Response ID ANON-YUEJ-TE1Y-Z

Submitted to Proposed update to evidence guidelines for listed medicines
Submitted on 2022-04-01 18:27:13

Introduction

1 What is your name?

Name:

John McEwen

2 What is your email address?

Email:
[redacted]

3 What is the name of the organisation you represent? If you are responding as an individual, type 'Individual'.

Organisation:

Individual

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

4 From the information provided in section 1, did you understand why a sponsor needs to provide a critical analysis of their evidence in an evidence package for their listed medicine?

Yes

Please describe why or why not:

"As such, it is important that an evidence package includes a persuasive critical analysis of the body of evidence."

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

Section 1 comments:

No

Tell us what you think about section 2 of the proposed Guidelines.

6 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:

"Evidence types that may be included in the evidence package of listed medicines with scientific indications can be derived from sources such as:

- A systematic review
- A randomised controlled trial (RCT)
- A pseudo-randomised controlled trial (alternate allocation or some other method)
- A comparative study with concurrent controls
- A comparative study without concurrent controls
- Case series with either post-test or pre-test/post-test outcomes
- A review article"

does not point out that this is in a descending order of evidential value. It would be worthwhile to emphasise this ahead of the reference to the NHMRC levels of evidence.
Further, there is a need for TGA to stress that submission of evidence of an effect of each of what are often multiple ingredients in a Listed Medicine is a sub-standard form of evidence when what is needed is the result of a well-conducted randomised controlled study of the actual proposed product.

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

section 2 comments:

No other

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

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

No

Please describe why or why not:

"Section 3.1.2 Active Ingredient
The evidence source should relate to the whole medicine or include the same active constituent/s and be similar or comparable to the medicine in terms of:

- dose
- dosage form
- dosage regimen (including duration and frequency of administration)
- route of administration"

It is convenient here to point out major deficiencies in the Guideline. There is no mention of a need to consider evidence relating to use by children yet numerous Listed Medicines are targetted at young children. Children are not young adults.

There is no mention of the need to consider interactions between the often multiple ingredients in a product- this cannot be adequately covered in the safety review prior to inclusion in the Permissible Ingredients Determination,

The Guideline is superficial in its consideration of the possible impact of the dose form. Listed Medicine dose forms include coated tablets, for example, and these may be inappropriate in the absence of formal bioavailability studies which themselves may be impossible to conduct (e.g. when a product contains 5 herbal ingredients).

9 Do you find that the removal of the terms 'primary' and 'secondary' sources and replacement with the concept of relevance and quality of evidence sources provides greater clarity when selecting evidence sources to include in an evidence package?

Not Answered

Please describe why or why not:

No comment

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

Section 3 comments:

No

Tell us what you think about section 4 of the proposed Guidelines.

11 Do you find the decision tool helpful for classifying indications?

Yes

Please describe why or why not:

But does not fully explore "Other considerations" such as Public Health and safety or Inappropriate Use of a medicine or use of Temporary as an action qualifier.

12 According to the decision tool, low-level biomarker indications (such as 'helps maintain/support healthy cholesterol' and 'helps maintain/support healthy blood sugar/glucose') are classified as 'non-specific', while previously these indications have been generally regarded as specific. Do you agree that the efficacy of listed medicines with these indications should be supported by Category B or C type evidence only?

Not Answered

Please describe why or why not:

No comment made

13 Does section 4.4.2. clarify when it might be appropriate for a supplement to only provide a minimum 25% of the Recommended Dietary Intake (RDI) (of a specified vitamin/mineral/nutrient) without the sponsor needing to hold additional evidence sources to support their medicine's indication? Do you agree with this proposed clarification?

Not Answered

Please describe why or why not:

No comment made

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

Not Answered

other (details):

No comment made

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

Not Answered

Please describe why or why not:

This is an inappropriate question.
Aside from issues of clarity, there are major issues with this section. See 4.4.4 below.

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

Section 4 comments:

4.4.1 4.4.1 Using 'clinically proven' in your indications
The first paragraph about clinically proven is supported. The wording of the second paragraph should be strengthened so as to say that the TGA regards such words as conveying the same implication as clinically proven.

4.4.4 Study duration for temporary weight loss indications
This section has no evidence basis. No references are cited. It may be that there are some special clinical circumstances supporting a need for temporary weight loss over three months but there is no clinical justification for the unfettered temporary weight loss indication and the absence of supporting evidence. The label statement "Weight loss may not be maintained for longer than 3 months" does not sufficiently convey that such a treatment is not intended to be repeated and does not guard against Inappropriate Use of the medicine.

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

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

Not Answered

Please describe why or why not:

No comment made

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

Not Answered

Please describe why or why not:

No comment made.

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

Section 5 comments:

No comments made.

Tell us what you think about the Appendices of the proposed Guidelines.

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

Vitamin B12 package comments: This Appendix 3 example is inadequate and should be withdrawn. The inadequacy flows from the last two paragraphs of the critical appraisal:
"The individual trials above included populations that may not be entirely representative of the Australian population. However, the body of evidence taken as a whole, shows that oral supplementation with vitamin B12 can increase plasma B12 levels and decrease MMA levels irrespective of differences in populations studied. While there is some evidence of genetic variants affecting vitamin B12 status in particular ethnicities , in the absence of information establishing significant impact on absorption in a particular ethnic group, the results from the RCTs are considered to be applicable to a generally healthy Australian population. For these reasons, the evidence presented in this statement is sufficient to establish that supplementation with vitamin B12 would maintain B12 levels in the bloodstream and within a normal range in generally healthy individuals with no B12 malabsorption conditions. Therefore by extrapolation, oral supplementation with vitamin B12 is likely to reduce the risk of a vitamin B12 dietary deficiency and thus assist in its prevention. This evidence however, does not extend to the treatment of either a dietary or clinical vitamin B12 deficiency."

