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Submission: Proposed update to evidence guidelines for listed medicines

Wednesday 13th April 2022

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Further, members of our team have worked closely within the requirements of the evidence guidelines since the original publication in 2001 and are therefore most qualified to provide input into how they have changed from version 1.0 to version 3.0 and then again to the proposed version 4.0. These changes will be discussed in further detail, however some of the changes include:

- The requirements to provide a critical analysis of the evidence in an evidence package for their listed medicine. This is a clear change. Previously we have been requested to complete checklists in the prescribed format, however we have never been requested to provide a critical analysis of the evidence. This provides a significant amount of additional work for every evidence package for every sponsor
- A change in the dosage of a nutrient required to make non-specific claims such as "Vitamin C supported healthy immune function". The indications have always been accepted at 25% RDI, as is evidenced by the justifications written into the advertising exemption approvals for calcium and vitamin D, and as per the information provided further within this document.

- A change in the amount of a nutrient that is required to make a claim that a product is a source of that nutrient. The old Evidence guidelines allowed for a claim that a product was a source of a nutrient at 10% RDI, however this has been increased to 25%.
- Implication of a greater number of databases the require searches and reviews for specific level indications, resulting in a far greater expense to industry in both time and subscriptions.
- The requirement to provide a justification for performing a non-systematic search for evidence for non-specific indications, instead of accepting evidence from high-quality and credible texts such as internationally recognised pharmacopoeias or monographs maintained by other international regulatory bodies or evidence-based reference texts as per previous Evidence Guidelines
- A note for herbal ingredients has been added stating “For listed medicines with herbal ingredients, additional information can be found in the Guidance on equivalence of herbal extracts in complementary medicine”. This is an addition to this version of the evidence guidelines and appears to be an intentional addition added specifically to limit the use of traditional references and therefore traditional indications, and utilises this guidance outside of the intended scope, which is to provide guidance on when a herbal ingredient can be a substitute, without the product being considered to be a separate and distinct good and requiring re-listing.
- Increased requirements for suitable evidence to support non-specific scientific evidence and an implication that systematic reviews of a number of databases are required to support general level health support indications such as “Maintain/support immune system health”, “Maintain/support brain health”, “Maintain/support nervous system health”, “Maintain/support healthy cardiovascular system function”, etc.

In recent years, industry has had to bear costs of changes in regulations, including a change to permissible indications, and to labelling, which has resulted in every evidence package for every ingredient requiring update and all labels requiring review and update. This has been at a cost several hundred thousand dollars to many companies.

The changes outlined in the evidence guidelines will result in a reduction of therapeutic indications able to be included on medicine labels. Many of the health claims allowable for foods that include only 10% RDI of a nutrient per serve will not be able to be supported under the new evidence guidelines document at any level, resulting in products being sold as foods instead of therapeutic goods and a high number of non-compliant food products.

Local Australian businesses and Australian exports have suffered in recent years due to COVID-19 and floods, and these changes to the evidence guidelines will only reduce the number of products on shelves, and risk further closures of local healthcare businesses. Further, with a decrease in locally available complementary medicines, Australian consumers will look for product to be purchased from overseas websites to be delivered to them directly. These products are of a lower quality, being made to food standards, rather than therapeutic goods GMP. As such, this is a detriment to the Australian consumers.

These changes to the Evidence Guidelines and resulting decrease in availability of Australian complementary medicines will have a follow-on effect, reducing Australian made products and result in reduced exports and job losses.

While it was extremely disappointing that despite industry requesting this update since 2016 it has only just been provided in 2022 and an inadequate 4 weeks afforded to industry to review, [redacted] appreciate the opportunity to contribute to the important and long overdue review of the 2014-19 Evidence guidelines. Guidelines on the evidence required to support indications for listed complementary medicines.

Our first concern involves the change to the title of the guidance from “Evidence guidelines - guidelines on evidence to support indications for listed complementary medicines” to “How to demonstrate efficacy for listed medicines” which is a significant change in terminology and immediately suggest a higher level of expectation for claims substantiation for low-risk medicines

that has not been required in the past. While this terminology has been creeping into TGA communications in recent years it has not been agreed to as the intent or expectation of TGA or industry in previous consultations.

Our second concern is the TGA's assertion at the webinars provided to explain the guidance that it "collaborated" with industry through COMTECH etc to get to this point. While we agree that the TGA communicated with some industry working groups, significant push back to many of the changes in this document were voiced. These concerns have mostly not been taken into consideration by the TGA, who appear to have simply ploughed forward with their own updated interpretations by staff who have little to no experience in the sector and no background as to industry.

Further TGA staff who have 'endorsed' the evidence guidelines as "not changing" have never worked closely with the evidence guidelines and are therefore completely unqualified to make such an assertion. These TGA staff include people at a higher level and people who therefore do not have the time or resources, particularly during COVID-19, to compare the 2014, 2019 and 2022 guidance documents closely and ascertain if changes have been made. As such, their endorsement of the evidence guidelines and assertion that no changes have been made relies on the people who have written the new guidance document. Industry members who have worked closely with the Evidence Guidelines since 2001 are certainly the most qualified in ascertaining if changes have been made.

The intent of the new evidence guidelines was to provide clarity on requirements and not to create change. The new evidence guidelines however make the requirements more confusing and open to the interpretation of the reviewer and change some requirements completely. It is also contradictory in many areas, providing for a specified level of evidence in some sections, but referring to a higher level of evidence in other sections and providing examples that either don't work, or are above the level of evidence stated as the minimum. This is likely to lead to future reviewers interpreting that the higher level of evidence is the minimum requirement. As such, the new evidence guidelines have failed in their intent. This is extremely disappointing, considering the amount of industry funded resources that have gone into the production of the document and further time provided by industry members during the 12-month pre-consultation period, where much of the feedback regarding obvious changes was disregarded and in fact group meetings, where industry representatives were aligned in their noting of the significant changes being made, were ceased.

