assessment of evidence of traditional use must have completed, as a minimum, the following: c. a three year tertiary degree in a health profession; **and** d. at least one of the following i. five years' experience as a practitioner or researcher in the relevant traditional medicine paradigm; or ii. five years' experience in an advisory or regulatory role related to the relevant traditional medicine paradigm; or iii. a PhD involving study of the relevant traditional medicine paradigm.	Whilst we agree that an "expert" should hold appropriate qualifications in order to assess traditional evidence, the new guidelines will mean that industry professionals who have been assessing and researching medicines may not hold sufficient qualifications to be considered an expert. Again, the outsourcing of such an expert will render many products financially unviable for sponsors. Again does the TGA have the same access to such experts that would be considered appropriately independent and again without increasing the cost to industry? For listed products the requirements for the "expert" should be in line with the requirements for those of the "approved person" in regards to release for supply.

11/2.1.2.2	Expert report	Refer to 10/2.1.1.2
12/2.2	**Evidence required to support listable indications** …Because of the nature of evidence of traditional use, traditional indications **must not** imply efficacy.	An indication or claim supported by traditional evidence, regardless of wording, will imply efficacy. The very nature of the claim, for example "Traditionally used in Traditional Chinese Medicine to reduce symptoms of a cold" will imply to the consumer that the product will reduce the symptom of a cold. This Section of the document creates some ambiguity as to how traditional claims can be made, if at all.
13/2.2.1	The assessment of evidence **Efficacy measures: the results of scientific studies must be assessed for statistical and clinical significance.**	Assessment of clinical significance is highly subjective and not straight forward and as such most clinical studies do not include assessments for clinical significance. As such the method by which clinical significance is required to be determined will in most cases be impossible due to a lack of reporting on required parameters. A well designed and executed study with statistical significance should not be ruled out due to a lack of reporting on clinical significance. While understanding the importance of clinical significance to high level claims (registered medicines) it has less implications to listed medicines where low to medium claims are made to alleviate symptoms as opposed to treating or curing a disease.
14/2.2.2.1	It is recommended that the help of a librarian is sought when conducting the literature search.	Given the criteria required to qualify as an expert it may be assumed that the expert may have sufficient skills in conducting a full and adequate literature search. As such utilization of a librarian for assessment of the full complement of clinical data on a given material may be an unnecessary and costly step.

16/2.2.2.3	**Assessing the relevance of evidence to listable indications** **Relevance to health benefit** Indications describe beneficial effects on biological or clinical targets. All (and only) evidence that directly relates to the target described in a listable indication must be considered when assessing the evidence base for a listable indication. Evidence relating to a particular clinical outcome, physiological process or health benefit cannot be drawn from data describing different clinical outcomes, physiological processes or health benefits (even if these are considered to be related).	Restricting health related benefits may cause scientific information to be presented in a manner that is not clearly communicated resulting in consumers being confused and potentially misusing the product. For example emotive claims such as potential improvement to lifestyle due to improved mobility, which may be a related health claim, will be restricted.
18/2.2.2.3	**Study duration**	The minimum study duration for a weight loss claim is 6 months. A short term study with statistical and potentially clinical significance, which has demonstrated weight loss over a 3 month period for example, should not be considered unacceptable simply because there is no data to support a longer term weight loss period. This should only be considered in relevant in the context of a weight loss claim with a claim for maintenance of healthy weight. Claims could be worded in such a way that consumers are aware of the short term effect of the ingredient.
18/2.2.2.3	***Relevance to the proposed medicine*** When evidence relates to a herb or herbal substance, the species (and subspecies if applicable), plant part, method of preparation and processing, the equivalent dry weight and the dose of active component used in the evidence held must be highly consistent with that of the herb or herbal substance in the medicine.	This information in its entirety is very rarely, if ever, included in a clinical study report. If assessed as part of a larger body of evidence which produce consistent outcomes from various clinical trials using various materials and methods of preparation studies should not be excluded based on lack of extraction details.

19/2.2.2.3	***When evidence supports a listable indication for one or more ingredients in the medicine (but not the medicine as a whole) indications*** *must* ***specify the ingredients for which evidence is held. Indications must only refer to medicines/substances for which a favourable evidence base exists (as described in subsequent sections). In order to establish the relevance of medicine to indications that relate to combinations of active ingredients, all studies included must involve the same combination of ingredients at comparable doses.***	This paragraph is ambiguous and already to some extent enforced however clarity is required as to whether this is intended for application to on pack indications because such differentiation would be impractical. Indicating the specific ingredients responsible for certain claims or indications would also be impractical for multi component formulas e.g. multivitamin and mineral tablets.
19-20/2.2.2.3	**Relevance to target population** For these reasons, it is unlikely that study populations with baseline biomarker levels greater than 10 to 15 per cent above the accepted upper limit of 'normal' would be considered relevant to support indications relating to favourable modulation of measurable biomarkers of disease in the healthy Australian population. **For studies that involve specific cohorts (e.g. subjects with a disease) rather than the target group for a claim (e.g. the general population), it is the responsibility of the expert to provide an evidence based justification that results from a study group other than the target population are generalizable to the target population. This process must consider biological factors as well as environmental and behavioural factors including the influence of health practitioner intervention which may differ**	Studies limited to subjects within 10-15% of "healthy" biomarkers are rare and financing of any new studies would not be viable as the results elicited are of no commercial benefit, given the results can only be used to make claim for health maintenance. Further to this some current food products make stronger claims, for example margarine containing phytosterol esters can claim to lower cholesterol.

