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Submission to the TGA
Consultation on the draft evidence guidelines for Listed Medicines.

31st March 2022

Complementary and OTC Medicines Branch
Therapeutic Goods Administration
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Dear Complementary and OTC Medicines Branch,

Thank you for providing the opportunity to industry to consult on the proposed Draft Listed medicines Evidence Guidelines. The time provided was unfortunately not sufficient to provide a comprehensive response, however we are nonetheless grateful that the opportunity was afforded to industry. We believe the context of the review of this guidance document (i.e. to clarify existing requirements), is not reflected by the actual changes made. For this reason, where we have identified a substantial change in position this has been highlighted.

Tell us what you think about section 1 of the proposed Guidelines.

Section 1 of the Guidelines outlines the purpose of the Guidelines and a sponsor's legal obligation to hold evidence.

Q4. 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?

The requirement to provide a critical analysis per section 1.3 seems to relate to instances where the Sponsor has chosen to diverge from the guidelines. This said, the remainder of the guidance implies a need in every instance for a critical analysis. This is contradictory and therefore requires clarification.

Q5. Do you have any other comments or feedback regarding section 1?

- The requirement for a critical analysis is a NEW requirement, not a clarification of existing requirements.
- The Permitted indications guidance may require updating. It is inappropriate to consider these new evidence guidelines without also considering other guidance/ legislation which are impacted since they go hand in hand.
- "These guidelines are primarily for sponsors who base their medicine's efficacy on publicly available published literature." It is not clear why clinical trials on a unique formulation wouldn't need to adopt at least some of the same guiding principles covered in these guidelines.
- The expectation that an evidence package must contain a persuasive critical appraisal is not appropriate, since the persuasiveness of such an appraisal is entirely subjective. The intention of this guidance is to 'improve clarity' which in turn theoretically improves compliance, however subjective assessments (per the critical analysis) does not allow for greater confidence in this area. The TGA have demonstrated through historical post-market surveillance that there is a bias for failure of arguments, despite that these arguments in the Sponsors opinion are persuasive. Furthermore, this requirement is unnecessarily cumbersome, especially for low-risk indications.
- A persuasive critical appraisal could ignore negative data/ information, emphasising favourable data/ information only.
- The intention of the 'walk through' per Figure 1 is not clear. Further, per the workshop provided by the TGA on 23rd March 2022, this is intended to be an *example* of the process, however this distinction is not clear in the guidance.

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- Figure 2 is superfluous. The intention of the index is to outline the structure of the guidance, it's unnecessarily duplicative to provide this again.
- Per bullet point 3 of the "TGA disclaimers" (page 8):
    - "These guidelines reflect what the TGA would consider when assessing whether the efficacy of a listed medicine is acceptable." Per the 26A(2)(ja) of the Therapeutic Goods Act, it is not beholden on the TGA to determine whether the *efficacy* of the medicine is *acceptable*. The Sponsor must certify that they hold evidence to support all indications. Per 30(2)(a) of the Act, the TGA may cancel an entry on the register if the *efficacy of the goods is unacceptable*. This is different in intent and meaning to what the TGA are describing in the revised evidence guidelines.
    - "…However, there may be individual circumstances that justify a departure from these guidelines and in this situation the TGA will consider the merits of each case against the regulatory requirements". This statement is not helpful. The intention of this guidance is to 'improve clarity' which in turn theoretically improves compliance, however subjective assessments by the TGA such as that described above does not allow for greater confidence. As explained above, the TGA have not demonstrated an ability to subjectively assess evidence presented to support therapeutic indications without bias, rather consistently demonstrating the application of a different set of rules and interpretations. By the time the TGA considers the efficacy to be acceptable (or not), it is too late because it would occur during post-market surveillance and in the event of non-compliance, it has already occurred.
    - The legislative requirement is that sponsors must hold evidence that supports indications and claims, and which is not unacceptable (as opposed to demonstrating acceptable efficacy for pre-market approval) is supported by the legislation and framework:
        - Low risk indications and claims are required to be supported by information and evidence, so that reasonable and not misleading statements are made. However they are not required to demonstrate clinical efficacy in the same manner as registered and listed assessed medicines that make higher risk indications including restricted representations.
        - TGA delegates are not required to determine whether a Listed medicine is definitively efficacious for the purposes of market supply (as occurs for listed assessed or registered medicines.) This is because listed medicines may only have low risk indications & claims (efficacy is supportive not determinative) and TGA delegates cannot request efficacy demonstration in Section 31 requests.
        - Instead, delegates may make legal decisions to propose market removal under legislative powers. The most key examples relating to evidence are if it appears that the efficacy is unacceptable, or an incorrect sponsor certification that they held evidence or information to support the indications (or claims).
        - By their very nature, low risk indications or claims must often translate or generalise the overall evidence base into health maintenance or enhancement, or are based on structure-function relationships based on mechanism of physiological action. Because of this they are often not "demonstrable" in "efficacy" – clinical evidence by an interventional trial design – they are only able to be reasonably supported by available evidence and information. For example, there are numerous permitted indications for which it is impossible to design a clinical trial for – therefore clinical efficacy cannot be demonstrated (proven) but for which reasonable supportive scientific information and evidence can be provided, for example "Helps enhance/promote healthy nerve conduction/transmission/neurotransmission", "Aid/assist/helps synthesis of neurotransmitters", "Maintain/support nerve conduction".

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- Similarly to sponsor certifications holding evidence to support indications and claims, the concept "unacceptable efficacy" also applies an equally lower legal bar for evidence/efficacy expectations for low risk claims. Both common meaning and legal interpretations of the term "unacceptable" do not mean that efficacy must be demonstrated to be acceptable. The term "unacceptable" means commonly and legally "so far from a required standard, norm, expectation, etc. as to not be allowed" (Macquarie Dictionary online 2022) or "too bad to be accepted, approved of, or allowed to continue" (Cambridge Dictionary online 2022). Therefore the reviewer is not required to evaluate that definitive efficacy is demonstrated, they are required by the Act to ensure that the efficacy is not so far from what is reasonable that it is "unacceptable".
- The Therapeutic Goods Act also distinguishes between different concepts of "acceptable"/"not acceptable" vs "unacceptable. The clearest example of "unacceptable" (very far from acceptable) being a different legal bar to "not acceptable" (not definitively acceptably efficacious) is Section 30(2)(aa), it appears to the Secretary that the presentation of the goods: "in the case of registered goods-is not acceptable; or in the case of listed goods-is unacceptable;"
- The Therapeutic Goods Act also demonstrates that sponsors are not required to "demonstrate efficacy" post-market review due to Section 31 of the Act, even though the goods should not be of "unacceptable" efficacy based on sponsor certification. Section 31(1) and 31(2)(fac) permits TGA delegates to request efficacy information for listed assessed and registered medicines, but not for listed medicines. Rather, for listed medicines, Section 31(fa) only permits the delegate to request information relating to their certifications – in this case, the information or evidence supporting indications and claims. This is different to "demonstrating efficacy". And it is by design – it purposefully recognises the above operation of the framework.
- The requirement of "demonstrating efficacy" (including a requirement to provide a persuasive critical appraisal and a requirement of the delegate to determine efficacy) is thus not one supported by the legislative framework because it is legally and materially different to both the finding of "unacceptable efficacy" as well as "sponsor certification… that evidence is held to support indications".
- This framework of not demonstrating/determining outright efficacy not only makes sense but is necessary due to the generalised format of many low risk health maintenance or enhancement indications). Nonetheless sponsors are able to "hold supportive evidence or information" to a level that is "not unacceptable" (different to acceptable / not acceptable).

  - The above considerations extend also to the revised name of the document "How to demonstrate the efficacy of listed medicines". This confuses everyone and is anticipated to cause ongoing issues relating to interpretation of the Act. The title of the existing document has always intended to reflect this separation between listed medicines, avoiding confusion.

- The purpose of the definition for effectiveness is not clear. Further, if definitions are considered to be important inclusions, it would be more user-friendly to include these definitions in a central location within the guidance rather than scattered throughout the guidance where they can be easily missed.
- Section 1.4, specifically question 3c "Is there competing data? If yes, which dataset best represents what the medicine will do?" requires greater clarity. What does 'which dataset best represents what the medicine will

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do?' actually mean? Is it the methodological robustness that predicts this? The degree of similarity to the medicine? Something else?

- Per the existing Evidence Guidelines "As traditional indications refer to a tradition of use rather than efficacy, efficacy data is not required (such as clinical trials or studies)." Hence, the expectation that Sponsors are to demonstrate efficacy, particularly for traditional indications is a NEW requirement, not a clarification of existing requirements.

Tell us what you think about section 2 of the proposed Guidelines.
Section 2 of the Guidelines provides guidance on how to conduct and document a relevant literature search.

Q6. Do you find the information and links presented in section 2 helpful in guiding you to conduct and document a literature search?
Yes, however the expectation set out by the information and links is not consistent with the 'low-risk' nature of listed medicines. It is understandable that such expectations exist for higher risk medicines, such as Listed Assessed and Registered Medicines, however the expectation presented here for listed medicines is unnecessarily complex and cumbersome. Furthermore, the expectation that this process should be followed for medicines which present the very lowest risk (for example, listed medicines with non-specific indications only), is unreasonable and impractical. The burden placed on Sponsors by Section 2 is entirely unreasonable and is not a clarification of requirements but rather a demonstration of regulatory overreach and unnecessary regulatory complexity which contradicts the outcomes of the MMDR. Further consideration of the requirement to conduct a rigorous literature search is strongly recommended and in our opinion such searches should be reserved for specific scientific indications only in relation to listed medicines.

Q7. Do you have any other comments or feedback regarding section 2?