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

TGA: 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?
Please describe why or why not

The TGA have continued to state in recent years that the reviewers are left to join the dots in the evidence and work out themselves if the evidence is relevant. We however have noted that at times, we have been asked by TGA reviewers to justify parts of the evidence that we would consider directly supported. Industry pays the TGA reviewers for their expertise and knowledge, however they lack specific knowledge in complementary medicines, and as such, appear to be unable to join the dots in a way that people with relevant expertise would easily be able to. Examples of this is an expectation that sponsors need to justify use of an extract using 100% water as a solvent for evidence that discussed the use of an infusion, which is also a 100% water extract. This type of justification requirement is simply misuse of industry paid resources that can be better applied to issues such as SUSMP updates, maintaining documents and legislative instruments in an up to date and consistent manner and issues of public health and safety.

1.1
Additional requirement and terminology.
According to the proposed guidelines evidence to support claims for low risk listed complementary medicines will be expected to contain a persuasive critical appraisal of the collated body of evidence to demonstrate a listed medicine's efficacy. Such expectation has never been communicated in previous evidence guidelines, nor has it been required in the many evidence submissions [redacted] have tendered on behalf of clients in relation to requests for information in the years between 2014 and 2022, that have been reviewed and considered acceptable by the reviewers at the time.

Additionally, the update refers to the body of evidence, however we have seen on many occasions in post market reviews that evidence is not reviewed as a body by the TGA, but as singular pieces of supporting evidence. It is important that TGA staff are able to review evidence consistently and through an unbiased lens and that they are held to the same expectations and standards when presenting arguments against proposed supporting evidence as sponsors.

This expectation is a significant change in requirement and will add considerable time and cost burden to an already extensive process of summaries, filters and justifications that was provided by the TGA with the 2014 Evidence Guidelines update. We consider the expectation of the inclusion of a critical appraisal a completely different or additional process as was communicated in the previous guidelines.

[redacted] find the inclusion of TGA disclaimers (page 8) to the effect that *indications used in these guidelines have been provided as examples only. These indications do not relate to actual medicines and whether there is evidence to support the indications has not been assessed by the TGA* are inappropriate and unhelpful. If the TGA cannot provide suitable examples of indications and evidence that they stand by then they should not be included because due to the ever changing interpretation of evidence requirements by the TGA. Industry look to examples specifically for that purpose. These kinds of disclaimers provide the TGA scope to again change interpretation over time. We request the removal of the disclaimer and inclusion of suitable examples that provide suitable substantiation so that in the spirit of the purpose of this update the TGA provide industry with clear guidance on how the TGA interprets and analyses different types of evidence and clarify specific technical concepts that have been problematic or unclear in the existing Guidelines.

1.4 When and how the TGA reviews efficacy

Suggest clarifying the following statements further:

- *the efficacy of the medicine is acceptable*? Listed medicines are not required to show efficacy they have been required to provide evidence to support the therapeutic indications which are being made by using appropriate references. The requirement to show the "efficacy" of the medicine is open to interpretation and requires significant clarification before such a statement is included.
- *whether the presentation of the medicine suggests it has characteristics it does not have*. What does "characteristics" entail? Therapeutic effects, irrelevant populations etc? Further clarification required so that it is not subjective, and sponsors are not disadvantaged by subjective interpretations by individual TGA reviewers.
- *If assumptions have been made, are these valid?* Additional terminology. **Assumption** (p 10) was never used in 2014-2019 guidelines. What validates an assumption?

Section 2 How to find Evidence

TGA: Do you find the information and links presented in section 2 helpful in guiding you to conduct and document a literature search?

No

Please describe why or why not

2.1 Different types of evidence

(Pg 11) *While most listed medicine sponsors rely on existing published literature, some sponsors may choose to generate their own scientific evidence for their medicine e.g.,. conduct a clinical trial. In such cases, sponsors should follow the appropriate guidelines for clinical trials to ensure the data is robust.*

In the spirit of the purpose of this update would the TGA provide industry with clear guidance on how the TGA interprets appropriate guidelines for clinical trials by providing in the Guidance a list of appropriate guidelines for clinical trials.

Evidence of traditional use.

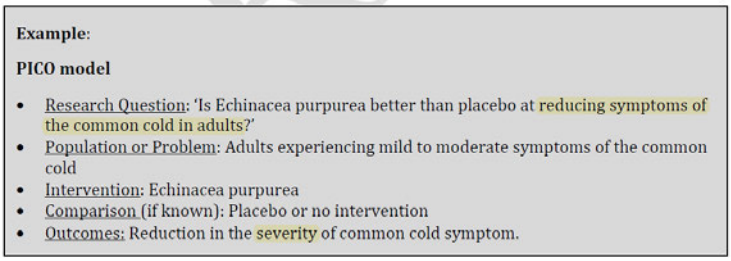
We find that there is insufficient guidance for traditional indications and evidence. The Guidelines are predominantly focused on scientific evidence. To ensure compliance for traditional indications and evidence, clear and concise guidance is required, with clear, correct, and relevant examples provided as case studies.

Systematic literature searches

The systematic review process outlined is protracted and over and above what has been expected in the past. The expectation around systematic reviews far exceeds low level indications for complementary medicines.

Further, the past evidence guidelines stated “Your database search should utilise MEDLINE/PubMed electronic databases and include at least one other relevant database” however this has been removed from the proposed Guidelines, and as such, combined with the long list of 10 databases, may be implied that every one of those 10 databases needs to be searched for specific scientific indications, providing a massive amount of further work for industry. Further if a good quality systematic review or meta-analysis, such as a Cochrane review, is available for the specific ingredient and indication, completing this review again by independently reviewing the databases is a complete waste of time and resources and completely unnecessary.

2.2.2.1 Systematic literature searches



Example:

PICO model

- Research Question: ‘Is Echinacea purpurea better than placebo at reducing symptoms of the common cold in adults?’
- Population or Problem: Adults experiencing mild to moderate symptoms of the common cold
- Intervention: Echinacea purpurea
- Comparison (if known): Placebo or no intervention
- Outcomes: Reduction in the severity of common cold symptom.

Research question is reducing symptoms of common cold, but the outcome is the reduction of severity of common cold symptoms. Permissible indications are:

- Decrease/reduce/relieve symptoms of common cold
- Decrease/reduce/relieve the severity of common cold symptoms

Can the TGA please provide a justification for discrepancy of research question and outcome and why they are relevant for this example.