	between healthy and unwell populations.	

21/2.2.2.3	**Ethnic, cultural and social factors** **The characteristics of study participants must also reflect the characteristics and lifestyle of the target population for the medicine. Consideration of genetic, ethnic and socio-cultural factors is important when assessing the relevance of scientific evidence used to substantiate indications as differences in any of these may results in discrepancies between results reported in study data and expected results in an Australian population. The Australian population is culturally and ethnically diverse. Scientific data obtained from studies conducted in homogenous ethnic populations may be limited in their relevance to the general Australian population. Factors such as diet, lifestyle, support networks and religious beliefs may all impact on the generalizability of study findings.**	Given the ethnic diversity of the Australian population one could conclude that studies from various parts of the world would be generalizable to the population. Additionally any factors such as diet, lifestyle, support networks and religious benefits are likely to have not been discussed in the clinical study findings as quantitative research, by definition does not consider such parameters.
31/2.2.2.6	**Assessing the balance of evidence** **If a grade C is achieved, additional qualification of the indication may be required in order to ensure that consumers remain informed regarding potential limitations of the evidence**	Grade C evidence is satisfactory to support the indication and all relevant evidence will have been included in the expert report leaving no need or scope for additional qualification.
34/2.2.3.2	**Level of evidence** **Texts such as the Natural Medicines Comprehensive Database, Natural Standard, Physicians Desk Reference, general textbooks and scientific journal articles (other than papers reporting original ethnobotanical research) cannot be used to support traditional listable indications.**	These references and textbooks are written histories of traditional use and in many instances the original texts may not be readily available, thus secondary references should be included as allowable references for traditional evidence.

34/2.2.3.3.	**Relevance to health benefit** Indications must remain true to the context of use from which substantiating evidence has been derived and must refer to a 'tradition of use'. When traditional use is limited to a particular paradigm or geographical region then the paradigm/region must be referenced in the indication. Terms used in traditional listable indications must be consistent with those referenced in the traditional evidence source and must **not**: reference specific anatomical, physiological or pharmacological effects that are not envisaged within the paradigm and/or require scientific substantiation such as stimulation or modulation of the immune system or antioxidant functions reference conditions that cannot be diagnosed within the identified healing paradigm such as the maintenance of normal glucose levels, blood pressure or cholesterol **be interpreted or extrapolated to infer benefits that were not readily recognised within the traditional paradigm such as weight loss, addiction cessation and providing specific vitamins, minerals or essential fatty acids**	It is important that consumers understand the indications for which the product is intended and by limiting communication to the specific traditional indication consumers will be confused as to the products purpose. For example in Traditional Chinese Medicine systems a claim relating to chi may not be understood. Considering the indications will be compiled by an expert in the paradigm, they should be able to extrapolate the evidence into laymen's terms that is relevant and will be understood by the general Australian population.
40/2.2.4	Potential clashes between traditional and scientific evidence Products with combinations of active ingredients, some of which have a history of traditional use and others which do not, cannot be regulated as traditional medicines.	This requires clarification; combination product containing one herb with scientific evidence and another with traditional evidence is allowed as long as the scientific claims are in context and differentiated from the scientific ones otherwise potentially rendering the inclusion of the herb with traditional claims pointless.

Recommendations:
As an organisation we encourage an update of the current levels of evidence documentation. However we propose that the current documentation should be retained and used as a base to build upon. We propose changes be implemented to make the current guidelines clear, more transparent and easier to follow.

In addition to this we encourage the allocation of extra resources to the TGA so that the TGA can be more transparent and more swift in responding to industry concerns.

We strongly believe that creation of a new draft document and system for complementary medicines, as is proposed, will cause more confusion and will unnecessarily and negatively affect the industry and consumers.

Further to building and improving from the current regulations we strongly believe that there should be more encouragement for innovation and research from the TGA to the industry. This may be enhanced by providing more incentives to the industry for listing new ingredients and conducting research – such as granting exclusivity periods and considering data protection. These models are currently being used successfully in other countries such as China and we strong encourage the TGA to seriously consider these actions.

Regards,