- The purpose of the reference to literature-based submission document is not clear
- Section 2.1 "In such cases, sponsors should follow the appropriate guidelines for clinical trials to ensure the data is robust". It is not clear why clinical trials on a unique formulation wouldn't need to adopt at least some of the same guiding principles covered in these guidelines.
- Section 2.1.1 "Traditional medicines are based on an extensive history of use, *often measured over thousands of years*" and "Usually when a medicine or a relevant ingredient in the medicine has been used over *a long period of time*". Throughout this document, and indeed in the previous Evidence Guidelines and the like, traditional use is characterized by use for >75 years or 3 generations. Whilst it is true that some traditional medicines have been used for thousands of years and for a long period of time, these statements do nothing to improve clarity (in fact it makes the characteristics of 'traditional use' unclear), and is not consistent with the agreed definition of traditional use.
- Section 2.1.1 "…traditional use claims cannot support … a mechanism of action or an underlying physiological process, as these require support by quantifiable scientific evidence." This statement is simply not true, inappropriate and diminishes the important place of traditional medicines in society. Traditional herbal monographs, for example, will often include the known 'actions' for the herb. It is these actions that form the basis for use of the herb for a specified indication. For example, an herbal medicine may be known traditionally to be an anti-inflammatory and it is on this basis that it may be used for rheumatic complaints. An herbal medicine may be considered a depurative and this action renders it useful for skin conditions. An herbal medicine could be known traditionally as a diuretic and therefore is recommended for fluid retention. If the literature describes a traditional action, the medicine should be able to refer to that action, particularly given

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the qualification of indications with the traditional qualifier and paradigm. Further to this, it is also inconsistent with the Permitted indication determination which clearly allows traditional indications for a variety of indications perceived to be related to a mechanism of action, for example "Anti-inflammatory/relieve inflammation" is able to be either a traditional or scientific indication. Finally, this is a NEW requirement, not a clarification of existing requirements.

- Section 2.1.1.1, Appendix 1 does not provide sufficient coverage for acceptable references for traditional use in paradigms outside of Western Herbal Medicine (WHM). If this appendix is to be of use for sponsors, it must provide greater breadth. If the TGA wishes not to provide a greater breadth of literature references for paradigms outside of WHM, the TGA should at least explain why these particular references are featured.
- Section 2.1.1.2 the differentiation between monographs (e.g. the Commission E monographs) and non-reference textbooks is not clear
- Section 2.1.1.2 Independent written histories and oral evidence sources are considered acceptable supportive evidence. It is not clear what is required to establish credibility of the reference (if required at all). For example, can a suitably qualified healthcare professional (e.g. a herbalist) provide an independent written history? Is the sponsor required to establish credibility of the person providing the statement? Are there any considerations relating to valuable consideration for such a statement? This section requires the addition of further consideration and detail. Furthermore, what is the value of oral evidence if corroboration is required from 2 other references?
- Section 2.1.1.2 It is not clear whether oral evidence must relate to broad use or individual historical case assessments.
- Section 2.1.1.1- Meta-analysis' are omitted from the list that has been provided. It would be helpful for those who are less experienced to include meta-analysis alongside systematic review to avoid any doubt or misinterpretation.
- The TGA have not provided any insight into use of meta-analysis or systematic review where the several different primary references which are slightly different are composited. For example, a meta-analysis may incorporate all types of Glucosamine (e.g. glucosamine hydrochloride, glucosamine sulfate, glucosamine sodium chloride, glucosamine sulfate potassium chloride etc) into the one analysis while the listed medicine contains only one form (e.g. glucosamine sulfate). Or the analysis may incorporate many population types (e.g. those with rheumatoid arthritis, osteoarthritis etc) into the one analysis. This practical information is lacking.
- Section 2.2- the expectation that a sponsor would engage a specialist librarian to conduct a literature search on their behalf is not only unrealistic but clearly demonstrates that the expectations here are unreasonably high. Refer to previous overarching comments regarding section 2.
- Section 2.2- the guidance clearly states that they are not relevant to Registered Medicines. Why, then, are registered medicines referred to within section 2.2?
- Section 2.2.1 "A literature search can be undertaken at any of the stages of a product lifecycle… periodically to ensure that the evidence package remains current". Greater clarity in terms of the frequency of repeated searches would be helpful.
- The proposed revised guidelines states repeatedly that the previous checklists are to be reviewed. Provision of the equivalent of Checklist 2 is essential, however I would urge the TGA to consider how user-friendly this particular checklist is. Furthermore, it is extremely unfortunate that the TGA have not afforded industry with the opportunity to consider such updates concurrently with this proposed guideline. This arrangement may result in sponsors not appropriately considering the proposed changes as they may not be able to visualise the practical implications of the changes proposed by the TGA.

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- Section 2.2.2.1 is not clear with regards to the TGAs expectation for repeated searches across multiple databases.
- Section 2.2.2.1 "Access to MEDLINE is through the PubMed search facility…". It would make more sense for this statement to appear with the Medline entry (bullet point 1) to avoid any confusion.
- Section 2.2.2.1 "General search engines (for example: Google) are not considered appropriate databases for conducting a literature search". Further clarity is required here, particularly with regard to Google Scholar as opposed to Google. Furthermore, given that Google crawls every web page on the internet, it is hard to understand why a general search on this engine is not appropriate, particularly when it is highly probable that it would deliver far more evidence than the suggested bibliographic databases suggested. It's unclear why the TGA would limit search on any particular database/ search engine when it could provide for more evidence to consider.
- Section 2.2.2.1 "Searches should not be limited to English" this expectation is completely unreasonable for SMEs. Furthermore, it is not consistent with later sections which have filtered results to English only.
- Section 2.2.2.1 "If a substantial number of results are received (hits) while searching a database, the search can be refined…". What does the TGA consider to be 'substantial'.
- Section 2.2.2.1 it is not clear whether or how a sponsor should go about eliminating evidence during the 'first pass' or how the elimination of such studies should be recorded (if at all).
- Section 2.2.2.1 "all references found, even those that may be discarded later… to show that a balance of evidence approach has been considered". There are several references to 'balance of evidence' throughout the proposed revised guidelines, however this contradicts the minimum evidence requirements. Further, the consideration of the 'balance of evidence' is extremely under-represented in terms of clarity. For example, how must a sponsor determine whether the balance of evidence is in favour of the indication? Is it simply that more references support the indication than not? Is it that the references which reflect the greatest methodological robustness support the indication than less robust evidence?
- Section 2.2.2.1 "all references found, even those that may be discarded later… to show that a balance of evidence approach has been considered". Do traditional indications also require the assessment of balance of evidence? How is the balance of evidence evaluated for traditional indications? Would the omission of an indication within a monograph, for example, render the reference as not supportive of that indication in terms of consideration of balance of evidence?
- Section 2.2.2.1 Table with example of search protocol- does the TGA expect for Sponsors to present all 395,064 results delivered by the search protocol performed within the evidence package? How does a Sponsor go about discarding evidence and recording of such (if required)? Is it a requirement to rationalise the discarding of each reference (one-by-one)?
- Section 2.2.2.2- We would strongly suggest that a definitive expectation regarding search process is provided. The TGA have implied that a non-systematic search may be appropriate for non-specific indications and traditional indications, but provides a caveat that systematic literature searches remain the TGA's preference. Whilst this may be the case, the TGA's preference is not relevant. The TGA have identified that there are challenges in undertaking a systematic literature search for these types of indications, and furthermore given the risk presented by these indications, it seems an absurd waste of time for no real benefit to the consumer. It would be appreciated if the TGA could definitively state here that systematic literature searches are not required for non-specific indications and traditional indications to avoid any doubt or interpretation otherwise.

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Tell us what you think about section 3 of the proposed Guidelines.

Section 3 of the Guidelines provides guidance on how to assess the relevance and quality of the evidence sources you have found for your medicine.

This section puts scientific evidence sources into three categories in a table format for increased clarity rather than the approach taken in the previous Guidelines, which categorised evidence sources as 'primary' or 'secondary' sources.

The reason for moving away from using the terms 'primary' or 'secondary' is that those terms allowed for confusion given the terms can have different meanings depending on their context. For example, when referring to types of literature, it is generally understood that primary sources give direct evidence about a subject of interest, whereas secondary sources describe, interprets, or synthesises primary sources.

In relation to providing a critical appraisal of the evidence landscape, primary sources may be interpreted to be the pivotal studies, whereas secondary sources provide additional supportive weight to the main pivotal studies. While the terminology has been updated for the proposed Guidelines to improve clarity, the meaning and intent behind the new categories has not changed.

Q8. Are the factors that are important for assessing relevance and quality of evidence sources clear and easy to understand and follow?

Yes, however a number of NEW requirements feature within the section (NOT clarifications). Further to this, the level of complexity introduced is not consistent with the low-risk nature of these goods nor the outcomes of the MMDR.

Q9. 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, however additional complexity and lack of clarity has been added in other areas. Furthermore, more needs to be done to better allow sponsors to self-categorise in the event that evidence is found which doesn't meet the pigeonholes that the TGA has included within the guidance. Finally, there must be an appropriate transition period to allow sponsors to update existing Evidence Packages per this revised terminology.

Q10. Do you have any other comments or feedback regarding section 3?

- Section 3.1 "The evidence package should demonstrate how each of the key parameters (such as those listed above) in the evidence source compares to the medicine design so that the therapeutic effect described in the source can be extrapolated to the medicine and thus support the efficacy of the medicine." This is unnecessarily cumbersome. If the evidence is presented in such a manner that facilitates comparison of the key parameters, additional effort here should not be required. We agree that if differences exist, a justification should be provided to demonstrate the relevance to the medicine, however with a caveat that simple definitions, descriptions of elementary anatomy and physiology and basic traditional philosophy, which should already be known to a competent and experienced reviewer, should not be necessary.
- Section3.1.1 "The health benefit described in the evidence source should match the therapeutic use described by the permitted indication/s selected for the medicine." At the time of the Permitted Indication consultation, industry provided significant feedback to the TGA regarding the use of 'synonymous' action words within permitted indications and relevance to evidence. Specifically, the inclusion of 'decrease/ reduce' alongside 'relieve' which is problematic for traditional indications. The terms 'decrease/ reduce' imply a level of quantification which is simply not relevant for traditional medicines. Therefore the health benefit described within traditional references often don't match that described in the permitted indication completely due to action descriptors (i.e. decrease/ reduce) which are not reflective of the context of traditional use.

