Consultation submission cover sheet

This form accompanies a submission on:

The document 'Evidence required to support indications for listed medicines (excluding sunscreens and disinfectants)'	
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I would like the comments I have provided to be kept confidential: *(Please give reasons and identify specific sections of response if applicable)*	☐ Yes ☒ No
I would like my name to be removed from all documents prior to publication and not be included within the list of submissions on the TGA website.	☐ Yes ☒ No

It would help in the analysis of stakeholder comments if you provide the information requested below.

I am, or I represent, a: *(tick all that apply)*

Business in the therapeutics industry *(please tick sector)*:

☐ Prescription medicines	☒ Complementary medicines	☐ OTC medicines
☐ Medical devices	☐ Blood, tissues, biological	☐ Other

☐ Sole trader	☒ Business with 49 employees		
☒ Importer	☒ Manufacturer	☐ Supplier	☐ Industry organisation
☐ Government	☐ Researcher	☐ Professional body	
☐ Consumer organisation	☐ Institution (e.g. university, hospital)		
☐ Regulatory affairs consultant	☐ Laboratory professional		

☐ Health professional – *please indicate type of practice*:

☐ Other - *please specify*:

It would help in the analysis of stakeholder comments if you provide the information requested below.

Comments

An assessment of how the proposed change will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.
Cost will be huge in time to get current product range compliant with the new evidence guidelines.
Whether or not you support the revised Evidence Requirements. If not supported, please provide reasons why.
Comvita do not support the current consultation document. We believe it imposes high pharmaceutical standards onto 'low risk' medicines, will add additional unnecessary costs to compliance, stifle innovation and is not proportionate to the complementary medicines industry.
Any additional information on issues not asked in the above questions. If your comments relate to specific parts of the document please provide the page number and reference.

If you would like to be kept informed about TGA activities, please subscribe to one of the TGA's email lists <http://www.tga.gov.au/newsroom/subscribe.htm>.

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KEEPING YOU WELL.
EVERY DAY.

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Date of submission: 19 October 2012
Closing Date for submissions: 22 October 2012

To Whom It May Concern:

Re: "Evidence required to support indications for listed medicines (excluding sunscreens and disinfectants)" Consultation

Comvita New Zealand would like to provide this submission in response to the consultation document entitled *"Evidence required to support indications for listed medicines (excluding sunscreens and disinfectants)"*.

In general Comvita would like to comment that the revised consultation document is an improvement on the original. Comvita are glad to see that TGA have accepted that it is the format and content of the evidence report that is important and not an 'expert' person. We also support the addition of the approved Sources of Established Evidence as this will save sponsors time in evaluating well documented ingredients.

Comvita previously expressed concerns with progressing the evidence guidance in isolation parallel to other reforms such as coded indications and labelling. The consultation periods now overlap and Comvita will not know the outcome or TGA's position on the coded indications project or labelling in a timely manner to inform this submission on evidence requirements. Therefore, Comvita are still considering this consultation in isolation of other major reforms being undertaken.

In addition, the requirements laid out in this document still appear to be equivalent or higher to those for registered over the counter medicines yet apply to medicines that can only carry listable claims. High level evidence will be required to support the lowest-level indications, and as such industry will incur large costs in order to meet these requirements.

Many of our concerns expressed in the first consultation have not been addressed and as such may be repeated here. In particular the requirements around preparing a review for each indication and ingredient not covered by a SEE remains just as onerous as in the previous draft.

Current TGA reforms will increase the burden on compliant sponsors without apparent provision for increased monitoring and enforcement activity. Without effective deterrents non-compliant sponsors will enjoy even greater market advantage.

Comvita feel the layout of the document could be made clearer by separating the evidence requirements for scientific versus traditional indications. Where there is overlap in discussions it can get quite confusing, and then reading later on in the document trying to

remember what you covered earlier makes compliance more difficult in terms of linking relevant information together.

In addition to the general comments cited above, Comvita would like to submit the following comments, questions and concerns:

3.1. Indications supported by sources of established evidence
General comment: While the list provided by the TGA is lengthy, it still excludes a large number of sources. There does not appear to be a provision for adding other high quality resources to the list.

RE: Page 9: Requirements for listed medicine table; "Ingredients (...) is identical, comparable, or not significantly different..."
Comment: Where ingredients are not 'identical' what justification is required to support the use of the SEE for a given ingredient? Especially as it relates to traditional evidence, where it will be difficult to obtain chemical profiles for comparison of active ingredients?

RE: Page 9: Requirements for listed medicine table; "...For extracts, the method of preparation must be the same as that described in the SEE (e.g. extraction conditions, solvent, extract ratio).
Comment: What are our options if this type of information is not available?

RE: Page 9: Requirements for listed medicine table; "Ingredients (...) is identical, comparable, or not significantly different..."
RE: Page 9: Requirements for listed medicine table; "...For extracts, the method of preparation must be the same as that described in the SEE (e.g. extraction conditions, solvent, extract ratio).
Comment: Same section, different clarifications. Something cannot be the same and comparable or not significantly different.

