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Dr Cheryl McRae
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Submitted via email to: complementary.medicines@health.gov.au

Dear Dr Cheryl McRae,

Consultation: Proposed update to the evidence guidelines for listed medicines

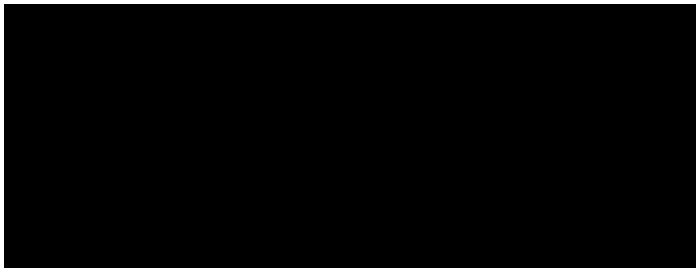
CHP Australia is the leading voice and industry body for manufacturers and distributors of consumer healthcare products, which includes non-prescription medicines. We strive to advance consumer health through responsible Self Care. Our key priorities for the industry include improving health literacy, growing the consumer healthcare products industry and increasing access to medicines where appropriate.

CHP Australia welcomes the opportunity to provide further feedback in the proposed update to the evidence guidelines for listed medicines (the Guidelines). We acknowledge the substantial amount of work that has taken place in the lead-up to this public consultation to facilitate input from industry to ensure the Guidelines remain workable and pragmatic. We note that the context of this proposed update was to improve readability and clarity of the document, and not to change the evidence requirements for listed medicines. For the most part, the background work between industry and the TGA has stayed consistent with this objective, however there are concerns that some aspects of the proposed document substantially increase the regulatory burden.

Responses to the individual sections of the Guideline and specific consultation questions are provided on the following pages.

CHP Australia remains available to provide any further information or assistance as needed.

Kind Regards



Section 1 – Introduction

Q.4 From the information provided in section 1, did you understand why a sponsor needs to provide a critical analysis of their evidence in an evidence package for their listed medicine?
Yes/No – Please describe

Yes.

The rationale provided around the value of a critical analysis of the evidence package is clear, however there are still concerns about the increased regulatory demand that this introduces. There is also uncertainty about whether a full critical appraisal would be required in all circumstances e.g. for non-specific indications or indications based on traditional use or only when the body of evidence demonstrates a range of outcomes and the sponsor needs to justify why their indication is supported by the overall balance of evidence.

There are two aspects of critical analysis that are discussed in the Guideline, the critique of the suitability of an individual piece of evidence and the critical appraisal of the body of evidence. It is sometimes difficult to distinguish which aspect of the critique is being discussed at each point of the Guideline, and at times these present conflicting expectations.

Q.5 Do you have any other comments or feedback regarding section 1?

Overall the revised presentation of the Guidelines is clear and easy to follow, there are concerns about the level of expectation presented within the Guidelines and the increased regulatory burden associated with the critical appraisal requirements.

There is some uncertainty regarding the scope of the document. The previous evidence guidelines were specific to listed complementary medicines; however these guidelines appear to capture all listed medicines (with an exclusion stated for sunscreens and listed assessed medicines). Some clarity around how the TGA expects these guidelines to be applied to listed OTC products would be helpful, particularly whether the publication of the Guidelines will impact on the existing dossier requirements and presentation expectations for listed OTC medicines. It should also be noted that the Assessed listed medicines evidence guidelines do refer back to the current listed complementary medicines evidence guidelines for secondary indications, so the delineation between these two documents is not entirely clear.

The Guidelines also attempt to distinguish evidence of efficacy from effectiveness; however this presents a paradox as many of the indications that the Guidelines are describing how to support are not typically able to be demonstrated in clinical studies. There are concerns that the Guidelines are describing an ideal evidence framework that is not consistent with the type of evidence actually available for many listed medicines. In this regard, producing critical appraisals for an evidence dossier for indications that are not consistent with the design for clinical studies is layering additional levels of administration and technical appraisal on top of data that simply will not fit. For products and indications that fit within a clinical research model, while there are concerns with the regulatory burden this full critical appraisal introduces, there is a certain rationale, however for indications that are poorly served by clinical trial design, there are concerns that this framework adds additional complexity for limited value outcomes.

Section 2 – How to find evidence

Q.6 Do you find the information and links presented in section 2 helpful in guiding you to conduct and document a literature search?
Yes/No Please describe why or why not

Yes.

The information is somewhat helpful, although there is still uncertainty about the expectations for literature reviews for non-specific and traditional indications where there is a reliance on established texts. While the information clearly communicates how to conduct and document a literature search there is still concern about the suitability of these requirements for a number of listed medicines where the indications are not consistent with a clinical research framework.