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- Section 3.1.2.1 "The method of preparation and processing, the equivalent dry weight and the dose of active component described in the evidence source should also be *comparable* to that in the medicine." What exactly is comparable? This is a major area of confusion and disagreement between the TGA and industry. More needs to be done to develop rational guidance in this area.
- Section 3.1.2.1, specifically the inclusion of the reference to 'guidance on equivalence of herbal extracts in complementary medicine' is not appropriate and has been the cause of a significant degree of angst for industry in the existing evidence guidelines. It must be removed, and replaced with sensible guidance for the purposes of supporting therapeutic indications.
    - Guidance on Equivalence of Herbal Extracts in Complementary Medicine was not developed with substantiation of indications in mind. The scope of the document states (emphasis added) "This guidance document describes the circumstances under which a herbal extract may be considered to be 'equivalent' to an ingredient currently included in a therapeutic good, and which therefore **may be used as a substitute for the ingredient, without the product being considered to be a separate and distinct good**." The introduction of this guidance states "Due to fluctuations in the availability of extracts, some sponsors / manufacturers at times **choose to accept extracts with different extraction profiles, and interchange these with nominated ingredients in product formulations.** Given that different solvents, solvent concentrations and extraction methodology may result in ingredient preparations with different safety and efficacy profiles, the question arises as to **what variation, if any, should be permitted for extracts of the same herbal substance**." As such, the purpose of this document is to provide industry with guidance regarding substitution of ingredients included in medicines already on the ARTG, and **specifically whether such a substitution would render the medicine as 'separate and distinct' per the Therapeutic Goods Act 16 (1A)**. The current application of this guidance document (i.e. in relation to the substantiation of indications) is substantially different to the purpose and intention of the document.
    - If the purpose of this guidance document was intended to be applied to the substantiation of indications, this should have been detailed as a part of the guidance consultation which was undertaken in 2007. If this were the case, industry would have had the opportunity to consult on the application of the guidance in this way specifically.
    - Guidance on Equivalence of Herbal Extracts in Complementary Medicine provides **arbitrary allowances** in terms of acceptable differences in phytochemical profile and major solvent variance. For example, it is unclear on what basis the opinion has been formed that a ± 10% variation in minor solvent (where the minor solvent constitutes 20 – 50% of the solvent mix) does not render a phytochemically distinct extract. Similarly, it is unclear how the TGA formed the opinion that a ± 10% variation in component responses for constituents of 'known therapeutic activity' is an appropriate limit in terms of impact on expected therapeutic outcome.
      There are many examples of such arbitrary allowances in the guidance document.
    - Based on the limited exploration and understanding of herbal phytochemistry and pharmacology, the expectation that a sponsor, laboratory, or even the TGA would able to fully determine the impact of phytochemical variation on therapeutic outcome is unrealistic.
    - Method of preparation including solvent mixtures, solvent concentrations, concentration/ extraction ratio, extraction temperature, pressure, physical modification (e.g. powderising crude herb prior to processing) etc is rarely defined in the literature. The fundamental reason for this is to protect the intellectual property related to the test material. Therefore, it is unrealistic to expect that equivalence may be demonstrated in this way by a Sponsor.

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- There is no opportunity for a sponsor, laboratory, the TGA or any research organisation to gain access to the original test materials for determination of phytochemical profile to serve as a reference standard. Even if one was able to access a sample of the original test material, significant deterioration is likely to have occurred since the time that the study was undertaken. Therefore the expectation that a Sponsor must demonstrate phytochemical equivalence is simply unrealistic.
- As detailed in the Guidance on Equivalence of Herbal Extracts in Complementary Medicine, "Due to the natural variation in the composition of a herbal starting material (raw herb), the native extract ratio may vary from batch to batch. That is, **herbs sourced at different times of the year, or from different climactic/ geographical situations, may provide differing amounts of extractable herbal components** (using defined extraction solvents, and a validated extraction procedure)." This means that even if a listed medicine used the same proprietary ingredient explored in scientific research, there is a **high probability** that this would vary somewhat from the original test material. As such, if a sponsor was to locate and source the same branded product today to demonstrate phytochemical equivalence, it may differ in profile compared with the original test material. This again demonstrates that the expectation of 'phytochemical equivalence' against a clinically studied test material is unreasonable and unrealistic.

We are of the opinion that the reference to the Guidance on Equivalence of Herbal Extracts in Complementary Medicine must be removed from the proposed Evidence Guidelines.

- Section 3.1.2.1 "Medicinal preparations described in early pharmacopoeias, materia medica and other traditional references may pre-date modern analytical techniques. These are unlikely to provide a comprehensive and satisfactory specification (for the characterisation and establishment of the quality of the ingredient or medicine). In such situations, the active ingredients and method of preparation should be comparable to that described in the traditional literature." The latter statement is unclear. Does this mean that evidence from an early pharmacopoeia/ materia medica etc may be used provided that an additional traditional reference is provided to describe the traditional active ingredient and method of preparation? Is it sufficient to provide one reference in this regard to support this justification? Does this additional reference need to support the indication, dose etc or does it simply need to characterize the traditional medicine? It seems ludicrous to discard high quality traditional references simply because they do not contain the full breadth of information deemed important by the TGA.
- Section 3.1.2.1 "In general, active ingredients may be considered as sufficiently comparable if there are no relevant differences in… dosage". It would be helpful for the TGA to address instances where the medicine *contains a higher dose* than that detailed by a reference (i.e. a different dosage). This is particularly important where the dosage is not consistent across the evidence base.
- Section 3.1.2.1 "This may include traditional medicines in which… the dosage forms have been modified to modern dosage forms (e.g.,. capsules or tablets) but the outputs have been demonstrated to be comparable."
    - This is a major source of inconsistent interpretation by the TGA and industry and requires further clarity. For example, most traditional references include the use of liquid extracts/ tinctures whereas modern consumers prefer to consume herbal medicines in capsule or tablet form, mostly due to taste and convenience. The sentence provided by the evidence guidelines implies that the evaporation of solvents from a liquid extract/ tincture (traditional medicine) to produce a dry extract for inclusion in a capsule or tablet (modern dosage format) is appropriate, however this interpretation does not appear to be shared by TGA evaluators. Furthermore what does the reference to "outputs" and "comparable" actually mean?

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- The wording suggests that a delegate which is engaging in post-market review shouldn't accept evidence from a different dosage form, when it is in fact common for medicines to be made available with different dosage formats, and for different dosage forms to remain perfectly relevant and capable of producing equivalent therapeutic outcomes.

- Section 3.1.2.1 "If the medicine uses traditional ingredients or formulations which have been significantly altered in their constituent profile from the traditional evidence source, a justification and/or additional information should be provided in the evidence package." This expectation is entirely unreasonable. First of all, traditional evidence does not provide the constituent profile of the traditional medicine because analytical methodology simply wasn't available broadly >75 years ago, and even if it were, the degree of analytical sophistication would have improved dramatically since that time. Secondly, it is impossible in practical terms to account for the constituent profile of traditional ingredients, particularly those based on a history of use in Traditional Chinese Medicine (TCM) or Western Herbal Medicine (WHM):
  - China has a vast geographical footprint and has more than one type of climate due to different geographical zones. In China, there is temperate monsoon, subtropical monsoon, tropical monsoon, temperate continental, and plateau and mountain climate zones[1].
    As detailed in the Guidance on Equivalence of Herbal Extracts in Complementary Medicine, "Due to the natural variation in the composition of a herbal starting material (raw herb), the native extract ratio may vary from batch to batch. That is, *herbs sourced at different times of the year, or from different climactic/ geographical situations, may provide differing amounts of extractable herbal components* (using defined extraction solvents, and a validated extraction procedure)." Given that the description of traditional Chinese medicine encompasses cultivation across a diverse climate, which are in and of themselves significantly different environments, the concept of phytochemical equivalence is at odds with the nature of the traditional use. Furthermore, it is highly unlikely that any consideration of harvest time, climactic or geographical situations and their impact on therapeutic outcome (or phytochemistry, obviously) would have occurred traditionally.
    Given the vastness in geographical location and history of use encompassed by the description 'traditional Chinese medicine', it is unclear how a reference standard of a traditional medicine could ever be attained to undertake a comparison against a 'modern' extract. This demonstrates that the expectation outlined here is unreasonable and unrealistic.
  - Origins of Western Herbal Medicines has an equally vast footprint and climacteric conditions. "Traditional Western herbal medicine evolved mostly from the ancient Greeks, who were strongly influenced by Egyptian and Middle Eastern civilizations. Western herbal medicine also has roots in the indigenous practices of the British Isles and ancient Roman traditions" and encompasses use of "European and Native American herbs; however, herbs from other parts of the world are sometimes used as well."[2]
    As detailed in the Guidance on Equivalence of Herbal Extracts in Complementary Medicine, "Due to the natural variation in the composition of a herbal starting material (raw herb), the native extract ratio may vary from batch to batch. That is, **herbs sourced at different times of the year, or from different climactic / geographical situations, may provide differing amounts of extractable herbal components** (using defined extraction solvents, and a validated extraction procedure)." Given that

[1] Song Y, Achberger C and Linderholm HW. Rain-season trends in precipitation and their effect in different climate regions of China during 1961–2008. Environ. Res. Lett. 6 (2011) 034025 (8pp). doi:10.1088/1748-9326/6/3/034025

[2] Australian Natural Therapists Association. Western Herbal Medicine. Available at: https://www.australiannaturaltherapistsassociation.com.au/Public/ANTA_Therapies/WesternHerbalMedicine.aspx

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the description of traditional western herbal medicine encompasses use in European, North African and West Asian continents, which are in and of themselves **significantly different environments**, not to mention the degree of variation within each of these continents, **the concept of demonstrating comparability in constituent profile is at odds with the nature of the traditional use**. Furthermore, it **is highly unlikely that any consideration of harvest time, climactic or geographical situations and their impact on therapeutic outcome (or phytochemistry, obviously) would have occurred traditionally**.