2.2.2.2 Non-systematic literature searches

This section states that "Generally, our preference is for a systematic literature search to be conducted in the first instance" and implies that a non-systematic literature search needs to be justified by the sponsor for non-specific indications. This is a clear change, where non-specific indications have always been supported by reference-based texts, pharmacopoeias, materia medica, etc. This is in fact a more suitable method for supporting indications for health maintenance, such as "Maintain/support immune system health", "Maintain/support brain health", "Maintain/support nervous system health", "Maintain/support healthy cardiovascular system function", etc, as these references based texts have already taken into consideration clinical trials in humans, as well as in vitro and animal studies, etc to justify the mechanism of actions that support these general level, non-specific indications. As such, instead of the need to justify a non-systematic literature search for non-specific indications, which is a new requirement, a non-systematic search should simply be accepted, and this should be written into the evidence guidelines so as not to change the status quo.

As per above, this section provides for little clarity and implies a greater level of review and work required. This will increase costs to industry significantly, as subscriptions to many of the databases listed are extremely expensive and will be cost prohibitive and unnecessary for the level of indications allowable for low risk listed medicines.

Section 3 How to assess evidence

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

No

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?

No

Please see the following for more details and specific concerns:

Section 3 How to assess evidence

Under section 3 there appears to be much more focus on chemical profiles of herbal ingredients being required to justify equivalence and efficacy.

Under **3.1.2.1 active ingredient** there is a new clause for evidence of traditional use:

*In general, active ingredients may be considered as sufficiently comparable if there are no relevant differences in the method of preparation (such that **comparable outputs** are yielded) and if the medicine has the same intended purpose, dosage and the same route of administration. This may include traditional medicines in which the indication, dosage and administration are based on*

traditional knowledge, the dosage forms have been modified to modern dosage forms (e.g.,. capsules or tablets) ***but the outputs have been demonstrated to be comparable****.*

What exactly is the expectation with regard to “outputs”? Can the TGA please define “outputs”.

This statement re “comparable outputs” is unsuitable for use for traditional herbal medicines, which can differ from season to season and depending on where they are grown, but have still been used for the same therapeutic purpose.

3.1.2.1 - Active ingredients from evidence of traditional use

A note for herbal ingredients has been added stating “For listed medicines with herbal ingredients, additional information can be found in the Guidance on equivalence of herbal extracts in complementary medicine”. This is an addition to this version of the evidence guidelines and appears to be an intentional addition to limit the use of traditional references and therefore traditional indications, and utilises this guidance outside of the intended scope, which is to provide guidance on when a herbal ingredient can be a substitute for the ingredient, without the product being considered to be a separate and distinct good and requiring re-listing. TGA reviewers have been attempting to use this document for several years as a reason not to accept evidence for traditional use of herbs, citing that the sponsor is not able to adequately justify suitability as per the Guidance on equivalence of herbal extracts in complementary medicine and that the extract ratio or solvent ratios, etc cannot be justified to be within the limits of this document and as stated in the evidence. It has been continuously pointed out to date that the post market reviewers have been taking the Guidance on equivalence of herbal extracts in complementary medicine completely out of context as it is clearly stated that the scope of that 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.** As such, it appears that the intent of the TGA in adding this section to the evidence guidelines is to intentionally limit relevant traditional evidence and therefore suitable traditional therapeutic indications for herbal extracts that have been used for the same purpose, but with varying amounts of extract solvents and varying extract ratios.

3.1.2.2 Active ingredients from scientific literature:

This section requires further clarification as it applies to herbal non-specific and specific indications, meaning data from monographs and textbooks, which according to the below appears it will be impossible to justify, due to the full composition of the herbal treatment is rarely adequately characterised. This is a significant move away from the soft touch regulation that was recommended as part of the MMDR and it will open sponsors to subjective interpretation by individuals within TGA when reviewing unstandardised extracts.

3.1.4
Figure 4
Is your evidence source relevant to your medicine indication?

This infers that all scientific indications need clinical trials to be substantiated as there is no flow chart for “if the scientific indication is NS”. This allows for too much room for misinterpretation or subjective reviews by TGA which is not appropriate as it provides an unlevel playing field for sponsors, which we have seen happen repeatedly in post market review outcomes of identical topics by different reviewers.

3.1.4 Target Population

The target population for the medicine should be consistent with the population described in the evidence source. It is important to note that, in general, listed medicines are intended for use by healthy individuals.

The general population is categorised as the following:

- male and female participants
- generally healthy
- aged 18–65 years
- socio-culturally similar to the Australian population

Table 1: Study populations

Indication	Relevant population
Helps increase weight loss when used in conjunction with a calorie or kilojoule-controlled diet and physical activity or exercise	Male and female participants aged 18-65 years; generally healthy population with BMI 25-30 kg/m² socio-culturally similar to the Australian population.
Relieve pain	Male and female participants aged 18-65 years; generally healthy population with a range of painful (non-serious) conditions.
Relieves cough in children	Male and female participants aged 2-12 years; generally healthy population with cough associated with a range of (non-serious) conditions.
Maintains bone strength	Male and female participants aged 18-65 years; generally healthy population; dietary and lifestyle pattern similar to the Australian population.

There is a lack of definition or description for population qualifiers. As seen above, TGA relevant population for “in children” is male and female participants aged 2-12 years. UNICEF definition for a child is “under 18”.

What is the TGA expectation or criteria for age range for all population qualifiers. Examples:

- In active individuals
- In adolescents
- In teenagers
- In aging individuals
- In children
- In elderly individuals
- In athletes
- In growing children
- In children under 2 years of age
- In infants
- In older males/ females

Without clear criteria, sponsors are unable to find studies that suit TGA expectation which is open to interpretation and change over time.

3.2

Section 3.2

The below is an addition that was not in the 2014-2019 guidance

While double blinded randomised controlled trials and systematic reviews of multiple randomised clinical trials are usually associated with low bias and high precision, they are not always available or feasible. Acknowledging this, the TGA allows other study types and a range of other sources of evidence to be submitted as potential support for the claimed efficacy of a medicine. The limitations of these other sources need to be considered e.g.,. case-control studies and cohort studies may not be a practical means of providing evidence for some indications and are limited in their ability to produce unbiased and unambiguous data regarding the true efficacy of a medicine. They can, however, provide valuable supportive data related to the likely efficacy of a medicine for the general population.
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.