Q.7 Do you have any other comments or feedback regarding section 2?

The claim that "For many traditional medicines there has been little quantifiable scientific research, scientific assessment or scrutiny undertaken on the medicine's mode of action or effect" is not helpful and should be removed. It is fair that traditional use does not substantiate scientific indications, however these are two distinct arguments that should not be conflated. Many traditional ingredients have undergone extensive scientific study, and some of these are now commonly accepted pharmaceutical ingredients. This representation also implies that there is little known about traditional ingredients, which undermines the TGA's role in ensuring that ingredients for listed medicines are of suitable quality and safety.

The Guidelines indicate that "A literature search is the first step in compiling a literature-based evidence package". This appears to suggest that even if established texts are being used to support non-specific indications or traditional indications, that a full literature review would still need to be conducted. For instance, even if the available data has been reviewed by an expert panel to develop a European Medicines Agency herbal monograph, that this work would still need to be duplicated by the sponsor. There are concerns

that the expectations set out in the Guidelines are designed from the perspective of meeting a set criteria list rather than based on activities that represent value. There are also concerns that the Guidelines appear to create the expectation that the sponsor will essentially be a peer reviewer, conducting the critical analysis and evaluation, which requires a level of technical expertise that is usually reserved for academic researchers.

Systematic literature reviews are often not meaningful for indications that are difficult to demonstrate in a clinical setting. Many indications do not have a clear research question or may be difficult to measure, however the Guidelines only identify the acceptance of non-systematic literature reviews for evidence of traditional use and some non-specific indications relating to health maintenance. This suggests quite a large gap between the types of indications expected to be supported by systematic literature reviews and the number of indications that are not measurable through clinical means. A greater degree of flexibility needs to be provided regarding the acceptability of non-systematic literature reviews.

The PICO model is useful for a number of clinically relevant research questions; however this can have limitations in the context of listed medicines. For instance, PICO is limited when looking at herbal ingredients as while a question may be framed around a herbal species, there is a lot of variability in preparation and dosage that can influence the outcome of the study. These aspects are often not easily captured in inclusion and exclusion criteria and can confound the results.

Section 3 – How to assess evidence

Q.8 Are the factors that are important for assessing relevance and quality of evidence sources clear and easy to understand and follow?
Yes/ No Please describe why or why not

Yes.

For the most part these are clear, however there are concerns with the level of technical expertise required to conduct the analysis as stipulated. This suggests a huge amount of work and technical expertise for the sponsor/agent to be

critically appraising each individual piece of evidence and then collating into a balanced and prioritised body of evidence.

There are also concerns about duplication of effort, such that the differentiation between the critical assessment of the evidence and the critical appraisal of the body of the evidence becomes quite indistinct while also creating conflicts about how to balance these two factors. If the individual piece of evidence is critically appraised as being relevant with low risk of bias there is no clarity regarding how is this to be weighed against the overarching body of evidence that may be more generalised.

Q.9 Do you find that the removal of the terms 'primary' and 'secondary' sources and replacement with the concept of relevance and quality of evidence sources provides greater clarity when selecting evidence sources to include in an evidence package?
Yes /No Please describe why or why not

Yes.

No concerns have been raised regarding the removal of 'primary' and 'secondary' evidence source terminology and re-categorisation as category A, B or C.

Q.10 Do you have any other comments or feedback regarding section 3?

There are concerns that the update to the Guidelines does not provide the level of clarity that industry has been seeking for traditional herbal ingredients. For instance, cross-referencing to the *Guidance on equivalence of herbal extracts in complementary medicines* is not ideal as these two documents serve different purposes. The interchangeability of herbal extracts in a product introduces different considerations to those required for efficacy data and reinforces an over-reliance on herbal chromatograms for demonstrating equivalence of herbal ingredients that isn't always meaningful.

The Guidelines describe the expected characterisation of herbal substances for active ingredients from scientific evidence, however there are concerns that the level of assurance that the materials are comparable is becoming unattainable. The Guidelines indicate that many trials inadequately describe or characterise

the composition of the herbal treatment, however, the Guidelines then go on to require the sponsor to conduct a full comparison of the materials and justify how any differences are not going to impact on the efficacy of the product. While it is important to ensure that the evidence used is relevant to the product being supported, there are concerns that TGA are requesting an impossible justification.