Given the vastness in geographical location and history of use encompassed by the description 'traditional western herbal medicine', it is unclear how a reference standard of a traditional medicine could ever be attained to undertake a comparison against a modern extract. This demonstrates that the expectation of comparability of the constituent profile against a traditional extract is unreasonable and unrealistic.

- References will regularly recommend substantially different preparations, for example crude herb, liquid extracts, tinctures, decoctions, dry extracts etc. The ongoing focus on 'comparability' or phytochemical equivalence is misguided since the original evidence supports a multitude of preparation methods in the first instance, demonstrating that the preparation in fact is not related to the established traditional therapeutic outcome. In fact, according to traditional herbal medicine philosophy, it is the herb itself which is responsible for the activity, not the compounds contained within it. There is still no acknowledgement regarding traditional references which support the use of a number of different preparation methods, and the interchangeability of use of these. This is another area of inconsistent interpretation which requires lengthy consideration.

- Section 3.1.2.2 "The active ingredient should be well characterised in the evidence source. Preparations used in the source should contain the same ingredient preparation and dosage form as the medicine" This statement does not provide for any reasonable justification of differences and therefore requires rewording, otherwise this will be a NEW requirement, not a clarification of existing requirements.
- Section 3.1.2.2 "If the processing used to prepare a particular herbal product is different to that used in the literature, evidence that the chemical profile of the resulting active ingredient/s is not substantially different from the active ingredient in the literature will need to be provided." What exactly does "not substantially different" mean? How does this relate to traditional indications where, as established above, phytochemical profile is of limited relevance and the traditional phytochemical profile is effectively unknown.
- Section 3.1.2.2 "Other characteristics of medicines used in clinical trials may also impact on their relevance to a proposed indication e.g.,. an evidence source with a dosage form designed for slow release of an active ingredient may not be relevant to medicines with indications that imply the health outcomes are achieved rapidly (e.g.,.'for the rapid relief of pain / fast acting formula to relieve pain')". Dosage forms are rarely determinative of a therapeutic effect, however of course the example provided (slow release dosage form) and some other very specific cases (e.g. a lozenge with a topical effect on relieving sore throat, or administration via sublingual rather than oral routes) are obvious. There are many examples of registered medicines which are available in different dosage formats (e.g. liquids, capsules etc) and this remains perfectly valid. The statement made indicates that all differences in dosage form will impact the ability of the sponsor to substantiate the therapeutic indication, which is simply not the case.

  Difficulties arise when differences in dosage forms are more nuanced. For example, would a sponsor need to justify the difference in hard capsule vs soft capsule? Liquid extract vs capsule? Effervescent tablet vs regular tablet? What do the TGA expect with regards to demonstration that the differences are insignificant?

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- Section 3.2, table 2 requires more detail regarding categorization of evidence. For example, where would a randomized controlled trial (not double blind) sit? Or a pseudo-randomised controlled trial (e.g. alternate allocation)?
- Section 3.2 "Ultimately, it is up to you, as the sponsor, to demonstrate in your evidence package why the evidence types are appropriate for your particular medicine (and indication/s) and *why the risks of bias* in those evidence types have no impact on the overall conclusion on the medicine's efficacy." This is a NEW requirement and expectation.
- Section 3.2.1 "Each evidence source must be considered on its own merit in relation to the medicine. An evidence source *can only be considered legitimate if it establishes a tradition of use*, is credible and relevant to the medicine and indication". I would challenge the TGA to build an evidence package for a common herbal medicine (e.g. Dandelion root), which encompasses all this information in each reference, particularly the establishment of the tradition of use (i.e. >75 years or 3 generations). The TGA have provided an appendix of many different traditional references, many of which do not establish a 'tradition of use'. It is not realistic to expect that the tradition of use is demonstrated by every reference presented. Provided that the evidence is from a reputable traditional reference (for example those included in Appendix 1) and that the evidence is not derived from scientific origins, the information should be considered traditional in nature.
- Section 3.2.2 "The Grading of Recommendations Assessment, Development and Evaluation approach to assessing the certainty of a body of evidence is considered best practice… It may also help determine how much weight to place on certain evidence sources during a critical appraisal of the body of evidence." This needs far more clarity to be of any use. Further, per the proposed revised guidelines, there are only 3 categories of evidence- Categories A, B and C. Why can't a sponsor use the category grading as rationale for the weight of that reference in the critical appraisal rather than introducing yet another overly cumbersome measurement tool?
- Section 3.2.2.4 "However, inclusion of the indication as a secondary outcome may possibly be justified in some cases if, the study design adequately controls for bias and the observed result is shown to be statistically and clinically significant." It is not clear why the evaluation of an outcome as secondary to the research question introduces bias. This is unnecessarily complicated.
- Section 3.2.2.5 "It is important to bear in mind that statistical significance does not provide information about the degree of health benefit produced or whether it is likely to be clinically meaningful and, as such, clinical significance should be considered in addition to statistical significance." Clinical significance is not considered or addressed in the vast majority of published clinical trial data. This is another unnecessarily cumbersome expectation which is not consistent with the reality of the evidence which Sponsors are working with.
- Section 3.2.2.5 "An evidence package should include an assessment of the results reported in each evidence source (taking into consideration all factors outlined in 3.2.2 Assessing the quality of scientific evidence) and a discussion of why the conclusions drawn by the author/s (as a result of the statistical analysis conducted) can be relied upon." This is a NEW requirement, not a clarification of existing.
- Section 3.2.2.5.1 "Things to consider relating to statistical significance and the p-value include whether…all the actual p-values (not just $p < 0.05$) are reported". The vast majority of published clinical trial data does not include this specific information. This is another unnecessarily cumbersome expectation which is not consistent with the reality of the evidence which Sponsors are working with. Why is not acceptable for the P value to be established at <0.05 and reported as 'significant' accordingly?
- Section 3.2.2.6 "There are a number of ways to assess risk of bias for different studies, with the most commonly employed tool for assessing risk of bias for randomised clinical trials being the Cochrane Risk of Bias tool. Whether you choose to use these tools or not, a discussion of why you believe the evidence sources included

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in your evidence package have adequately controlled for bias should be included in your package." This is a NEW requirement, not a clarification of existing, and is entirely excessive.

Tell us what you think about section 4 of the proposed Guidelines.
Section 4 of the Guidelines describes the different types of claims and indications for listed medicines and outlines the evidence requirements to support them. This section includes a new decision tool which has been developed to help increase the consistency of classifying scientific indications as non-specific or specific.

Q11. Do you find the decision tool helpful for classifying indications?
Yes, however there is a significant NEW requirement for the classification of indications, specifically the consideration of whether the indication wording includes "symptoms of". Further, there are a number of indications which simply aren't accounted for in this decision tool, therefore if the TGA are not intending to provide industry with a robust tool which works for all permitted indications, consideration of the exceptions should be undertaken and industry should be provided with guidance on these specifically.

Q12. 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 'nonspecific', 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.

Q13. 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 additional clarity has been provided, however no, I do not agree with the proposed 'clarification'. We consider this a NEW requirement, not a clarification.

The TGA have ignored non-specific health maintenance indications for vitamins/ minerals with regards to establishing an applicable "dose" and appropriate supportive evidence. The role of vitamins and minerals in supporting/ contributing to normal physiological processes is well established. The vast majority of other international regulators (e.g. EFSA, Health Canada, South African Health Products Regulatory Agency, Abu Dhabi Agriculture and Food Safety Authority etc) and even our very own Food Standards Australia New Zealand, permit low level health claims based on a simple consideration of the contribution of that product to the daily intake of the respective vitamin/ mineral (i.e. % RDI/ AI). The vast majority of industry has interpreted non-specific indications relating to vitamins and minerals as 'supplementation claims' and have therefore adopted the 25% RDI rule. That is, provided that the medicine is eligible for a supplementation claim (i.e. the product contains $\geq$ 25% RDI/ AI/ NRV for that population group etc) and the sponsor holds evidence to support the role of that vitamin/ mineral in the body (i.e. a health maintenance role), the indication is widely considered to be supported. This practice has been adopted and historically accepted by the TGA, for at least 15 years according to my professional experience.

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Furthermore, according to the current Evidence Guidelines:

- "If a listed medicine states that it is intended to supplement a named nutrient, it must provide a t least 25% of the Recommended Dietary Intake (RDI), Adequate Intake (AI) or nutrient reference value for that nutrient…
- Non-specific supplementation indications are those commonly linked to medicines that only contain vitamins, minerals or nutritional substances as ingredients.
- Statements relating to supplementation with vitamins, minerals or other essential nutrients (for example: a source of calcium) that imply a general health benefit (such as the **maintenance of good health**) are often supported by high-quality and credible scientific literature, such as internationally recognised pharmacopoeias or monographs, descriptive studies, case series or reports of relevant expert committees.
- Providing the listed medicine provides the required amount of the nutrient, vitamin or mineral; reference texts, such as pharmacopoeias or monographs, or other evidence-based reference texts, are sufficient to support non-specific claims.