From experience the above is not true in practice. TGA has only accepted flawless, high quality randomised controlled trials, assessed individually, rather than as a body of evidence. Other study types have always been rejected, due to the limitations TGA have stated in the above themselves. In fact, the above contradicts itself by stating that other sources can be submitted as potential support for claimed efficacy and are likely to only provide valuable supportive data. In other words, flawless trials are still required, which TGA acknowledges are lacking. This paragraph needs to be written in a truthful manner by TGA which reflects how evidence is actually assessed by the post market review department in order to avoid confusion.

Overall, the onus is on the sponsor to tell a story of why the evidence should be accepted, which is clearly unfair when all sponsors are drawing from the same pool of evidence. It then comes down to who can put together a suitable justification for the acceptance of the data, which is completely reliant on the interpretation of an individual TGA reviewer and as we have seen in the past create differing TGA interpretation of what is accepted as evidence and create an unfair playing field for sponsors. The acceptance of the evidence should be reliant on the actual evidence and not who can tell the best story.

3.2.2 Assessing the quality of scientific evidence
Recommendation to use the 'Grading of Recommendation Assessment, Development and Evaluation' approach.
3.2.2.5 Statistical analysis
Recommendation for statistical analysis to apply principles outlined in 'Note for Guidance on Statistical Principles for Clinical Trials (ICH topic E9).

3.2.2.6 Tolls for assessing risk of bias
References tools for assessing risk of bias such as Cochrane Risk of Bias tool, PRISMA, CONSORT, EQUATOR etc.
TGA states: whether you choose to use these tools or not, a discussion of why you believe the evidence sources included in your evidence package have adequately controlled for bias should be included in your package.

The new inclusion of above 3.2.2, 3.2.25 and 3.2.2.6 shows a significantly increased level of expectation as to the requirements to support indications for low-risk listed medicines and are akin to doing a full systematic review for each ingredient and indication which based on the 2014-2019 guidance AND the evidence summaries and filters provided by the TGA with the 2014 guidelines is a significant change in the requirements to support indications for listed medicines. This proposal is more in line with requirements for registered medicines which defeats the purpose of having low risk medicines. If the requirements are such that sponsors of listed complementary medicines must tick all the same boxes for evidence for low-risk listed medicines as is required for registered medicines

then it is only fair that dossiers are reviewed by the TGA prior to submission to ensure a level playing field for all sponsors otherwise those who cannot or do not read the requirements for medicines will not comply and have a commercial advantage of being able to sell a product that is allowed in all other international markets that those who follow these extraordinary expectations will not be able to bring to market.

By over regulating low-risk medicines the TGA are pushing consumers to buy unregulated products online from overseas markets which goes against of the TGA's goal of consumer safety and also has the flow on effect of effecting jobs in sponsor businesses, retail and manufacturing.

As the guidelines are not changing in their intent, this section needs to be reviewed and rewritten and further information on supporting non-specific indications such as "Maintain/support immune system health", "Maintain/support brain health", "Maintain/support nervous system health", "Maintain/support healthy cardiovascular system function", etc, needs to be added.

Section 4 How to use evidence
describes the different types of claims and indications for listed medicines and outlines the evidence requirements to support them.

TGA: 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.

Do you find the decision tool helpful for classifying indications?

No

The decision tree will provide greater confusion. The TGA have stated "we acknowledge that there may be some indications that are difficult to categorise for individual medicines", which is not good enough. Many years ago, the TGA classified coded indications as general or medium, and the TGA have changed much of this interpretation with the excused that "that document was a draft version only". It is confusing as to why the TGA have continuously refused to sit down with industry and categorise the indications together, with the knowledge the indications are being classified on their merit and the level of indication may change depending on the overall presentation, which is a separate compliance issue to the level of indication alone.

According to the decision tool, low-level biomarker indications (such as 'helps maintain/support healthy cholesterol' and 'helps maintain/support healthy blood sugar/glucose') are classified as 'non-specific', while previously these indications have been generally regarded as specific. Do you agree that the efficacy of listed medicines with these indications should be supported by Category B or C type evidence only? Can this please be clarified and confirmed as this has been an ongoing issue since 2016 and has resulted in a significant waste of industry funded resources and time and costs for sponsors in changing indications on the ARTG and relabelling.

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 it does, however it has removed the section that refers to a sponsor being able to make a claim to the effect "Is a source of vitamin/mineral/nutrient" at 10% RDI. It appears that these claims are not only suitable is a product contains 25% RDI, which is a significant change in requirements and puts an even greater gap between health claims allowable for foods, which can be made at 10% RDI of

the nutrients per serve, and indications and claims that can be made for listed medicines. This will only lead to more non-complaint foods being produced and sold in Australia, making allowable health claims at 10% RDI and that are outside of the jurisdiction of the TGA.

Following is a screenshot of the previous 2014 Evidence Guidelines:

> Sponsors must ensure they are compliant with any requirements relating to the use of a permitted indication as included in Therapeutic Goods (Permissible Indications) Determination.
>
> Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the medicine provides at least 25% of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Indications / claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

What do you interpret the indication 'maintain vitamin levels' to mean?

Other (please describe below)

We interpret this to mean that supplementation of the nutrient will maintain the levels of the nutrient in the body/blood.
We interpret the indication "Helps prevent dietary (state vitamin/mineral/nutrient) deficiency" to mean that it will simply top up levels of vitamins obtained in the diet. This is due to the very specific reference to dietary deficiency.

Do you find the evidence requirements for weight loss indications clear and easy to understand?
Yes

Please find following further information and comments:

The current evidence guidance document stated the following for supplementation indications:

Table 5: Minimum evidence requirements of supplementation claims and two permissible indications

Claims/indications	Minimum evidence requirements
Supplementation claims	a. Provides at least 25% of RDI, AI or NRV b. Nutrient is in a form that can be absorbed by the body c. Medicine must also have at least one permissible indication in the medicine's ARTG entry and on the medicine label.

Claims/indications	Minimum evidence requirements
Permissible indications with special evidence requirements 1. 'Maintain/support (state vitamin/mineral/nutrient) levels in the body' 2. 'Maintain/support (state vitamin/mineral) within normal range'	a. Provides at least 25% of RDI, AI or NRV b. Nutrient is in a form that can be absorbed by the body

The old evidence guidelines stated the following for 25% RDI supplementation indications.