Other specific comments from members, include:

- We note that the concept of precision is introduced in section 3.2 without any definition or discussion. Given that this is a specific term in research methodology, a definition would be advantageous.
- Poor study design/poor selection of placebo/poor research question – these can all impact on the value of Category A evidence. Just because a study may have a lower risk of bias from an evidence hierarchy perspective does not mean that these are relevant studies.
- States "Depending on your chosen indication, cohort and case-control studies may not be enough to substantiate the indications (i.e. efficacy) due to the higher risk of bias associated with these types of studies" – further explanation of this point needed as it is not clear how the indication influences the risk of bias.
- The information provided on evaluating the study design for scientific evidence is clear, however this represents a limited and best-case scenario for evidence. In the cases where there are relevant clinical studies that align between the research question and the indication, with consistency in the critical research parameters, the evaluation is straight-forward. 3.2.2.5 is fine, however it needs to be accepted by the TGA that this is not the most common scenario for efficacy data for listed medicines and will only work for those ingredients/indications where there is a clear, measurable outcome that does not rely on studies in populations with serious health conditions.
- Introduction of new tools for assessing risk of bias – these are fine in certain contexts, however there are limitations for listed/complementary medicines.
- Discussion of clinical significance vs statistical significance – further clarity requested on how to determine what is a reasonable 'degree of health benefit' for the consumer.

Section 4 – How to use evidence

Q.11 Do you find the decision tool helpful for classifying indications? Yes/ No Please describe why or why not

Yes.

Feedback is that it is still difficult to determine whether an indication is specific or non-specific. The tool is somewhat helpful, however it can still present challenges and inconsistent outputs depending on the user's level of experience or interpretation.

Q.12 According to the decision tool, low-level biomarker indications (such as 'helps maintain/support healthy cholesterol' and 'helps maintain/support healthy blood sugar/glucose') are classified as 'non-specific', while previously these indications have been generally regarded as specific. Do you agree that the efficacy of listed medicines with these indications should be supported by Category B or C type evidence only? Yes/No Please describe why or why not

Yes.

These indications fit within the framework for non-specific, assuming that the presentation of the product does not alter the intent of the indications, so it would make sense for these to be classified as non-specific. The challenges faced by industry in trying to supply suitable scientific evidence to support these as specific indications has also been acknowledged. "Maintenance of a biomarker in a normal healthy population" is just not consistent with a suitable primary outcome for a clinical trial. Specific comments from members, include:

Further advice is sought on the statement that "Because of the continuum between health and disease, all biomarker and risk reduction indications for listed medicines should include a disclaimer that recommends consumers to consult a healthcare practitioner if they are concerned about their health status". We note that this is a direct reproduction from the previous version of

the evidence guidelines, however query if this advice is included in any other TGA documents or flagged within the listing system.

Q.13 Does section 4.4.2. clarify when it might be appropriate for a supplement to only provide a minimum 25% of the Recommended Dietary Intake (RDI) (of a specified vitamin/mineral/nutrient) without the sponsor needing to hold additional evidence sources to support their medicine's indication? Do you agree with this proposed clarification?
Yes/No Please describe why or why not

No.

There are some concerns with the current proposal that this may still be too limited in its applicability, allowing only the two supplementation indications to be supported at 25% of RDI.

There are a number of indications that relate to the functional role of vitamins/minerals/nutrients and providing 25% of RDI still contributes to these health outcomes. For example, the claim vitamin B2 (riboflavin) supports energy production (indication: maintains/supports energy production) – the functional role of vitamin B2 in the body relates to energy production and carbohydrate metabolism, and without adequate quantities these systems do not function efficiently. This is a non-specific indication and supplementation of vitamin B2 (riboflavin) of at least 25% of RDI would assist in maintaining this function. It does not appear that TGA would accept an indication for "supports energy production" for vitamin B2 when provided at 25% of the RDI for this vitamin.

There are also concerns about the removal of the guidance around 10% of RDI supporting content claims for vitamins/minerals/nutrients. This section of the Guidelines has previously contributed to a lot of confusion about when claims regarding the presence of a vitamin/mineral are a "content claim", and when it becomes a supplementation claim. We note that the draft Guidelines refer to "source of magnesium" as a supplementation claim that would require 25% of the RDI of the mineral, however some clarity is requested over the distinction. While content claims related to 10% of RDI of vitamins/minerals have historically been confusing, it will result in a significant change to the evidence requirements if this is now removed from the Guideline. The context of the current consultation is that there were not to be changes to the evidence

requirements, however removal of all information around 10% of RDI would have a substantial regulatory impact on a number of products on the ARTG.

