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Comparison of Evidence Guidelines v 3.0, January 2019

to the Draft Evidence Guidelines March 2022

Feedback on the Content, Presentation, and Usability of the updated Guidelines.

As per the TGA consultation hub https://consultations.tga.gov.au/medicines-regulation-division/proposed-update-to-evidence-guidelines-listed-meds/ ***The purpose of this update is to:***

- *Enhance the readability and utility of the Evidence Guidelines (EG);*
- *Clarify the way the TGA interprets and analyses the different types of evidence; and*
- *Clarify specific technical concepts that have been problematic or unclear in the existing Guidelines*

The update of the Guidelines is not intended to change the regulatory requirements for listed medicines and will not change the existing requirements to substantiate indications. Nevertheless, it is inevitable that some clarifications may appear to be a change to some readers, given that the previous lack of clarity would have resulted in different interpretations.

TGAs Version history notes for Vs.4.0:

- Restructured - no longer parts A and B, instead has been put into sections that align with the process a sponsor would follow.
- Added information to consider when undertaking a critical appraisal of evidence.
- Updated the types of sources of evidence and the levels of evidence.
- Added information relating to non-systematic searches to the literature search section.
- Added an example of a literature search strategy.
- Updated statistical analysis section.
- Clarification of the specific/non-specific classification and the removal of this classification for traditional indications.
- New decision tool to assist classification of specific/non-specific indications.
- Updated evidence requirements for supplementation claims and indications
- Updated the weight loss section to differentiate between long-term and short-term weight loss.
- Update to the minimum levels of evidence requirements for traditional and scientific indications.
- Updated/ new figures, tables and decision trees.
- Removed references to journal impact factors.
- Added a justification section and examples of where a sponsor would provide a justification as part of their evidence package.
- Evidence package checklists have been removed (a link to the TGA website provided) as these are under currently review.
- Added an appendix with theoretical case studies.
- Added an example of an evidence package.

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SECTION 1 – Introduction

Questions 1-3 request name, email and organisational details of the respondent.

[redacted]

[redacted]appreciates the opportunity to provide feedback on the Draft Listed Medicines evidence guidelines. However believe the short period on this consultation is not sufficient time to be able to provide an in-depth analysis of the document as such commentary included may not cover all concerns that may later be discovered.

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?

Section 1 attempts to explain the relationship between the Act and Regulations, and the Evidence Guidelines.

In this section it is argued that the Act and Regulations require us to have on file a critical analysis of the evidence in support of indications.

While we understand the importance of a critical analysis from a scientific perspective, it is unclear from a legal perspective why a critical analysis is required. That is, the legislation and legislative instruments referenced in Section 1 state that we need only have 'supporting evidence on file', and not that we need have 'supporting evidence and a critical analysis of the evidence on file'.

For instance, *subparagraph 26A(2)(ja) of the Act*, referenced in Section 1.2, simply states:

(ja) both:

(i) the applicant holds information or evidence to support each indication proposed to be accepted in relation to the inclusion of the medicine in the Register; and

(ii) the information or evidence complies with any requirements specified in a determination under subsection (2B); and

We therefore fail to understand, from a legal point of view, why a critical analysis of the evidence is required over a simple reference list, and would appreciate the TGA clarifying this point.

Therefore, the need for a critical analysis is a new requirement, however we understand and agree that we need to hold supporting evidence on file.

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

Refer to Q22

[redacted]

SECTION 2 – How to find evidence

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, but some areas are not very clear (see below feedback on section 2)

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

2.1.2.1 Scientific evidence sources - sponsors are encouraged to refer to the document 'NHMRC levels of evidence and grades for recommendations for developers of guidelines', available from: NHMRC levels of evidence and grades for recommendations for developers of guidelines 24 page document - this is new

2.1.2.2 Other sources of evidence for traditional use - How is a 'monograph' and a 'publication from various international regulatory authorities' (presumably from Health Canada or EMA) different from 'modern monographs' described under 'Other sources of evidence for traditional use' (2.1.1.2)? Examples would be helpful.