Table 3: Specific indications for listed medicines

Specific indications (may be scientific or traditional)

Health benefit	Definition of health benefit	Example of an indication
Health enhancement	Specific beneficial effects of nutrients and other substances on the physiological and psychological state of the body above and beyond normal growth, development and functions of the body.	*'Helps enhance blood circulation to the peripheral areas of the body (legs, hands and feet)'* *'Traditionally used in Western herbal medicine to promote healthy digestion'*
Reduce occurrence or frequency of a named condition, symptoms or discrete event	Reduce the occurrence of a specified, non-serious illness, condition, disease or disorder.	*'Help reduce occurrence of symptoms of medically diagnosed Irritable Bowel Syndrome'* *'Traditionally used in Australian indigenous medicine to help reduce occurrence of abdominal bloating'*
Management or relief of symptoms linked to a named symptom/disease/ disorder condition	Reduces the frequency, duration and/or severity of symptoms associated with a named illness.	*'Relieve symptoms of hayfever'* *'Traditionally used in Western herbal medicine to relieve symptoms of indigestion/dyspepsia'*
	Improved quality of life without resolution of the underlying non-serious illness, condition, disease or disorder.	*'Enhance/improve/promote/increase bowel regularity'* *'Traditionally used in Western herbal medicine to decrease symptoms of mild arthritis/osteoarthritis'*
Supplementation indications linked to a specific therapeutic benefit (scientific indications only)	If a supplementation indication is linked to a specific therapeutic benefit, additional supportive scientific evidence is required (as well as the requirement to provide 25% of the RDI for that nutrient).	*'Support calcium absorption in bones to promote bone strength'* *'Helps increase body utilisation of magnesium to help reduce occurrence of muscle cramp'*

As well as the following for non-specific indications:

General nutritional supplementation (scientific indications only)	Supplementation with vitamins, minerals or other essential nutrients that imply a general health benefit such as the maintenance of good health. Note: to make a supplementation claim for a named vitamin or mineral, the product must provide at least 25% of the recommended dietary intake (RDI) for that vitamin or mineral.	*'Maintain/support calcium levels in the body'*

Based on the above, it is clear that the evidence requirements for supporting non-specific scientific indications for vitamins and minerals at 25% RDI is a very clear change in this version of the evidence Guidelines.

There is a clear lack of any examples of how health maintenance claims can be adequately supported, however the above examples form the past evidence Guidelines should be reinstated and included.

4.3 – Classifying scientific indications as specific or non-specific is a means to determine when it is acceptable for sponsors to hold a lower level of evidence

The evidence guidance document is contradictory throughout in the type of evidence expected for non-specific indications. Examples need to be provided as case studies of non-specific, health maintenance indications that are adequately supported by the evidence presented applicable in table 4

Maintain/support indication classification

There is a considerable change in the interpretation of maintain/support indications that now could be considered specific indications depending on the nature of the indication, even in the context of general healthy adult population, and as such under the new guidelines these indications now require high-quality clinical studies or systematic reviews as supporting evidence, which is not available for these general level, health maintenance indications and has always been accepted in the past and, for many indications, are suitable for use for food products that contain only 10% RDI per serve.

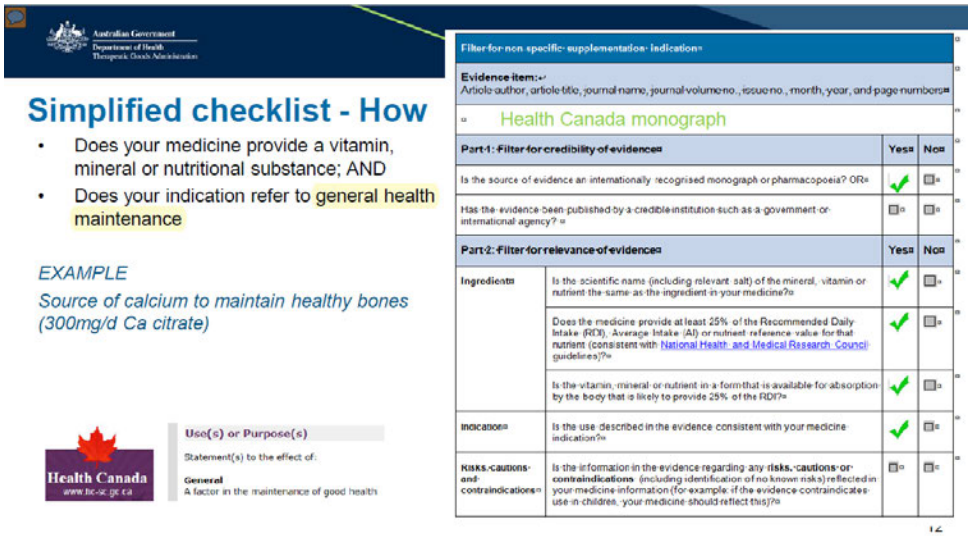
In the past, maintain/support indications were always considered non-specific indications, which were permitted to be supported by internationally recognised pharmacopoeias or monographs, descriptive studies, case series, or reports of relevant expert committees.

Below are the screenshots of previous Evidence guidelines (EG). Evidence guidelines (EG) 2014:

Table 2a: Non-specific indications for listed medicines

Non-specific indications (scientific or traditional)		
Health benefit	**Definition of health benefit**	**Example of an indication**
Health maintenance	Normal physiological effects of substances in growth, development and normal functions of the body.	*'Helps maintain general health and wellbeing'* *'Traditionally used in Ayurvedic medicine to support a healthy digestion function'.*
Relief of general symptoms	Symptoms not related to a named condition	*'Helps soothe dry skin'* *'Traditionally used in homoeopathic medicine to relieve muscle aches and pains'.*
General nutritional supplementation(scientific indications only)	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. Note: to make a supplementation claim for a named vitamin or mineral, the product must provide at least 25% of the recommended dietary intake (RDI) for that vitamin or mineral.	*'Provides vitamins and minerals to help support the body's nutritional needs'* *'Provides vitamin A to help maintain healthy hair and skin'.*

TGA presentation Evidence Guidelines & Checklists Benefits for Sponsors and Consumers by [redacted], OCM, June 2014:



Simplified checklist - How

- Does your medicine provide a vitamin, mineral or nutritional substance; AND
- Does your indication refer to general health maintenance