Q.14 What do you interpret the indication 'maintain vitamin levels' to mean?
It will just top up what vitamins I get from my diet
It will provide my full recommended daily allowance
Other (please describe below)

While this question appears to be focused on understanding consumer perceptions, CHP Australia would like to reiterate that listed medicines for vitamin/mineral/nutrient supplementation are required to carry a label statement indicating either that supplements can only be of assistance if dietary intake is inadequate or that supplements should not replace a balanced diet. Any presentation that suggests that supplements can provide a complete source of nutrition is not permitted.

Q.15 Do you find the evidence requirements for weight loss indications clear and easy to understand?
Yes/No Please describe why or why not

Yes.

The requirements for weight loss indications appear to be consistent with the previous evidence guidelines, noting the inclusion of a new indication with its specific parameters for use has been added.

Further clarification is requested regarding the "use of terminology that implies weight loss" and whether these are taken by the TGA to always imply weight loss or if the interpretation is dependent on other contextual factors. While some of the terminology is extremely difficult to separate from weight loss, other indications are likely to be more ambiguous/context dependent e.g. metabolism, body composition/fat mass or appetite suppression.

Q.16 Do you have any other comments or feedback regarding section 4?

There are ongoing concerns about the distinction between specific and non-specific indications, and the difficulty that these create in establishing a functional evidence hierarchy. We recognise that removing this distinction is beyond the scope of this review of the evidence guidelines. However, there are concerns that the evidence guidelines are overly complicated by trying to differentiate between specific and non-specific, literature review and indication categorisation, and critical appraisal of individual evidence sources vs critical evaluation of the body of evidence. While the current document is clearer and easier to read, there are concerns from industry that this will not result in a practical improvement in compliance. There are also concerns that the expectations presented represent such a narrow "gold standard" of evidence that there will be an effective increase in non-compliance as the TGA's expectations are going to be difficult to meet for many products.

Specific comments from members, include:

- Label statement regarding "this traditional use is not supported by scientific evidence" creates some concerns, such as how to weight scientific evidence when it is not reflective of the traditional modality or preparation i.e. the relevance of the scientific evidence. Additionally, is this the only reference to this label statement, or is it reinforced within the listing system or other labelling requirements.
- The claim that combining herbal ingredients with homoeopathic is not consistent with the paradigm and may alter the efficacy of the ingredients is not based on any evidence. There are many combination products on the ARTG and this statement suggests that unless the sponsor can provide some compelling justification for the formulation that the evidence for the product may not be considered substantiated. While concentrated herbal extracts are not used in the same way as homoeopathic products, there is no evidence that the combination is less effective than the individual products. This statement in the Guideline should be removed.
- Statement that "traditional indications are not classified into 'specific' and 'non-specific' as the evidence expectations for non-specific and specific traditional indications are fundamentally the same" should be removed. This reintroduces the concept that traditional indications could be classified as specific or non-specific, however earlier in the Guidelines it is made clear that the terminology used for many traditional indications does not align with a specific vs non-

specific division. This new statement contradicts the earlier statement and creates confusion about the distinction between specific and non-specific indications.

- Concerns that the specificity of some indications is still being determined by comparison to other permitted indications. It is concerning that it has still not been possible to establish clear and objective definitions for specific vs non-specific.
- Many studies state that further investigation is recommended even though they establish an effect for the medicine, as this is in the interests of the researchers, and this statement should not be taken to invalidate the study outcomes/value of the research.

Section 5 – How to document and present evidence

Q.17 Is it clear what the TGA might consider as gaps and discrepancies in the evidence source?
Yes/No Please describe why or why not

Not Answered.

It is difficult to distinguish between the gaps and discrepancies for an individual piece of evidence subject to a critical assessment and the details to be considered as part of the final critical appraisal of the evidence package. There seems to be a large amount of duplication of workload. The critical appraisal requirements being introduced also require a high level of technical expertise to be able to assess to a level that is likely to be acceptable by the TGA. There are concerns that this level of requirement is creating an unduly high standard.

Q.18 Is it clear why it is important to include a persuasive critical appraisal of the body of evidence in an evidence package?
Yes/No Please describe why or why not

Yes.

The need to critique evidence and provide a justification for any gaps is clear, however there are concerns about the level of expectations being required.

The critical appraisal requirements are a new section of the Guidelines. While the previous guidelines did present an expectation that the body of evidence is considered, this new section expands substantially on these requirements without really clearly identifying how the balance of evidence should be assessed. The expectations being presented appear to imply that each piece of evidence is evaluated for bias and relevance, and these are somehow appraised to identify how each of these studies should be weighted and the relative importance given to each piece of evidence. This is essentially requiring that the sponsor conduct a detailed systematic review of their evidence package, which is a highly technical process. While CHP Australia understands the value of appraising an evidence package and providing justification for any discrepancies or data gaps, the Guidelines are overly complex in the expectations.