In the new draft EG, under 2.2 Literature Searches, TGA now refers to the document 'Literature-based submissions for listed medicines and registered complementary medicines', Vs1.0, 2020, available from: https://www.tga.gov.au/resource/literature-based-submissions-listed-medicines-and-registered-complementary-medicines, as well as The Cochrane Handbook of Systematic Reviews of Interventions available from https://training.cochrane.org/handbook 728-page document for detailed guidance on best-practice standards -> this is new.

TGA stresses that systematic reviews of the literature are required (and preferred to non-systematic reviews – see page 22) and that manual searches are deemed useful, as well as the use of the PICO model to formulate a 'research question' (see 2.2.2.1). Nevertheless, full details of the search methodology used to obtain evidence sources should be provided in an evidence package, including a clear explanation and justification for using it**.** This applies to both scientific and traditional indications – this is a new requirement**.** The inclusion and exclusion criteria need to be established in the search protocol – this is new. These are listed (see page 18).

A detailed search process for each database should be documented (see page 20); examples of search protocols are provided (see page21 and 76-79)

Overall, these new requirements present a dramatic change, despite the fact that the new EG were supposed to not contain any, but merely '*enhance readability and utility; clarify the way the TGA interprets and analyses the different types of evidence; and clarify specific technical concepts that have been problematic or unclear in the existing Guidelines'*.

[redacted]

This section is a little confusing: at the beginning of this section there is an explanation that the TGA is not mandating a particular search strategy; however, at various points throughout this section there are references to requirements that do feel mandatory (such as "Searches should not be limited to English" on page 18), leading us to wonder what is and isn't mandatory in this section.

On page 15, there is an explanation that we need to explain and justify the search strategy. This sounds like we need to explain the specifics of our search strategy (such as explaining why we chose to search in PubMed). However, in Appendix 3, no such explanation or justification of the search strategies is given. It would be appreciated if this comment was clarified – what does the TGA expect us to provide to 'explain and justify' the search strategy?

On page 20, it explains that we need to record all references found, even those that weren't used. This is a new requirement, and I wonder the utility of managing such large reference lists when a clear inclusion and exclusion criteria are provided – from our experience it is quite rare for even peer reviewed systematic reviews to list every single reference that was filtered out.

SECTION 3 – How to assess evidence

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?

Overall, there is an immense amount of complex information, numerous links to additional guidance documents, and additional recommendations as to what analyses, justifications and discussions should be added to an evidence package.

[redacted]

While TGA intends to increase clarity and usability of the current evidence guidelines, it is obvious that the new draft guidelines are in fact far more complex which diminishes their usability.

We believe this is a substantial amount of additional work for industry that would potentially come to additional financial costs for sponsors and industry

We note that while the proposed risk of bias tools are well known and highly respected, they are more comprehensive than the current Evidence Checklist 4. Therefore, while the TGA acknowledges that any ROB tool could be used, we are concerned that we would need a very persuasive justification to use the current Checklist 4 over these peer-reviewed tools.

1. Consider for instance, the CASP ROB Tool which asks, 'Were the study groups similar at the start of the randomised controlled trial?'
2. Checklist 4 doesn't ask this question, so, if this question is not considered by a sponsor when evaluating a piece of evidence, the TGA could be expected to seek clarification from sponsors as to why this component wasn't considered. It would be hard to argue that this wasn't an important consideration given the CASP ROB Tool asks this question!
3. Consider further that the guidance document for the Cochrane ROB tool is 76 pages long! Much more comprehensive than the current Checklist 4. Therefore, there would be many questions and considerations present in the Cochrane ROB Tool that are not considered by Checklist 4.

Therefore, the use of these standard ROB tools can be considered a new requirement, which will increase the workload associated with new LoEs, and necessitate a thorough review and update of existing LoEs.

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?

I believe the previous arrangement was fine; changing or removing the terms 'primary' and 'secondary' does not enhance clarity

The new EG no longer refer to 'primary supportive' sources, and 'secondary supportive' sources. I believe that the differentiation is helpful, especially as the new evidence guidelines still refer to supporting evidence.

On page 29 we did find it surprising that publicised international regulatory authority articles are only Category C. We would have expected these to be at least Category B.

[redacted]

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

Yes, the following changes have been noted:

The hierarchy of scientific evidence sources into three categories in table format was designed to increase clarity. However, the studies are categorised based on bias (as per heading) not overall quality & significance as in the 2019 EGs. This potentially diminished clarity as bias is just one factor to consider in order to determine quality of evidence.