Non-specific health maintenance indications for vitamins/ minerals in many cases cannot be proven by clinical trials and/or are already so well established that additional clinical trials in this area are superfluous. This is considered to be an incredibly wasteful use of financial resources, considering industry are trying to use any extra available resource for clinically trialling useful interventional outcomes. If there is a biologically plausible or well demonstrated link between these functional roles of vitamins and minerals with human health, these indications should be permitted without the need for tenuous clinical trials, excessive dosing, complex systematic search strategies, critical appraisal etc.

The introduction of permitted indications introduced a new requirement where structure-function claims (such as physiological description of action of a vitamin/ mineral), previously permitted under the free text system which provided for the entry of indications which did not fit any of the available coded indications, must now be in the form of a permitted indication "helps maintain/support…" etc.

The inability for sponsors to use non-clinical evidence means that an applicable permitted indication cannot be used and similarly, the structure-function claim cannot be made even though it is based on reliable scientific evidence-based information. This is damaging for consumers whom are unable to receive interpretative information about the action of the nutrients; and damaging for industry for no reason other than unnecessary red tape and bureaucracy. It sets industry up to fail as the action of the substances /product must be described in some way, shape or form.

For these reasons, it does not appear that the TGA has considered these inter-related implications, nor considered that if low risk, mitigating statements (permitted indications/structure-function claims) cannot be made because of the reasons outlined above, that consumers will be more likely to believe the more outlandish or higher risk statements made on the internet generally about substances and products. If these Guidelines intend to clarify, it is this area of structure-function claims, non-clinical evidence, and changed landscape due to new permitted indication requirements that is one of the most important to address.

To illustrate the importance of guidance and flexibility in this area, please see the below practical example of the challenges sponsors face in building evidence for non-specific, health maintenance, indications for vitamins and minerals.

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In the monograph for Vitamin C, as presented by Braun[3], a reference which is relied upon prolifically by industry and is considered to be one of the pre-eminent Australian publications in the area of complementary medicines, the following information is provided:

- Vitamin C is an essential water-soluble nutrient for humans and required in the diet on a regular basis, as we are one of few species of animals that cannot synthesise it.
- Vitamin C, consumed either in the diet or as dietary supplements, is absorbed by the epithelial cells of the small intestine…. Then passes into the circulatory system.
- Vitamin C is an electron donor (reducing agent or antioxidant), and this accounts for most of its biochemical and molecular functions. It is involved in many biochemical processes in the body, such as:
    - Energy release from fatty acids
    - Metabolism of cholesterol
    - Reduction of nitrosamine formation in the stomach
    - Formation of thyroid hormone
    - Carnitine biosynthesis
    - Modulation of iron and copper absorption
    - Corticosteroid biosynthesis
    - Protection of folic acid reductase, which converts folic acid to folinic acid
    - Collagen biosynthesis
    - Tyrosine biosynthesis and catabolism
    - Neurotransmitter

  The reference goes on to discuss each of these actions in greater detail.
  In addition, the reference discusses 'clinical use' of vitamin C, including the prevention and treatment of deficiency, iron-deficiency anaemia, dermatological uses including wound healing, photodamaged skin, prevention of sunburn, hyperpigmentation, anti-ageing, along with use for upper respiratory tract infections, reduction in all-cause mortality, prevention of cardiovascular disease etc.

[3] Braun L & Cohen M (2015) Herbs & Natural Supplements, An evidence-based guide, Volume 2. 4th edition. Churchill Livingstone, Elsevier, Australia. Pp 1101 – 1124.

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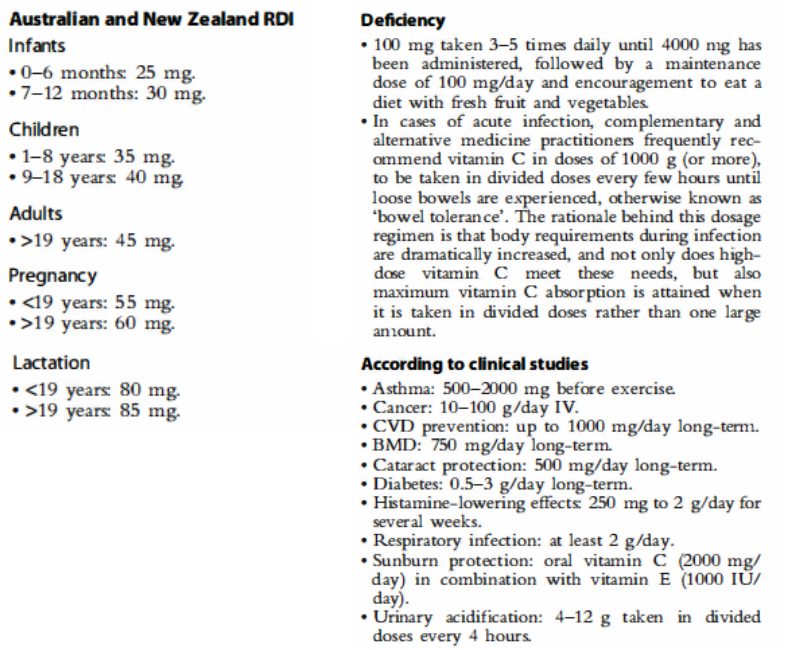
- Dosage range:



Australian and New Zealand RDI

Infants
- 0–6 months: 25 mg.
- 7–12 months: 30 mg.

Children
- 1–8 years: 35 mg.
- 9–18 years: 40 mg.

Adults
- >19 years: 45 mg.

Pregnancy
- <19 years: 55 mg.
- >19 years: 60 mg.

Lactation
- <19 years: 80 mg.
- >19 years: 85 mg.

Deficiency
- 100 mg taken 3–5 times daily until 4000 mg has been administered, followed by a maintenance dose of 100 mg/day and encouragement to eat a diet with fresh fruit and vegetables.
- In cases of acute infection, complementary and alternative medicine practitioners frequently recommend vitamin C in doses of 1000 g (or more), to be taken in divided doses every few hours until loose bowels are experienced, otherwise known as 'bowel tolerance'. The rationale behind this dosage regimen is that body requirements during infection are dramatically increased, and not only does high-dose vitamin C meet these needs, but also maximum vitamin C absorption is attained when it is taken in divided doses rather than one large amount.

According to clinical studies
- Asthma: 500–2000 mg before exercise.
- Cancer: 10–100 g/day IV.
- CVD prevention: up to 1000 mg/day long-term.
- BMD: 750 mg/day long-term.
- Cataract protection: 500 mg/day long-term.
- Diabetes: 0.5–3 g/day long-term.
- Histamine-lowering effects: 250 mg to 2 g/day for several weeks.
- Respiratory infection: at least 2 g/day.
- Sunburn protection: oral vitamin C (2000 mg/day) in combination with vitamin E (1000 IU/day).
- Urinary acidification: 4–12 g taken in divided doses every 4 hours.

This reference clearly distinguishes between the role of Vitamin C for health maintenance purposes (i.e. to support the normal physiology of the body) and for the purpose of health enhancement or management or relief of named conditions (i.e. the treatment or prevention of specific health challenges or specific beneficial effects on the physiological state of the body). It must be highlighted that the dosages presented by the reference reflect the RDI (for maintaining normal physiological processes), while deficiency states have their own dosing framework as do those for health enhancement/ management of named conditions.

If it is of assistance, we would be pleased to share similar summaries from other references commonly used and adopted by industry, however we would encourage the TGA to undertake their own assessment of the evidence landscape in this regard.

The NHMRC[4] discusses the importance of establishing recommended daily intakes (RDI), stating "physiological needs are the primary determinant of NRVs", "After due consideration, the Working Party decided to adopt the approach of the US:Canadian Dietary Reference Intakes (DRIs)" including "Recommended Dietary Intake: The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97–98 per cent) healthy individuals in a particular life stage and gender group." In addition, the proposed updated Evidence Guidelines states "Nutrient Reference Value (NRV) – the daily amount of nutrients required for good health, as well as an upper safe level of nutrient intake." As such, the RDIs set forth by the NHMRC, and established NRVs, reflect the daily amount of each nutrient required to support the normal physiological activities of the body for good health.

[4] National Health and Medical Research Council, Australian Government Department of Health and Ageing, New Zealand Ministry of Health (2006) Nutrient Reference Values for Australia and New Zealand. National Health and Medical Research Council, Canberra Australia.

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Dietary supplements are not intended to replace consumption of vitamins and minerals through the diet, but rather they contribute to the daily intake of such nutrients. This is reinforced by the proposed evidence guidelines "a supplementation claim for a listed medicine is an explicit or implicit statement that a medicine provides a vitamin/mineral/nutrient for oral ingestion, which is ordinarily consumed from the diet (i.e. from food). A supplementation claim simply conveys that by consuming the medicine, the consumer will ingest additional vitamin/mineral/nutrient than otherwise ingested from dietary sources alone." In addition, the proposed Evidence Guidelines and Permitted Indication Determination require supplementation indications to be accompanied by the label statement "(Vitamins/minerals/nutrients/dietary supplements) can only be of assistance if dietary intake is inadequate OR (Vitamins/minerals/nutrients/dietary supplements) should not replace a balanced diet (or words to that effect)", reinforcing that supplementation is not intended to replace intake via the diet.

With this in mind, if a medicine is providing nutritional supplementation (i.e. ≥ 25% RDI), the consumer is directed to ensure that supplements do not replace a balanced diet, and the purpose of the consumption of the RDI is to support the normal physiological activities of the body (i.e. low level, non-specific health maintenance indications), it remains a mystery as to why the process adopted by industry for many years, that is for a medicine to "supplement" nutritional intake (via 25% RDI) alongside holding substantiation supporting the role of that nutrient in contributing to those normal physiological processes, is now not acceptable to the TGA.