It needs to be clearer which parts of this section are simply talking to the presentation expectations of the evidence assessment described under Section 2 and which parts relate to an overall critical appraisal of the body of evidence.

Q.19 Do you have any other comments or feedback regarding section 5?

Specific comments from members, include:

- The limitations for the example for how to present evidence is that this is focused on a single active product and the requirements become exponentially more complex for multi-ingredient formulas. While we understand the value and benefits of presenting a critical appraisal for the evidence package, the presented examples are difficult to apply and introduce a substantial amount of additional work.
- Introduction of a section on cautions and contraindications raises concerns about the expectations from the TGA about what this information may capture and how it is expected to be used/presented. For instance, are these as per the ingredient restrictions from the Determination/SUSMP or should these be drawn from other data. Does the inclusion of a caution or contraindication in this section result in an expectation that there is a label statement that reflects this information? For listed medicines, labels are not reviewed pre-market and there has historically been a position from the TGA that sponsors should not typically be adding warnings that are not required through legislation e.g. validation requirements in the listing system. If a range of warnings end up being added to labels without any regulatory oversight this could result in

excessive warnings that are not meaningful to the consumer, consumer confusion if comparable products don't carry the same warnings or could reduce the legibility of other critical label information. The addition of warning statements not underpinned in legislation could also result in further compliance issues if sponsors are to add warnings that are restricted representations without the suitable approval. [CHP Australia does not seek to limit a sponsor's ability to add a warning statement where this is assessed as being necessary, however we do have concerns about the implications of the current "cautions and contraindications" in the Guidelines without any further explanation or without clearly setting expectations for what this means.]

- Further consideration of how life cycle management should be maintained for listed medicines would be helpful. The Guidelines identify expectations that the body of evidence is regularly reviewed, and new information evaluated to ensure that the product remains relevant. The Guidelines do not provide any instruction on the frequency of this review, or when to consider new and contradictory information as relevant to the product.
- Figure 6 states that "The evidence source should represent a balanced view of the body of evidence" however this overstates the scope for an evidence source. Figure 6 also appears to suggest that sponsors should be re-evaluating monographs, reference texts and international regulatory authority articles that have typically been prepared by expert committees. There are concerns with the extent of work that is being expected by the TGA, and the devaluing of existing expert information.

Appendices

Q.20 A case study showing an example evidence package for vitamin B12 has been developed for the Guidelines, demonstrating an example critical appraisal format that sponsors may wish to follow for their own medicine evidence package. Do you have any comments or feedback on the example evidence package for vitamin B12?

The inclusion of supplementation indications in the example is confusing as there is no explanation of how these fit into the critical appraisal. There is also no justification provided for the example only including English language papers. While this is likely justifiable given the amount of data available, the Guidelines specifically state that non-English language papers should be included unless a justification is provided as to why they're not.

There are also concerns about the extent of data that TGA is expecting to be assessed for a fairly standard indication relating to supplementation. The outcome of the search of systematic reviews identifies 30 papers, while the search of randomised controlled clinical trials identifies 27 papers remaining after each of the clinical trials have been evaluated for Risk of Bias (ROB). The ROB analysis typically requires a full text of the study to be available to assess each of the possible domains of bias, as the detailed information required is not available in an abstract. Given that only a limited number of studies are published in full as open access, this represents a huge cost burden for industry. While it is important that indications are substantiated, CHP Australia holds concerns that the critical appraisal framework presented introduces a disproportionate cost compared to the value that adds.

Additional examples of an evidence package for the following indication types would be helpful:

- Containing herbal material(s) with a traditional indication
- Containing herbal material(s) with a specific indication
- Containing herbal material(s) with a non-specific indication

There would also be value in seeing an example where a justification needs to be provided in the case where the evidence found does not completely match the requirements in the Guidelines.

Q.21 Is there a case study that you would like to see included in the Guidelines that would help you better understand the evidence requirements for listed medicines?

Further examples of sufficiently supported non-specific indications for vitamins/minerals/nutrients would be helpful in understanding the TGA's expectations. For example, further examples that address non-specific "maintain/support" type indications.

Q.22 Do you have any other comments or feedback on the Appendices of the proposed Guidelines?

Feedback was that Appendix 1 is extremely limited and it would be helpful to see a wider range of more contemporary resources listed. For instance, there are a number of academic texts used in tertiary courses that could be helpful to reference.