Regarding evidence on active ingredients in traditional medicines, the 2019 EG state (in comparison to the new draft EG, 3.1.2.1 on page 24-25): *In general, active ingredients may be considered as sufficiently identical* - now: 'comparable' - *if there are no relevant differences in the method of preparation* - newly included here is: '*such that comparable outputs are yielded'*- *and if the medicine has the same intended purpose, dosage and the same route of administration. This includes traditional medicines in which the therapeutic indication, dosage and administration are based on traditional knowledge but the* dosage forms have *been modified to modern dosage forms, for example: capsules or tablets* - newly included here is '*but the outputs have been demonstrated to be comparable*' – the change from 'identical' to 'comparable' appears to be a positive one.

2019 EG: *When evidence relates to a herb or herbal substance, the species (and subspecies where applicable), plant part and route of administration should be identical to that described in the evidence. The method of preparation and processing, the equivalent dry weight and the dose of active component described in the evidence should be consistent* – newly includes 'comparable' - *with that in the medicine.*

2019 EG: *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, your active ingredients and method of preparation should be identical* - newly includes 'comparable' - *to that described in the classical literature.*

The above paragraph is newly accompanied by additional clarifications on page 25 of the new draft EG: *Where there are differences in parameters, such as the dosage or method of preparation, justifications (substantiated by evidence) should be included in the evidence package to explain why the discrepancies have no impact on the extrapolation of the traditional evidence to your medicine.*

2019 EG (page 19): *(Traditional) Medicines that have been altered significantly in their constituent profile from the traditional medicine on which the indication is based will require scientific evidence to substantiate their claimed action.* The latter part of the sentence was changed to *a justification and/or additional information should be provided in the evidence package.* This is now clearer.

2019 EG (Part B, page 36): Regarding the 'Equivalency of ingredient, preparation, dosage and dosage form between the evidence and your medicine' – more specifically 'potential

differences in components that were not standardised which may result in different pharmacological activity' where processing methods differ, the new draft EG additionally state '*This should be documented in the evidence package accompanied with a justification for why the differences have no impact on the extrapolation of the data in the evidence source to your medicine.*

Essentially, there is no change to this requirement, however, (as also stated in the new draft GL), many trials do not provide a chemical profile of all components in the studied active ingredient in addition to the standardised component. It would be difficult to provide such evidence. Due to proprietary reasons, to provide such evidence may not be possible and Processing methods are rarely provided

2019 EG (page 36-37) - In regard to the relevance of a study population (for scientific indications): *The health status of the study population should be representative of the target population for your medicine… However, in circumstances where a positive modulation of a health benefit is noted in a diseased study population, it may be possible to use these clinical outcomes to provide secondary evidentiary support for your indication.*

In the new draft EG, it is stated (on page 27): *However, in cases where there is data to suggest that the pathophysiology of the disease does not change the way the active ingredient works in the milder form of disease, compared to the more serious form of disease, the relevance of these evidence sources may be justified. Extrapolation of results obtained from subjects outside the target population of the medicine should be appropriately justified* – this is new.

Note, the hierarchy of scientific evidence depicted as a pyramid (on page 26 of the 2019 RG) has been changed to a table (page 29 of new draft EG) with less detail: As per the 2019 EG:

Suitable evidence to support a scientific indication can be obtained from:
- *high quality, preferably multi-centre, random controlled trials (RCT)*
- *well-designed controlled trials with randomisation; or*
- *well-designed analytical studies preferably from more than one research group, including cohort and case-control studies.*

However, in the new draft EG, use of case-control studies is somewhat discouraged: *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…these studies may be included in conjunction with other evidence sources… They can, however, provide valuable supportive data… 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.*

3.2.2 Assessing the quality of scientific evidence (page 30 of new draft EG) – here it is recommended that sponsors *use the* Grading of Recommendations Assessment, Development and Evaluation *approach to assessing the certainty of a body of evidence and which is considered best practice by many international organisations.*. This is new and adds

[redacted]

another layer of complexity to assessing evidence (using the GRADE approach to assess evidence OR adding a discussion of the impact of potential bias on data if it is NOT used).