EXAMPLE

Source of calcium to maintain healthy bones (300mg/d Ca citrate)

Health Canada www.hc-sc.gc.ca

Use(s) or Purpose(s)

Statement(s) to the effect of:

General

A factor in the maintenance of good health

Filter for non specific supplementation indication

Evidence item:
Article author, article title, journal name, journal volume no., issue no., month, year, and page numbers

Health Canada monograph

Part 1: Filter for credibility of evidence		Yes	No
Is the source of evidence an internationally recognised monograph or pharmacopoeia? OR		✓	
Has the evidence been published by a credible institution such as a government or international agency?			
Part 2: Filter for relevance of evidence		**Yes**	**No**
Ingredient	Is the scientific name (including relevant salt) of the mineral, vitamin or nutrient the same as the ingredient in your medicine?	✓	
	Does the medicine provide at least 25% of the Recommended Daily Intake (RDI), Average Intake (AI) or nutrient reference value for that nutrient (consistent with National Health and Medical Research Council guidelines)?	✓	
	Is the vitamin, mineral or nutrient in a form that is available for absorption by the body that is likely to provide 25% of the RDI?	✓	
Indication	Is the use described in the evidence consistent with your medicine indication?	✓	
Risks, cautions and contraindications	Is the information in the evidence regarding any risks, cautions or contraindications (including identification of no known risks) reflected in your medicine information (for example if the evidence contraindicates use in children, your medicine should reflect this)?		

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TGA Checklist 4 Scientific evidence filter provides 2 filters:
4a for NS supplementation indication: Use this filter for non-specific (general) supplementation indications. → No separate checkbox for dosage as seen for Specific indications. That means the indications can be accepted when the medicine provides at least 25% of RDI of a vitamin/mineral/nutrient.

Part 2: Filter for relevance of evidence		**Yes**	**No**
Ingredient	Is the scientific name (including relevant salt) of the mineral, vitamin or nutrient the same as the ingredient in your medicine?	☐	☐
	Does the medicine provide at least 25% of the Recommended Daily Intake (RDI), Average Intake (AI) or nutrient reference value for that nutrient (consistent with National Health and Medical Research Council guidelines)?	☐	☐
	Is the vitamin, mineral or nutrient in a form that is available for absorption by the body that is likely to provide 25% of the RDI?	☐	☐

4b for specific scientific indications:

Dosage	How similar are the dosing details (dosage form, dose or dosage range and dosage frequency) described in the evidence to your medicine?	☐	☐	☐	☐

That means Maintain/support healthy bones, Maintain/support healthy hair and skin have been considered as NS by Evidence Guidelines 2014.
The checklist hasn't been updated since 2014 however there has been a distinct change in TGA interpretation since EG 2019:

Table 2: Non-specific indications for listed medicines

Non-specific indications (scientific or traditional)

Health benefit	Definition of health benefit	Example of an indication
Health maintenance	Normal physiological effects of substances in growth, development and normal functions of the body.	*'Maintain general health and wellbeing'* *'Traditionally used in Ayurvedic medicine to maintain/support healthy digestion'*
Relief of general symptoms	Symptoms not related to a named condition	*'Decrease/reduce/relieve skin redness'* *'Traditionally used in Chinese medicine to relieve muscle pain'*
General nutritional supplementation (scientific indications only)	Supplementation with vitamins, minerals or other essential nutrients that imply a general health benefit such as the maintenance of good health. Note: to make a supplementation claim for a named vitamin or mineral, the product must provide at least 25% of the recommended dietary intake (RDI) for that vitamin or mineral.	*'Maintain/support calcium levels in the body'*

"Provides vitamins and minerals to help support the body's nutritional needs" was removed, most likely due to it not being as per permissible indications.
However, the permissible indication "maintain healthy hair and skin" has been removed from the examples in EG 2019 without consultation.

Maintain/support indications should be non-specific indications when the target population is general healthy population, such as children, adults, men and women.

If the TGA considers they can become specific indications, please provide a clear set of criteria to avoid open interpretation in the future.

For example:

- Which maintain/support indications? Or criteria?
- Which target population/ population qualifier/ or which qualifier when used with M/S indications that would turn the indications into specific?
- What if support general health (e.g. support healthy bone density), instead of maintaining bone density? (Although bone density decreases as a normal process of ageing in certain subpopulation, there should be a shift in the mindset that this should not happen if nutritional needs of the body at that age are met)

With this in mind, "maintenance of health" should be removed from the below section in 3.1.3 (pg 26) in the draft:

Examples of such long-term benefits include: maintenance of health; risk reduction; or favourable modulation of body weight, as the body's homeostatic processes may reduce early gains. This is of particular importance for medicines designed for weight loss. This is explained in further detail in 4.4.4 Weight loss indications

4.3.1 and 4.3.2 and the table – Leave the categorisation of specific and non-specific indications completely ambiguous and open to interpretation and in many instances, categorise indications differently (both higher and lower level) than previously categorised by the TGA. Successful regulation is consistent, easy to follow and predictable, however this is not.

4.4 - Often clinical studies conclude that an effect *might* be present, but that further investigation is needed – Most studies will provide for a statistically significant effect, but none will confirm that an ingredient or product is effective in all cases, as this is not true. We need examples of what will be accepted here.

4.4. What types of evidence are expected for each type of indication?
The options presented in Table 4 may not be suitable for every medicine. These requirements represent the lowest threshold below which the efficacy of the medicine cannot be reasonably assessed.
This table provides for Minimum evidence requirements for scientific and traditional indications**;** however it lists evidence that we know the TGA have not accepted in the past and are very unlikely to accept in the future, e.g. "Observational studies, for example: "cohort and case-controlled studies" and "Comparative studies (non-controlled)". The TGA has not in the past 5 years accepted Observational studies, for example: cohort and case-controlled studies with evidence-based texts for specific indications nor, are they likely to under these evidence guidelines. In fact section 3.2 states "Depending on your chosen indication, cohort and case-control studies may not be enough to substantiate the indication (i.e. efficacy) due to the higher risk of bias associated with these types of studies. In these situations, the studies may be included in your evidence package to be critically appraised in conjunction with other evidence sources". When will observational studies such as cohort and case control studies be accepted for a specific indication? Please provide an example and case study.