If the TGA intends to re-calibrate/ change expectations with regards to the acceptability of use of 25% RDI as the basis for supporting for health maintenance supplementation claims, it is incumbent on the TGA to provide insight as to what percentage of the RDI *would* be considered acceptable. In doing so, it is imperative to consider the potential safety implication of increasing the % RDI expectation beyond 25%, particularly for fat-soluble vitamins and some minerals where a person may already be consuming amounts through the diet (i.e. naturally occurring or via fortification) or use of several supplements concurrently.

A simple proportion of the established RDI to support the 'dose' for vitamins and minerals in maintaining normal physiological processes in the body is imperative for industry, and put simply this matter cannot go on ignored. Our recommendation is to support current practice in industry and set 25% RDI as the expectation, or at a maximum 50% RDI in order to account for dietary contribution and/or concomitant supplement use.

Q14. 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)
We believe that it is inappropriate to consider the impact of this indication on a reasonable consumer without also considering the label statements which would be required to accompany such an indication "(Vitamins/minerals/nutrients/dietary supplements) can only be of assistance if dietary intake is inadequate OR (Vitamins/minerals/nutrients/dietary supplements) should not replace a balanced diet (or words to that effect)". With the totality of presentation in mind, we interpret the statement 'maintain vitamin levels' as 'it will just top up what vitamins I get from my diet'.

Q15. Do you find the evidence requirements for weight loss indications clear and easy to understand?
Yes, although we find them unnecessarily excessive.

Q16. Do you have any other comments or feedback regarding section 4?

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- Section 4.1.2 The proposed revised evidence guidelines distinguishes between indications and claims (as do several other guidance documents), however there is still no clarification as to 1) whether the TGA can, will or do evaluate the accuracy of 'claims'; 2) what the expectation is for evidence to support 'claims'.
- Section 4.2.1 Whilst we support the removal of specificity for traditional indications, this must be acknowledged as a change in guidance, not a clarification
- Section 4.2.1 "Traditional indications present factual statements of a health benefit relating to a historical record of use… the TGA's focus for traditional indications is whether efficacy is supported". This is a substantially different view to the current Evidence Guidelines which state "As traditional indications refer to a tradition of use rather than efficacy, efficacy data is not required". This is an entirely NEW position, not a clarification of the existing position.
- Section 4.2.1 There is a fundamental challenge related to the expectation that every reference presented to support an indication (with consistent dose, preparation, dosage form etc etc) will also support a tradition of use. In fact, the references presented in Appendix 1 don't necessarily provide detail relating to the tradition of use (i.e. 3 generations or 75 years of use). We believe this expectation is unrealistic and overly cumbersome. Our recommendation is that 'traditional use' should be established based on one reference only and should be independent of support of indication. Of course it goes without saying that evidence supporting an indication should not be based on scientific evidence.
- Section 4.2.1 "Traditional indications cannot: refer to … physiological or pharmacological effects that are not envisaged within the specified paradigm". This is a NEW requirement and furthermore the requirement is unacceptable. We would encourage the TGA to consider Permitted Indications including 'anti-inflammatory', 'adaptogen', 'diaphoretic', 'depurative/ alterative', 'diuretic' which according to the Permitted Indication Determination may be classified as traditional indications, although they may not be 'envisaged within the specified paradigm'. It remains unclear as to how such indications would be featured in traditional references but not be 'envisaged within the specified paradigm'.
- Section 4.2.1 "In some instances, multiple sources of evidence of traditional use may be needed to support the efficacy of a listed medicine with a traditional ingredient or formulation". This statement is confusing considering the minimum evidence requirements to support traditional indications is specified as 2 references.
- Section 4.2.1 The requirement of critical appraisal of the collective body of evidence supporting traditional indications is a NEW requirement, not a clarification.
- Section 4.2.1.1 "However, when combining ingredients from traditional paradigms, sponsors should ensure that the combination 'makes sense' and does not contradict the traditional use of the individual ingredient/s e.g.,. combining highly dilute homoeopathic preparations with highly concentrated herbal extracts is not consistent with the homoeopathic paradigm and may alter the efficacy of the ingredients in the formulation." This is a NEW requirement, not a clarification. Furthermore, this statement is not appropriate. According to Naturopathic philosophy, several different medicines (e.g. homoeopathics, flower essences, herbal medicines) are regularly combined.
- Section 4.2.3, Example 1, cross paradigm indications (page 41) states that "the following indications listed in the ARTG: 'Traditionally used in Western herbal medicine to enhance/improve/promote immune system function' and 'Maintain/support immune system health'. These indications can be combined on the medicine's label as follows:
  'This medicine has been formulated from traditional and modern ingredients for a healthy immune system function. Echinacea purpurea has been traditionally used in Western herbal medicine to promote immune system function. Vitamin C supports immune system health'." It remains unclear as to how 'promoting the

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immune system function' is the same as 'for healthy immune system function' or 'supports immune system health'. This example will simply confuse Sponsors more than they are currently.

- Section 4.3.2 "health enhancement, with therapeutic actions such as: enhance, reduce, improve, increase, promote, relieve, decrease or those with similar intent". The terms 'relieve, decrease' must be removed from this statement because these actions do not in and of themselves render the indication as specific. If it is the TGAs expectation that these terms do render the indication as specific, this is a substantial NEW requirement, not a clarification
- Section 4.3.2 "nutritional supplementation that restore, correct or modify a physiological or mental process/function/state". This is a NEW requirement, not a clarification. As included in other areas of the revised guidelines, this wording should be amended to "modify (i.e. increase or decrease) a physiological or mental process/function/state"
- Section 4.3.2, Table 3
    - Requires the consideration and addition of 'action' indications for example anti-inflammatory, adaptogen, hepatoprotectant, laxative, antioxidant which remain ignored and is an area of contention for industry.
    - "Reduce risk or occurrence or frequency of symptoms, a discrete event or a named condition. This includes reducing the duration or severity of symptoms, a discrete event or a named condition." The underlined aspects are not clarifications but in fact NEW requirements.
    - "Relieve urinary frequency" as an example of a specific indication is a NEW classification as a result of the abovementioned change. It would have historically been considered as non-specific.
    - Category 3, and specifically the NEW requirement (not clarification) relating to permitted indications which include the words "symptoms of" is unacceptable unless the TGA also proactively include Permitted Indications in the determination with this phrasing omitted in the event that the symptom could in fact be a stand-alone symptom. For example: "Relieves indigestion", "Relieve stomach upset", "Relieve headache", "Relieve sore throat"
    - Example "improve bowel regularity" in relation to category 3 indication (i.e. Management or relief of symptoms/ signs linked to a named condition". This example is confusing. It is unclear why this example isn't simply included in the "health enhancement" category (i.e. category 1)
    - Category 5 exclusion "Maintain/support joint health in elderly people", specifically classification as a specific indication (which, for the record is not clear by the way the statement is written) is a NEW requirement, not a clarification.
    - Category 6 "Relief of general symptoms/ signs", examples should be provided which include the action words "reduce/ decrease" per the permitted indication, otherwise the requirements here are confusing, particularly because in 4.3.2.1 it is clarified that these action terms may be synonymous.
    - Category 7 should include health maintenance indications related to supplementation of vitamins and minerals per the rationale provided above.
- Section 4.3.2, Note relating to the inclusion of population qualifiers is a NEW requirement, not a clarification.
- Section 4.3.2, Figure 5
    - It is unclear how the relief of mild tissue oedema is not referring to a single symptoms/ sign. It is not necessarily indicative of a specific named condition.
    - "Does the indication explicitly refer to 'symptoms of' is an unacceptable NEW requirement (not clarification). It is incumbent on the TGA that if this NEW requirement is included, the TGA must also proactively include Permitted Indications in the determination with this phrasing omitted in the event that the symptom could in fact be a stand-alone symptom. For example: "Relieves indigestion",

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"Relieve stomach upset", "Relieve headache", "Relieve sore throat". Furthermore a fee-free period should be applicable to sponsors who will be required to update ARTG listings as a result of this change.

- Section 4.3.2.1, example states that "decrease/ reduce time to fall asleep" does not have the same meaning and intent as relief. This may be the case, however, the proposed decision tool does not facilitate classification of this indication.
- Section 4.3.2.1, example- we fail to see how "Helps maintain weight after weight loss' is not a health maintenance indication. The rational that "the indication is represented to help maintain weight after weight loss by continuously correcting or modifying the physiological process/function" could be argued to be relevant to *all* health maintenance indications.
- Section 4.3.2.1, example "Maintain/support testosterone level in older males" is a NEW requirement, not a clarification.
- Section 4.4 "Additionally, the evidence sources should contain independent sources of information e.g.,. two publications referencing the same clinical trial or information are not considered to be two independent sources of information". The whole objective of evidence development for the purposes of supporting therapeutic indications is to present consistent information from various independent sources. The inclusion of the term 'information' in this context could be confusing.
- Section 4.4 "Often clinical studies conclude that an effect might be present, but that further investigation is needed." This statement is misguided. The nature of scientific exploration is that further investigation is generally always warranted. This in and of itself should not impact the relevance or significance of the reference.
- Section 4.4, Table 4
    - According to this table, it appears that a Category A reference can no longer be used to support non-specific scientific indications. Not only is this inappropriate, it is a NEW requirement (not a clarification). Sponsors should be able to use Category A evidence to support a non-specific scientific indication.
    - It is unclear why the examples of evidence categories (i.e. category A, B and C) are duplicated in Table 4 when this has already been included in Table 2. Furthermore, please see previous feedback relating to Table 2.
- Section 4.4.1
    - "Such a claim should be supported unequivocally by robustly designed, published peer-reviewed clinical trial/s conducted on the actual medicine (i.e. not based on trials of individual ingredients found in the medicine) being advertised, or an identical formulation and dose (as a minimum)." The rationale for this clarification would be appreciated. Given that it is appropriate to apply evidence relating to an individual ingredient to a multi-ingredient formulation, it is unclear why this it is inappropriate to do that in the context of 'clinically proven' claims
    - "Due to the additional evidence required to support the use of these terms, indications that include these types of claims are classified as specific scientific indications." This is a NEW requirement, not a clarification. In addition, why is it simply not enough to hold robust evidence as described within the evidence guidelines?
- Section 4.4.2.1, "Examples of supplementation claims in relation to the mineral magnesium are….". Further clarification is required relating to the use of the term 'dietary supplement' on medicine labels. Such a term is a regulatory requirement for the New Zealand market. Many Sponsors will supply their medicines to Australia and New Zealand from the same stock (i.e. the product sold in New Zealand and Australia are one in the same).