3.2.2.1 Evaluating the study design (page 31 of the new draft EG) - includes the following
Note: Not all evidence sources will have applied or discussed all the factors described below. If a sponsor chooses to include such evidence sources in the evidence package, it is the sponsor's responsibility to justify how the limitations in the evidence sources do not impact on the conclusions about the body of evidence (included in the evidence package) and the efficacy of the medicine.

The EG from 2019 merely state (page 40) *If you choose to use a clinical study to support a scientific indication, you are not expected to perform power calculations, but to consider any limitations of the statistical calculations that the study authors have reported, including the number of drop outs and the impact this may have on the reported study outcomes.*

Effectively, the recommendation '*to consider limitations of statistical calculations*' has changed to '*justify how the limitations in the evidence sources do not impact on the conclusions about the body of evidence included in the evidence package and the efficacy of the medicine*'. Again, this adds another high level of complexity for sponsors when preparing an evidence package. Moreover, the draft EG refer to the highest calibre of (ideal) clinical research there is (also see 3.2.2.2 to 3.2.2.7 on pages 31-35) and the most precise way to assess it, while the quality of complementary medicine research – in reality – is often of lesser quality and provides fewer details to be critically assessed by sponsors.

OTHER NEW REQUIREMENTS WHEN ASSESSING EVIDENCE INCLUDE that add additional layers of complexity:

3.2.2.4 Study outcome: primary and secondary clinical outcomes:
Where information about method validation is not reported in a study, the impact of this on the conclusions drawn from that study should be accounted for. Whether there is confidence in the measurement method to generate reliable and accurate results should be considered and documented for each evidence source included in the evidence package.

3.2.2.5 Statistical analysis:
In general, the principles outlined in Note for Guidance on Statistical Principles for Clinical Trials (ICH Topic E9) Note for Guidance on Statistical Principles for Clinical Trials should be considered when assessing whether the statistical analysis of a clinical study has been conducted in a robust manner… 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.

3.2.2.5.1 Statistical significance (p-value):
Things to consider relating to statistical significance and the p-value include whether:

- *the statistical test used to derive the p-value is appropriate and reliable*
- *the p-value obtained for the primary outcome is less than 0.05*
- *all the actual p-values (not just p < 0.05) are reported*

RE power calculations, sponsors were previously encouraging *to consider any limitations of a statistical calculation that the study authors have reported, including the number of drop outs and the impact this may have on the reported study outcomes* (2019 EG, page 40), while now (new draft EG, page 34) they are encouraged to *consider why a certain effect size was selected; number of dropouts; and how these factors impact on the reported study outcomes. If you choose to include an underpowered clinical study in your evidence package, you should include a justification for why you think the study outcomes can be relied upon to reflect the efficacy of your medicine in the context of the body of evidence included in your package.*

3.2.2.6 Tools for assessing risk of bias:

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 in your evidence package have adequately controlled for bias should be included in your package.

Note: The following tools may assist when assessing the quality of the evidence source (page 34-35):

- *PRISMA / AMSTAR – developed to evaluate systematic reviews of randomised and non-randomised trials*
- *CASP – series of critical appraisal checklists designed for use with systematic reviews, RCTs, cohort studies, case control studies etc.*
- *CEBM – has a selection of tools to assist with critically appraising literature*
- *CONSORT Statement – provides the international standards for reporting randomised trials*
- *EQUATOR Network – provides reporting guidelines for all main study types*

This all seems over complex and not in the spirit of the MMDR review for the listed medicine category when these are low risk medicines with a pre-determine list of indications to choose from and are limited to indications relating to a health enhancement, health Maintenance, prevention of a non-serious vitamin or mineral deficiency and indications for non-serious forms of disease ailment defect or injury.

[redacted]

SECTION 4 – How to use evidence

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

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 '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?

If adequate evidence form category A in a healthy population is available, I believe sponsor would include it. Otherwise, evidence from category B and C should be considered sufficient given that these indications are deemed non-specific; no exemptions from the rule should be made.

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

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)

The answer depends on how much of the nutrient is supplied in the listed medicine, i.e. at least 25% may still not add up to the full RDI if a diet is very deficient; however, if the full RDI is provided by the medicine, it can be considered to be met in full. Any indications currently

[redacted]

using a supplementation claim must include a label warning, this should inform the consumer that the medicine is not providing a full spectrum of supplementation.