The information provided does not establish that generally healthy individuals need supplementation with Vitamin B12 to maintain their B12 concentrations within the accepted normal range and does not establish that such individuals are at any risk of a vitamin B12 dietary deficiency that needs prevention. The sponsor is seeking to market a sop to the worried well.

Further, there are inconsistencies in this document prepared by the TGA:
-Dosage form (page 73 of 85) is stated as tablets, capsules but there is no further reference to capsules.
-Recommended dose is One tablet twice daily but two sections below the Directions for use are "Use daily or weekly as directed."

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

other case studies?:

See below.

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

Appendix other comments:

The Appendix 2 Case Studies are problematic and the Appendix 2 should be extensively revised.
Notwithstanding the TGA disclaimer that the case studies are "hypothetical only" the use of actual Permitted Ingredients in some of the case studies has created a mix ranging from the plausible to the grossly misleading. It is unclear why the ingredients in the studies were not designated as for example Substance A or Herbal extract B. In some case studies, the expression should be reviewed. In other examples, more detailed review is needed. Examples follow.

Case Study 1. "As such, the clinical trial is not considered applicable to the medicine." Should this not say "As such, the clinical trial is not considered applicable to the proposed indication"?

Case Study 3. It is confusing to say that "The active ingredient dose in the evidence source does not match the medicine. " Subjects taking the upper recommended dose (2 capsules a day) of Beans Joint might be expected to have the same outcome (not described) as in the clinical trial.

Case Study 7, seeking to demonstrate that the sponsor's evidence is relevant to the medicine and indication and is of sufficient quality, has chosen extraordinarily to use Vitamin C for the decrease/reduce/relieve symptoms of common cold. That is, Vitamin C has a therapeutic effect if taken at or after the onset of symptoms of a cold.
That is precisely the area in which a Cochrane review stated that "Regular supplementation trials have shown that vitamin C reduces the duration of colds, but this was not replicated in the few therapeutic trials that have been carried out." What is purportedly a hypothetical example risks being misleadingly read by many as an example acceptable to the TGA in support of the indication

Case study 11 is intended to show that the submitted evidence does not support relief from constipation. It is muddled because of the choice of the hypothetical product. Cascara sagrada has been the subject of official monographs for more than a century and it seems implausible that a sponsor could not submit appropriate references . The BPC 1911 entry is reproduced at https://www.henriettes-herb.com/eclectic/bpc1911/rhamnus-purs.html The EMA/HMPC/909434/2019 Committee on Herbal Medicinal Products (HMPC) Assessment report on Rhamnus purshiana DC., cortex Final – Revision 1, 6 May 2020 states "The accepted historical use of cascara bark led to the establishment of the German Kommission E Monograph (Kommission E 1993), the European Scientific Cooperative on Phytotherapy (ESCOP)monograph on Cascara Bark (ESCOP 1999) and the WHO monograph (WHO 2002)." It is noted that the website of a current Listed Medicine sponsor states "XXXX's Cascara has been traditionally used in Western herbal medicine to help promote healthy bowel function." It might further be questioned why the TGA Assessment has not commented on the proposed product name which includes reference to the stomach, which is inconsistent with the proposed indication. The criticism of the relevance of the proposed method of extraction is supported. It is worth noting that the EMA/HMPC/726270/2016 Monograph 6 May 2020 contraindicates use in children aged under 12 years of age.

Case study 12 conveys that evidence of relief of headache pain by "a medicine" (presumably a Listed Medicine) is sufficient evidence of relief of mild migraine. The example is not clinically acceptable. First, the diagnosis of "mild migraine" should always be reviewed as clinically migraine is an illness that usually interferes with the ability to function normally (i.e. not mild). The diagnosis of migraine should include other symptoms such as nausea, photophobia or other auras and consideration of the distribution of the pain (headache). In the absence of explicit reference to other study endpoints in the case description the hypothetical TGA assessor might have reasonably queried the proposition that the studied patients had migraine.

Further, the statistical manipulation to get a study over the line should not be accepted. What constitutes "reduction" in headache pain is not disclosed. What in effect has been done is a post-hoc recalculation of the needed sample size aimed at achieving statistical significance. That cannot be taken as demonstrating an effect which the consumer of the listed medicine would perceive as worthwhile. The hypothetical TGA assessor might more appropriately have taken into account the usual numbers of subjects needed in an adequately powered study of the now OTC migraine therapies and insisted the Bean Company submitted evidence from one or more studies with a robust definition, be it of either "headache" or appropriately defined migraine, and a pre-study calculation of sample size based on a clearly defined desired effect.

Case Study 13 curiously refers to a discrepancy in the formulation between the evidence source and the medicine. It is suggested that what the case study relates to is a difference between active ingredients and not a "discrepancy in the formulation." Further, this case study has conflicting information. The description of the evidence states that "The study demonstrates that the bioavailability of zinc bisglycinate was greater than that of zinc gluconate." The TGA assessment states that the bioavailability of zinc bisglycinate was at least equal to, or greater than, zinc gluconate. The TGA assessment has not differentiated between whether within conventional limits bisglyconate was bioequivalent to gluconate or that the bisglyconate delivered a greater amount of zinc, by how much and whether that would be acceptable.

Consent to publish

23 Consent to publish your submission

Publish submission in full, including my name and organisation