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In our experience with TGA post-market surveillance, evaluators have considered such a statement as a supplementation claim. Our recommendation is that, this should be addressed in the examples provided.

- Section 4.4.2.1 and 4.4.2.2 Table 5 "A listed medicine can make a named vitamin/mineral/nutrient 'supplementation claim' on the medicine label, if the medicine:… the nutrient is in a form able to be absorbed by the body". This is markedly different from the statement in the current Evidence Guidelines "The salt of the nutrient/mineral/vitamins *should be* in a form that is readily absorbed by the body." This subtle difference in wording results in a NEW requirement, not a clarification. Furthermore, it is unclear why this is a requirement- surely ALL substances (not just vitamins and minerals for supplementation) should be provided in a form which is able to be absorbed by the body. Our recommendation is that the wording should revert to the current evidence guidelines in this regard.
- Section 4.4.2.1, Supplementation indications- refer to previous commentary provided in Question 13.
- Section 4.4.3 "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." Firstly, this is a NEW requirement, not a clarification. Secondly, the prominence of this statement should be increased because it could be easily missed as it stands

Tell us what you think about section 5 of the proposed Guidelines.

Section 5 of the Guidelines provides guidance on how to document and present a critical appraisal of the evidence, including providing justifications where appropriate.

Q17. Is it clear what the TGA might consider as gaps and discrepancies in the evidence source?

Yes, however we believe that in practice, there are many more examples of gaps and discrepancies which regularly form the basis of compliance breaches as deemed by the TGA.

Q18. Is it clear why it is important to include a persuasive critical appraisal of the body of evidence in an evidence package?

No, and this is a NEW requirement, not a clarification.

Q19. Do you have any other comments or feedback regarding section 5?

- The proposed updated evidence guidelines refers to the evidence package checklists being currently under review. By not providing these WITH the proposed updated guidelines, the TGA is effectively obstructing Sponsors from being in a position to provide comprehensive feedback. This same strategy was employed by the TGA in recent regulatory reforms (e.g. Permissible Indications Determination, where the guidance document was only made available after the consultation on and publication of the Determination). This strategy of consultation along with the extremely truncated timeline for this particular consultation simply adds to the cultural discomfort experienced between industry and the TGA.
- "Sponsors may also choose to follow a similar format as demonstrated in the example evidence package for vitamin B12 in Appendix 3." It would be very helpful if Appendix 3 in fact presented the entire evidence presentation (including the references relied upon and summary of that evidence), because as it stands the Appendix can be very easily misconstrued and the comprehension of the example is limited. In addition, Appendix 3 does not include a search strategy as expected.
- "Provide reasons for why, based on the body of evidence collected, the medicine is likely to produce the therapeutic effects described by the indications." This is a NEW requirement, not a clarification. It also

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doesn't account for the fact that traditional indications "present factual statements of a health benefit relating to a historical record of use" rather than a statement of efficacy.

- The inclusion of 'ethnicity' with relation to Intended population appears to be misguided considering that an indication is assumed to relate to "socio-culturally similar to the Australian population". This should not be included as a requirement in Evidence Packages
- Inclusion of an MRDD in the Evidence package is unnecessarily repetitive, considering the recommended daily dosage should be consistent with the maximum recommended dosage
- The inclusion of 'Cautions and contraindications' as a requirement for inclusion in the Evidence Package requires further clarification. What is expected here?
- The inclusion of the requirement to include 'a comprehensive list of references' is unclear. Does this have to take the form of a reference list or can it simply be footnotes throughout the document?
- Section 5.1.1 The requirement for a critical appraisal is an entirely NEW requirement, not a clarification. We vehemently oppose the inclusion of the requirement to include a critical appraisal. Refer to the feedback provided above in Q5.
  Sponsors are not required to provide a critical analysis. These are common supplements with common indications and a common purpose. Doing this analysis for 100x of the same supplements is duplicative and ineffective.
  This requirement adds unnecessary complexity for sponsors and underpins subjective assessment by the TGA, which has historically been an area of contention between industry and the TGA due to unbalanced and/or bias subjective assessments by the TGA. Whilst we do agree that justifications providing rationale for differences/ inconsistencies between the medicine (including indications) and evidence along with justification where evidence is weak or of low quality is appropriate, we do not agree that such justifications should take the form of a critical appraisal. There are other aspects of this critical appraisal which are unnecessarily cumbersome, particularly for low-level indications per the Listed Medicne framework.
- Section 5.1.2 The requirement to consider a balanced view of evidence specifically for traditional indications and non-specific scientific indications is NEW, not a clarification. Furthermore, it is not consistent with the minimum evidence requirements presented in Table 4.
- Section 5.1.2 "For scientific indications, a sponsor should regularly check for new relevant data to ensure that the balance of evidence continues to support the efficacy of their medicine". The term "regularly" is extraordinarily subjective. If the objective of this revised guidance is to provide clarity, the use of the term "regularly" does not meet this objective. Furthermore, consideration should be given with regards to the applicability of this statement to non-specific indications where the evidence landscape is unlikely to change substantially over time.
- Section 5.1.3 Further information should be provided in relation to the expectation for the inclusions and elements to be considered in justifications.
- Section 5.1.3 "Examples of when a justification should be provided in your evidence package may include (but are not limited to): Where an evidence source: is not relevant to your medicine's design (e.g.,. different ingredients…" This is extraordinarily confusing considering the Guidelines stipulate that ingredients must be 'comparable'.
- Section 5.1.3 The proposed revised guideline continues to document the need for justifications where the evidence is not identical to the medicine, however it provides no insight as to what such a justification should entail.
- Section 5.1.3, Figure 6- It is unclear how Category C evidence can follow this process, particular considerations around study design and methods, study outcomes, statistical and clinical significance, target population etc.

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Tell us what you think about the Appendices of the proposed Guidelines.
The appendices of the Guidelines include case studies to assist interpretation of the Guidelines content.

Q20. 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?
Yes, this example is woefully deficient in some areas and unnecessarily cumbersome in others. It also doesn't help that the evidence checklists are "currently under review" and have not been provided to industry to be considered alongside the proposed draft Evidence Guidelines. Furthermore, it needs to be made clearer that this is a suggested example only and that sponsors are able to design their evidence packages in any way that they see fit. Many sponsors already have established templates, systems and methods of recording evidence and provided that these contain the necessary information relating to the substantiation of indications specifically, additional information should not be required.

- The inclusion of the Sponsor name and Sponsor contact details is not necessary. The AUST L is included in the cover page, therefore the Sponsor name and contact details can be accessed very simply and easily. It also has no impact on the evidence presented and support of therapeutic indications
- The inclusion of ethnicity is superfluous, considering the purpose of these Guidelines relate to substantiation of therapeutic indications within the Australian region only and therefore the ethnicity recorded in this context should only be Australian.
- MRDD is superfluous information given the MRDD should reflect the maximum dose included in the 'Recommended dosage' row.
- Cautions and contraindications are recorded as "NA". This is not helpful considering the expectations in this regard are not clarified anywhere within the Guidelines.
- Footnote(?) to table 3 "A: Include all relevant ingredient information…." is not linked to anything.
- A Non-specific, health maintenance indication is required, accounting for the discussion points raised in Q13.
    - Non-clinical studies may in some cases be the only way in which an indication may be sensibly supported. This is *especially* the case with 'structure/function' indications. For example, there are a number of indications for Vitamin B12 that are reasonably supported by the large body of non-clinical evidence and accepted by the scientific community, for example "Supports healthy red blood cell production", "supports healthy nerve conduction/transmission/neurotransmission", "supports the synthesis of neurotransmitters", Maintain/support nerve conduction.
- No evidence has been provided to enable sponsors to visualise and comprehend the TGAs expectation with regards to the evidence presented.
- The first paragraph included in "5: Additional information" is confusing. The relevance of this paragraph is not clear.
- The statement justifying that all forms of B12 can be absorbed, specifically "The three chemical forms of cobalamin … all appear to be absorbed…" is unreferenced. It is surprising that such a statement would be acceptable to the TGA- this doesn't appear to be the case in any post-market reviews we have been involved in.
- The inclusion of the name and signature of the person completing the evidence package is not necessary.
- Search strategy and critical appraisal/ justification:
    - It is unclear why the medicine name and AUST L should be repeated again. This is an unnecessary duplication