However, there is concern around the implied higher level of evidence required to support a supplementation indication in cases such as where a specific population group is mentioned, where these indications may no longer be considered non-specific. This needs to be clarified.

We should at the very least be able to make claims in line with FSANZ Schedule 4 Nutrition, health, and related claims

Q15. Do you find the evidence requirements for weight loss indications clear and easy to understand?

Yes

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

Yes, table 4 on page 49 under 4.4 on the 'Minimum evidence required for scientific and traditional indications' is very helpful.

Other new changes include:

''specific' versus 'non-specific'

Regarding traditional indications, the TGA's now focuses on whether efficacy is supported by legitimate traditional sources of evidence rather than the specificity of the indication.

The 2019 EG page 15 states, Traditional indications present factual statements of a health benefit relating to a historical record of use within a traditional paradigm. Traditional indications cannot make a scientific claim of efficacy.

However the new draft EG page 37 is asking for efficacy. This is new

Traditional indications no longer require to be categorised into 'specific' or 'non-specific'. This is a positive regulatory change.

Health maintenance as a non-specific indication

Excluded here is 'Maintain/support joint health in elderly people' (see table 3, page 42 in new draft EG). This is new and implies (based on the example below) that this indication - in the context of age (elderly people) - would be considered 'health enhancement', as joint health decreases as a normal process of ageing in this subpopulation.

When is health maintenance a specific indication?

As per the Note on page 43 of the new draft EG: The presence of the term 'maintains/supports' in a permitted indication does not automatically mean that the indication relates to a 'health maintenance' action and therefore, is a non-specific indication. When determining whether your indication is about health maintenance or health enhancement, you should consider the indication holistically, considering factors such as the

target population or the nature of the condition that is referred to in the indication e.g., 'Maintains/supports healthy bone density' when in the context of postmenopausal women would be considered 'health enhancement', as bone density decreases as a normal process of ageing in this subpopulation. Therefore, referring to maintaining bone density in this subpopulation goes beyond normal functions of the body.

We should at the very least be able to make claims in line with FSANZ Schedule 4 Nutrition, health, and related claims

On page 48, there is an explanation that 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.

This is a new requirement, and problematic as:

- Given that there is only a limited pool of scientific studies and traditional sources which support the use of listed medicine ingredients for the permitted indications, there is often overlap between the references cited by Category B and Category C sources.

  This means that many existing LoEs may be found to be non-compliant.

- Searching through the reference list of evidence-based textbooks to ensure identical references aren't used will significantly increase the workload to generate new LoEs.

SECTION 5 – How to document and present evidence

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

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

In general, we understand that evidence is required, however we feel that the requirement of a critical appraisal for every indication is not commensurate with the low risk nature of AUST L medicines.

With reference to Section 1.4, we understand that the TGA needs to understand the basis upon which it can be concluded that the medicine will likely result in the stated therapeutic effect.

We also understand that all sources of evidence are subject to bias, and that there are times when:

- particular sources of evidence may be subject to significant bias or confounding;
- particular sources of evidence may be missing critical pieces of information;

[redacted]

- particular sources of evidence may not perfectly match the medicine; and/or
- where the evidence landscape is mixed with positive and negative findings.

However, we find it surprising that all indications now require a critical appraisal which considers and explains these factors, including very straight forward indications such as non-specific scientific indications which may have as their supporting evidence only two Category B/Category C references.

Based on the current Evidence Checklists, it was our understanding that a simple table of evidence was sufficient unless there were specific issues with bias, missing information, mixed evidence, etc. which necessitated a justification.

In summary, we understand that a critical appraisal is sometimes necessary, but we do not understand why it is always necessary, particularly in cases where the evidence is self-explanatory, of high quality and evidently subject to low risk of bias.

We believe significant additional resources will be required based on these guidelines, which is not in the spirit of the MMDR objectives. We believe the overall industry cost of compliance will be enormous for what are effectively low risk, and safe medicines and the level of evaluation is disproportionate to the allowable claims. We feel the approach is more suited to OTC / Prescription based medicines not freely available off the shelf self-select medicines

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

Yes - The new draft EG state: ***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… Evidence packages* ***can*** *be submitted using the existing Evidence package checklists (currently under review) available on the TGA website. Sponsors* ***may*** *also choose to follow a similar format as demonstrated in the example evidence package for vitamin B12 in Appendix 3*.