This section needs to be truthful in stating what reviewers will accept so as to avoid confusion and frustration on the part of the sponsor and further distrust in an unpredictable regulatory model. If the table lists "cohort and case-controlled studies" and "Comparative studies (non-controlled)" as being acceptable, as they should be for these low-risk medicines with low level indications, these types of studies MUST be accepted by TGA reviewers. If they won't be accepted, this is a clear change, and it must be truthfully acknowledged to industry.
As per the information above, this information combined provides for confusing and inconsistent information that is completely open to the interpretation and acceptance of the reviewer, which fails the intent of the new Evidence Guidelines.

We need examples and case studies of when the evidence in table 4 will be accepted, as currently the rest of the evidence guidelines contradicts this table.

4.4.2.1 – states:
Examples of supplementation claims in relation to the mineral magnesium are:
- 'magnesium supplement'
- 'dietary magnesium supplement'
- **'source of magnesium'**

2019 evidence guidelines states:

Indications / claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

As such, a claim to the effect "Contains magnesium" was previously able to be used at 10% RDI. The above implies this is being increased to 25% RDI. This needs to be amended.

4.4.2.2 Supplementation claims minimum evidence requirements states:

a. Provides at least 25% of RDI, AI or NRV
b. Nutrient is in a form that can be absorbed by the body

c. Medicine must also have at least one permissible indication in the medicine's ARTG entry and on the medicine label

"Nutrient is in a form that can be absorbed by the body" should be amended to read "Nutrient intended for supplementation can be absorbed when provided in the form supplied in the supplement". This will avoid interpretation that the nutrient must be absorbed in the form as provided in the supplement, e.g. minerals salts as the mineral salt or P-5-P.

4.4.3 Lists the two biomarker claims as:

- 'Aid/assist/helps glucose/sugar/carbohydrate metabolism'
- 'Helps maintain/support healthy cholesterol'

'Aid/assist/helps glucose/sugar/carbohydrate metabolism' should be 'Helps maintain/support healthy blood sugar/glucose'

It is disappointing that such an important document has not been proofread before consultation.

Cheryl has stated that the advertising exemption/restricted representation approvals for calcium and vitamin D at 25% RDI were based on assessment of data specific for these two nutrients and the data and the indications remain relevant under the new evidence guidelines as there has been no change in the requirements. As such, and in order to avoid a change in interpretation at a later date and to future proof the guidance, this information and the following must be included as case studies for both the vitamin D restricted representation and calcium restricted representation claims as to what is suitable for justifying 25% RDI:

The advertising exemption for calcium and vitamin D restricted representations

- In relation to the data used by the TGA to make its decision for the minimum dose of calcium, the explanatory statement is available on the TGA website, published in 2015, at: https://www.tga.gov.au/advert-exempt/advertising-exemption-calcium-minimum-recommended-daily-dosage-290-mg-elemental-calcium. You will note the data taken into consideration included: the bioavailability of calcium; the RDI; the average consumer consumption of calcium; as well as the requirements in the Evidence Guidelines. The reference list, as published in the published explanatory statement, is replicated below. Sponsors that wish to use 25% RDI as a dose for a particular indication can follow a similar approach to justify the efficacy of their listed medicine and this type of evidence will be deemed acceptable by the TGA as per the examples provided in the calcium and vitamin D restricted representation approvals:

1.Schedule 4 to the Therapeutic Goods Regulations 1990 (https://www.comlaw.gov.au/Series/F1996B00406) (the Regulations) states that for a medicine to be eligible for listing in the ARTG, the sponsor of the medicine cannot propose an indication that refers to the *treatment* of any of the diseases, conditions, ailments or defects specified in Appendix 6 Parts 1 or 2 of the Therapeutic Goods Advertising Code (//www.tga.gov.au/publication/therapeuticgoods-advertising-code). Medicines with these indications must be registered, rather than listed, in the ARTG. See also the Overview of listed complementary medicines (//www.tga.gov.au/book-page/overview-listed-complementarymedicines) in the Australian Regulatory Guidelines for Complementary Medicines.

2. Australian Government National Health and Medical Research Council and New Zealand Ministry of Health, Nutrient Reference Values, Calcium (https://www.nrv.gov.au/nutrients/calcium).

3. According to the Australian Bureau of Statistics, 2014. Australian Health Survey: Nutrition First Results – Foods and Nutrients, 201122-12 - Australia: "In 2011-12, the daily amount of calcium consumed from foods and beverages averaged 865 mg among males and 745 mg among females" Calcium (http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.007~2011-12~Main%20Features~Calcium~714)

4. *Evidence Guidelines: Guidelines on the evidence required to support indications for listed complementary medicines (//www.tga.gov.au/publication/evidence-guidelines)*, p.52.

5. Food Standard 1.2.7 requires that such a claim only be made where accompanied by words to the effect that it is effective where a person has a diet high in calcium and adequate vitamin D status.

Section 5 How to document and present evidence

Is it clear what the TGA might consider as gaps and discrepancies in the evidence source?
Yes. It is clear; however, it is completely open to interpretation of the reviewer. This Evidence Guidance document has failed to provide the intended clarification. Further, the critical appraisal of the body of evidence generated from the literature searches is a new requirement, and although the TGA will continue to say it's not a requirement, and only a suggestion, we know that as time goes on, it will be considered a requirement and evidence will not be accepted if this is not provided for.

This additional requirement means that a full critical appraisal is required for every ingredient and every indication, resulting in a massive increase in work and costs for the sponsor. While we agree that if there are significant gaps in the evidence, this critical appraisal may be required, for evidence and indications that are directly relevant, it should not be required, and common sense should be used by the reviewer.

Is it clear why it is important to include a persuasive critical appraisal of the body of evidence in an evidence package?
No

As per above, a critical appraisal should not always be required. If the evidence directly supported the indication, or if anyone using common sense should be able to assess the relevance of the evidence to the indication, a critical appraisal will simply waste valuable resources by increasing the size of the evidence package for review. As such, it should only be required if there are gaps in the evidence that require explanation. Further, if the TGA feel that a critical appraisal is required because TGA reviewers don't have the experience or expertise to ascertain if the evidence is suitable and relevant, two people with the same evidence may obtain completely different results depending on the reviewer and if the person writing the critical appraisal can tell a good story. This is not scientifically correct and inappropriate when industry funds are being used to employ people in the review section who should have the experience and expertise to adequately review the evidence.