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- Sponsors are not required to provide details of searches conducted. Further, there is no benchmark to assess it against. What action could be taken for a search which has been conducted in a way which is not aligned with TGAs expectation? A medicine can't be cancelled for having a search strategy which is not aligned with the TGAs expectation or in a "preferred" format.
- The date of search was October 2019- does this mean that review of evidence/ search every 2 years is considered appropriately "regular" per Section 5.1.2. Further clarification on the regularity of re-assessment is required.
- It is unrealistic and quite frankly absurd to expect that industry will consult with 6 different databases to support a single indication. NB: indications 2 and 3 do not require a systematic search to be performed since they have unique evidence requirements (i.e. Provides at least 25% of RDI, AI or NRV, Nutrient is in a form that can be absorbed by the body, Medicine must also have at least one permissible indication in the medicine's ARTG entry and on the medicine label.)
- The search terms will draw in ALL research related to Vitamin B12 that fit the publication type criteria. It is unclear why the TGA expect a sponsor to trawl through every piece of literature (randomised/ placebo-controlled/ clinical trial) related to Vitamin B12, to support a very specific indication relating to the prevention of dietary B12 deficiency.
- The inclusion criteria included "Where interventions included more than one active ingredient, B12 had to be the main active ingredient". This is substantially different to the previous interpretation by the TGA, whereby if a test medicine contained more than one active ingredient (regardless of whether it was the "main" ingredient or not), the medicine would be considered substantially different if all ingredients included in the test medicine were not included in the medicine formulation. Whilst we don't object to this change, it is nonetheless a change.
- It is unclear why the search was limited to the English language only, where the earlier sections of the Guidance suggests that searches should not be limited to English only.
- It is unclear why a non-systematic search has been completed for Vitamin B6, considering that according to table 3, the medicine does not contain Vitamin B6. Presuming that this is a typographical error and should state Vitamin B12, it is still unclear why such references have been consulted with considering the indication is Specific and these references are not considered strong enough to support such an indication.
- It is unclear why the TGA are suggesting that an additional search of randomised controlled clinical trials is being completed in addition to the search for systematic reviews and meta-analysis. Surely if the systematic reviews and meta-analysis were robust enough and that the search appeared to be successful, consulting with the original clinical trial data should not be required.
- The purpose of the "Non-systematic search of scientific literature that provides support to additional claims not directly supported through human clinical trials" is entirely unclear.
- Although it is not our intention to criticise the work undertaken to prepare the critical appraise, it must be noted that it suffers with significant limitations. Such limitations have either not been identified by the TGA or seem to be acceptable to the TGA without justification. Due to the subjective nature of the assessment of critical appraisals, it is very possible to find flaws and limitations, should you approach assessment with a negative bias (which the industry sees repeatedly in post-market evaluation), despite the appraisal being of high quality. The following limitations have been identified following a very brief review (in line with the extremely short consultation timeline), however we are confident that further limitations could be identified if sufficient time was allowed to do so:

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- "Results from studies that investigated vitamin B12 as part of a multi-ingredient supplement were considered relevant to the above indications as the absorption of B12 is unlikely to be confounded by concomitant supplementation in generally healthy individuals without B12 malabsorption conditions (and therefore intake of other vitamins and minerals is unlikely to impact the absorption of dietary B12 into the blood stream)." Firstly, this statement is not supported by the reference provided. The reference merely evaluates the efficacy and utility of different forms of Cobalamin on Vitamin B12 deficiency. Furthermore, no evidence has been presented to support the case that multi-ingredient supplementation does not impact the therapeutic outcomes observed.
- "The dosage of vitamin B12 ranged from 9 µg/day to 1000 µg/day". The medicine contains a MRDD of 200mcg per day. It is unclear how the evidence related to doses of >200 mcg/day is relevant to the medicine.
- "This included an RCT that studied Bangladeshi women (n=68, 11-14 weeks pregnant) taking 250 µg/day vitamin B12 (type unspecified) throughout pregnancy and 3 months postpartum". The medicine contains a MRDD of 200mcg per day. It is unclear how the evidence related to doses of >200 mcg/day is relevant to the medicine.
- "A 2019 Italian study in vegans and vegetarians (n=36) who had marginal B12 deficiency (<220 pmol/L), showed that cyanocobalamin supplementation with two different sublingual doses (350 µg/week given as 50 µg/day and 2,000 µg/week given as a single dose) both restored vitamin B12 status (>240 pmol/L)". Given that the medicine in question is an oral tablet/ capsule, the relevance of sublingual route of administration is unclear. Furthermore, the medicine contains a MRDD of 200mcg per day. The relevance of evidence relating to an alternative dosing frequency (i.e. once per week), or the weekly dose of 2000mcg where the medicine provides 200mcg per day (1400mcg/week) in unclear.
- "A 2005 study in healthy older people (n=117; >70 years old) with mild B12 deficiency (serum vitamin B12 level of 100 to 300 pmol/L and a methylmalonic acid level of 0.26 µmol/L or greater) in the Netherlands assessed the effects of five doses of vitamin B12 (2.5, 100, 250, 500 and 1,000µg/day)". The relevance of the population (>70 years), where the medicine is indicated for "healthy adults" (considered 18 – 65 years old) is unclear. Furthermore it is unclear how the evidence related to doses of >200 mcg/day is relevant to the medicine.

- The great majority of the content contained in the critical appraisal simply wouldn't be necessary if the evidence was presented thoroughly in a table such as that included in Checklist 5 or 6 of the previous evidence checklists

Q21. 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?

- An example of a compliant case where the sponsor has successfully justified differences in the method of preparation of a herbal extract. It would also be helpful to provide an example of a compliance case where the difference in crude herb and a herbal preparation is confirmed.
- An example of a compliant case where the sponsor has successfully justified differences in the method of preparation from a traditional preparation to a modern preparation for a herbal extract.
- An example of a compliant case where the sponsor has successfully justified minor differences in the dosage form

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- An example of a non-specific scientific indication (health maintenance) relating to a vitamin/ mineral with an established RDI serving as the dosage reference
- An example of a successful attempt at extrapolation of evidence from a diseased population
- An example of a successful attempt at extrapolation of dosage which is not identical
- An example of a successful attempt at extrapolating dosing for herbal medicines for children, according to the aged- and weight-based calculations commonly adopted, particularly for traditional indications
- An example of a case study where 'phytochemical equivalence' via analytical data (e.g. HPLC chromatogram) is confirmed.
- More complex (less obvious) examples to assist Sponsors who are more experienced in evidence development.

Q22. Do you have any other comments or feedback on the Appendices of the proposed Guidelines?

- Appendix 1 has remained largely unchanged since the version which was published by the TGA in the 2001 version of the "Guidelines for Levels of Evidence to Support Indications and Claims". It would be helpful for this list to be expanded.
- Appendix 2:
    - The inclusion of case studies are a welcome improvement and very much appreciated.
    - Case studies are hypothetical, these are not helpful to industry because the challenges occur where there are real-life, practical nuances.
    - The examples provided are of little use in terms of clarity of comprehension without the inclusion of the evidence itself. These examples to not allow a sponsor to visualise or identify where differences have occurred nor the content of the justifications which render them acceptable or not.
    - Many of the examples provided are very obvious examples of compliance/ non-compliance. Per the abovementioned point, real-life situations are far more nuanced. This is especially the case for differences in expectation around herbal preparation consistency.
    - Case Study 2-
        - If the medicine had 20mg of Ginger, would this be acceptable even though it is not 'consistent' per se with the evidence? Does the dose provided by the Listed Medicine need to be identical with the evidence or may it be higher? This is of particular importance because dosing is rarely identical across the evidence base.
        - The indication "anti-inflammatory" was supported by other ingredients, therefore the sponsor has met their legislative obligations. Further, there is no evidence that the efficacy is "unacceptable" which is the threshold per the Act.
    - Case Study 4- This example implies that no difference in extract ratio is acceptable, however this is a significant NEW requirement which is not supported in other guidance, particularly not the current Evidence Guideline. If a sponsor can effectively establish that the extract ratio is consistent or that differences are not relevant, this must be considered as acceptable
    - Case Study 7- This example, particularly "The treatment was identical in formulation, dosage form and dose to the medicine", is not helpful and especially obvious in terms of compliance position. It would be far more helpful to provide an example of a borderline case which has provided an acceptable justification.
    - Case Study 8- "Any minor discrepancies in the extract solvent were sufficiently justified by the sponsor." It would be far more useful to have actually provided those justifications to illustrate acceptability.

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- Case Study 9- This case study details that hypocholesterolemic effects were demonstrated in experimental models, healthy volunteers and type II hypercholesterolemic patients. As addressed in the 'biomarker' section of the proposed updated guidelines, it is unclear how the lowering of cholesterol is demonstrated in healthy individuals, unless they have slightly elevated cholesterol and are otherwise healthy. The monograph and textbook evidence sources may not refer to clinical trials, but other scientific data. Furthermore, it is unclear how such an effect is reflective of the indication "Helps maintain/support healthy cholesterol" (not "helps decrease/ reduce cholesterol"). Further clarification is required.
- Case Study 13- It is unclear how the justification included in the sponsor's evidence package (i.e. discussion of equivalent bioavailability) is deemed acceptable. Is it not possible for the salt form to be related to the therapeutic outcome? For example, Magnesium oxide has a well established laxative effect, see "Outcomes: Low-negligible risk changes to Permissible Ingredients - 2020-2021". Magnesium gluconate, as an example of an organic magnesium salt does not have this same laxative effect. The bioavailability of Magnesium gluconate is better than oxide, however that is not to say that it will produce the same therapeutic outcome. Furthermore, the laxative effect can be impacted by the dosage and dosage frequency, however this is also not accounted for in the consideration of bioavailability.
- Case Study 14- This example would be far more meaningful if it contained an acceptable justification for the use of unvalidated or modified methods.
- Case study 15- "The evidence source is not considered relevant to the medicine, as long-term for example: pain relief that occurs 2 weeks after treatment, is not considered relevant to the therapeutic benefit described by the medicine's indication of temporary (and impliedly, immediate) relief." The definition for temporary, as provided by the Cambridge Dictionary is "not lasting or needed for very long". The interpretation that "temporary relief" implies "immediate relief" is quite simply incorrect and will likely lead to more confusion than already exists.
- Additional case studies must be added:

Thank you for your consideration.

Best Regards,

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