The wording suggests that sponsors are not obliged to present their evidence packages in either of the two suggested ways, but are encouraged to follow the new EG.
Sponsors are therefore more likely to meet their legal requirements by updating any evidence packages of products for which a post-market compliance review is requested by the TGA.

In relation to evidence packages – and as covered in detail in section 3 - sponsors need to demonstrate that the data or information collected is a true and accurate representation of the evidence landscape by (amongst other things) by (amongst other things – see page 57) demonstrating that assumptions made are valid, biases do not impact data validity, and evaluations of the impacts of competing data on the conclusions have been made.

Evidence packages can be submitted using the existing Evidence package checklists (currently under review) available on the TGA website. Sponsors may also choose to follow a similar

[redacted]

format as demonstrated in the example evidence package for vitamin B12 in Appendix 3… holding a combination of moderate and low-quality sources, or several weak or low-quality sources that meet the relevance and quality criteria when combined, may help strengthen arguments to support your conclusion – this advice is more helpful than that given in the 2019 EG which states (on page 61): *Items that are considered to be of low quality should be disregarded unless you can provide a justification.*

5.1.3 Justifications in your critical appraisal - It is helpful that TGA provides an example here on the use of source that include unhealthy population groups (e.g., adults with a serious disease): *In some circumstances, a combination of in vitro, non-clinical and clinical data may show that the mechanism of action of an active ingredient works independently of the disease state and any pathophysiological differences of the study participants. In this instance, data from a diseased population may be justified to be generalisable to a healthy population.* Overall, it is helpful that this draft EG includes more detailed advice – including a summary - on when justification may be required to support indications (generally where data gaps are evident).

On page 58, there is an explanation that:

"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 previous evidence guidelines weren't as specific on this point, only stating:

"You should also ensure that the evidence supporting your indications remains valid for the life of the medicine, and this is best achieved using a body of evidence approach. As research advances, the body of scientific evidence supporting a particular health benefit may change. Newer clinical studies may enhance the strength of the evidence supporting your claim, or it may be inconsistent with the strength of previous research. Having a body of supporting evidence will allow you to ensure that the indications claimed for your medicine remain true, valid, are not misleading and consistent with scientific evidence for the life your medicine." (page 31)

This new wording raises the concern that the TGA will expect evidence of regular searches to maintain LoEs, like the pharmacovigilance requirements. It would be appreciated if the TGA could clarify this point.

APPENDICES

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?

[redacted]

Yes. The non-systematic search of the scientific literature would normally result in finding various international monographs and evidence-based textbooks, i.e., the Health Canada monograph, NHMRC monograph and Braun & Cohen text (2015)

It is our understanding that Appendix 3 is an LoE exemplar – and yet there are no tables as in the current Checklist 6. It would be appreciated if the TGA could clarify whether we no longer require the evidence to be tabulated, and rather only need a critical appraisal. If so, this is clearly a new requirement, as Checklist 6 would no longer be the appropriate format for the bulk of the LoE.

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?

A case study demonstrating an acceptable justification for the translation of evidence on a traditional raw herb preparation method to a modern extract method would be appreciated

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

YES

A minor point: The 'Search terms' for the 'Non-systematic search' in Appendix 3 is 'Vitamin B6' – this should be corrected.

We would also like to reiterate this all seems over complex and not in the spirit of the MMDR review, which was to reduce red tape and burden on industry.

We should at the very least be able to make claims in line with FSANZ Schedule 4: Nutrition, health, and related claims for foods without this complexity of assessing evidence as outline in the draft EG 2022.

Listed medicine only contains pre-approved low-risk ingredients from a list of TGA approved permissible ingredients known as the Permissible Ingredients Determination, and only makes low-level indications selected from a list of TGA approved permitted indications known as the Permissible Indications Determination. Which are limited to indications relating to a health enhancement, health maintenance, prevention of a non-serious vitamin or mineral deficiency and indications for non-serious forms of disease, ailment, defect or injury.