Further comments are provided below:

The note at the start of this section states:
Evidence packages provided to the TGA as part of an evidence review are not required to comply with a specified format. However, following the guidance set out in this section will increase your ability to show the TGA that your medicine is efficacious and meets the requirements as set out in 1.2 Sponsors' legal responsibilities

Based on industry experience with the TGA, we know this not to be the case, and the TGA take the wording of the evidence guidelines to be legislation, which is why it is so important to industry to get it right.

The appendices of the Guidelines include case studies to assist interpretation of the Guidelines content.

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 is a terrible example! Please provide information that is relevant to the evidence guidelines and that will be accepted by reviewers.

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?

Yes. Please include the following case studies:

- Calcium supplementation at 25% RDI to use and support the following indications at a dose of 290 mg per day, without a restriction on calcium salts:
  Representations to the effect:
  '... may assist in the prevention of osteoporosis when dietary intake is inadequate' and;
  'Source of calcium. A diet deficient in calcium can lead to osteoporosis in later life'.
  The following is the evidence used and should be the evidence cited as suitable for use in the case study:

1. Schedule 4 to the Therapeutic Goods Regulations 1990(link is external) (the Regulations) states that for a medicine to be eligible for listing in the ARTG, the sponsor of the medicine cannot propose an indication that refers to the *treatment* of any of the diseases, conditions, ailments or defects specified in Appendix 6 Parts 1 or 2 of the Therapeutic Goods Advertising Code. Medicines with these indications must be registered, rather than listed, in the ARTG. See also the Overview of listed complementary medicines in the Australian Regulatory Guidelines for Complementary Medicines.
2. Australian Government National Health and Medical Research Council and New Zealand Ministry of Health, Nutrient Reference Values, Calcium(link is external).
3. According to the Australian Bureau of Statistics, 2014. Australian Health Survey: Nutrition First Results - Foods and Nutrients, 201122-12 - Australia: "In 2011-12, the daily amount of calcium consumed from foods and beverages averaged 865 mg among males and 745 mg among females" Calcium(link is external)
4. *Evidence Guidelines: Guidelines on the evidence required to support indications for listed complementary medicines*, p.52.
5. Food Standard 1.2.7 requires that such a claim only be made where accompanied by words to the effect that it is effective where a person has a diet high in calcium and adequate vitamin D status.

   Please include vitamin D supplementation at 25% RDI to support the following indication Vitamin D helps calcium absorption (or words of like intent) and a diet deficient in calcium can lead to osteoporosis in later life". Please include the evidence that is suitable at 25% RDI to support this particular indication.

   Please include a case study providing for suitable evidence for non-specific indications such as “Vitamin C supported healthy immune system function”. Please provide an example of a suitable non-systematic review including sources such as reference based textbooks.

Please present the ingredients as per the requirement within TGO 92. It is a repeated occurrence within TGA that examples, whilst they are hypothetical are not consistent with terminology and other regulatory guidelines in their presentation which is confusing to sponsors.

Case study 2:
Equiv. to = this terminology for presentation of ingredients is no longer acceptable to TGA under TGO 92.

Case study 4:

Different solvent extraction preparation method (acetone vs ethanol/water in the literature)
TGA states:
The profile of phytochemicals extracted into any solvent depends on the solubility of the compound of interest in the solvent of choice. The sponsor did not provide a justification to demonstrate that similar chemical constituents would be extracted by using the stated acetone: water mixture instead of the ethanol: water mixture. Therefore, in the absence of sufficient justification and/or supporting documents to demonstrate the **comparability of the extracted components**, this evidence source is not considered applicable to the sponsor's medicine.

All preparation methods for herbal medicine refer to justification of comparable components.
This is not feasible due to the inherent nature of herbs differing in chemical profile and constituent amounts from batch to batch even with the same extraction method. Please provide an example of where a preparation method is acceptable, e.g., evidence references an infusion, which is essentially a 100% water extract, however as the product uses an extract made using 100% water as the solvent, and the and the same solvent (water) will extract the same components, and the equivalent dried weight of the starting herbal material is the same as the evidence, the evidence is suitable for use.

Case study 5:
Preparation method (raw) does not match
Panax ginseng literature states root in powder form. Formulation is Panax ginseng ethanol:water extract.

The use of a solvent extracts certain components of the whole herb material, thereby changing the chemical constituents of the extract in comparison to the whole herb.
The sponsor did not provide any justification to demonstrate that the different method of preparation would result in the same **therapeutic effects** as the whole herb that has undergone physical processing only. Therefore, as the method of preparation used in the evidence source is not comparable with the method used for Beans Root, the therapeutic effect described in the evidence source cannot be extrapolated to the medicine.

How do you justify 'same therapeutic effect'. Why is this different to the Milk thistle case 4, which needs to demonstrate similar chemical constituents? Expectation and terminology must be consistent.

Case study 8
Traditional indication for SMT, evidence from suitable sources described method of preparation (extract ratio) dose and plant part were consistent with the medicine. **Minor** discrepancies in solvent were justified by sponsor.
The difference in the extract solvent was sufficiently justified by the sponsor that the solvent used for the medicine extracted **comparable active components** of the herb without toxic solvent residues.

Please provide more information here on the minor discrepancies in the solvents and the justification provided by the sponsor.

Case study 9
Policosanol
Helps maintain/support healthy cholesterol.
Suggests a monograph states policosanol 'maintains serum lipid profiles'. Benefit is described in a way relevant to the medicine including conditions of use and population which it is intended for.
Evidence based text also describes beneficial effects in a way that is consistent with the medicine use, including intended population – healthy populations. Text describes policosanols hypocholesterolemic effects in healthy volunteers and type II hypercholesteraemic.

This is an unrealistic example. TGA has not accepted evidence that states hypercholesterolemia when the target population is healthy. TGA previously stated it is potentially dangerous for biomarkers to be reduced in healthy individuals.

Previous TGA interpretation:

While it is understood that chromium is involved in carbohydrate metabolism, it is not clear from the evidence you provided how chromium supplementation would have any additional benefit in maintaining healthy glucose metabolism in healthy individuals who are expected to have normal chromium intake. Therefore, the indication relating to maintaining normal glucose metabolism is not supported by the evidence you hold.