Re: Page 11: 3.2.1.4 Identification of evidence; "The search must utilize MEDLINE/PubMed and should involve at least one other relevant database."
Comment: Will TGA be providing a list of databases they deem to be 'relevant'. It would be useful to sponsors if an acceptable list was produced.

Re: Page 13: 3.2.1.7 Quality of relevant evidence; "...quality of every relevant item of evidence must be assessed utilizing a published, critical appraisal instrument that is appropriate for the type of evidence being considered."
Comment: Will TGA be providing a list of acceptable appraisal instruments? It would be useful to sponsors if an acceptable list was produced. Further, do the tables for assessing relevance of the study in the evidence reports not cover this?

Re: Page 13: 3.2.1.7 Quality of relevant evidence; "...critical appraisal tool must then be used to classify each relevant item of evidence as a high or low quality study."
Comment: Comvita are not sure this was in the previous draft. But doesn't assessing the evidence against the relevance of study table negate the need for such appraisal?

Re: Page 14: 3.2.1.9 Assessment of the balance of relevant evidence
Comment: Can TGA please define 'balance'. How many studies are required to support indications. Is one good quality study sufficient? Or do you need at least 2? That is, do you need a minimum of 2 studies so that the second can validate the results of the first. Note, it

is Comvita's opinion that one good quality study should be sufficient, as high quality clinical trials are expensive. Given there is no IP protection in complementary medicines there is no incentive to undertake such trials. So when a sponsor does undertake a trial to gain a claim the need to validate with a second is not reasonable.

Re: Page 14: 3.2.1.9 Assessment of the balance of relevant evidence; "Only if the balance of high quality evidence is equivocal are the outcomes of lower quality studies to be included."
Comment: Can you be please clarify if low quality studies alone can be used to support indications? Especially in support of the lowest level indications for use.

Re: Page 11: 3.2.2.4 Identification of evidence; ".....transparent and reproducible review..."
Comment: This requirement is onerous to the sponsor in recording all this detail and then providing justification for inclusion/exclusion of paper for further evaluation. How would TGA monitor this? Given research is constantly evolving and sponsors cannot be expected to keep up to date on all new publications in literature following the initial report. Further, thought needs to be considered when you look at collecting oral histories of use. This sourced information becomes the IP of the sponsor.

1. Listable indications
Re: Page 18: Bullet point at top of page 18 refers to indications not referring to a disease, ailment etc.
Comment: Should there not be some prompt or reference here to include the prohibited claims list? This will help clarify to new sponsors what they cannot claim on.

2.3 Nutrients and nutrient supplementation
Re: Page 21: The requirement that a product deliver a certain percentage of the recommended daily intake for an essential nutrient has been added to Part B, section 2.3.
Comment: The percentages required are higher than the amounts originally prescribed in the Therapeutic Goods Advertising Code. In addition these requirements are higher than that for 'source of' and 'good source of' claims on food products.

3.1 Meeting evidence requirements through sources of established evidence
Re: Page 22: "Where there are multiple editions or versions of SEE, the latest edition/version of SEEs should be used."
Comment: Comvita can see issue with this in terms of pharmacopoeia which are usually updated annually or biannually. The frequency with which some of these are republished puts high costs on the sponsor both in terms of cost to get the new version and in time to ensure all products previously listed using this reference are still current based on the new version.

Re: Page 24: 3.1.3 Including indications sourced from SEE in the ARTG
Comment: Fail to understand how this prescription of proposed wording of the indication fits with the coded indications project.

3.2.1 Evidence required to support listable scientific indications
Re: Page 27: 3.2.1.1 Sponsor details
Comment: While Comvita appreciate that TGA have removed the need for an 'expert' to produce the evidence reports, this section states the importance of listing the relevant qualifications and experience of the report's author to demonstrate appropriate skills for critical appraisal of the evidence. Comvita are concerned that this may provide TGA with the

opportunity to not accept the report based on the qualifications of the individual conducting the report.

Re: Page 28: 3.2.1.4 Identification of Evidence; "Non-english language publications will need to be translated and considered if a substantial amount of scientific work has been reported in the non-English literature."
Comment: It is not reasonable for sponsors to hold such documentation. Official translations are extremely expensive and given sponsors search in the English language any substantial work in another language would likely not show up in their search results.

Re: Page 29: Relevance to target population; "Only human studies are considered sufficient to support indications for listed medicines."
Comment: Please clarify if there is any type of human evidence that cannot be considered.

Re: Page 29: Relevance to target population; "male and female participants."
Comment: Comvita do not feel that this requirement is always achievable. Many studies will not be conducted on females as their menstrual cycles can interfere with the clinical parameters being measured (E.g. blood glucose and blood pressure can vary naturally in women depending on the stage of their cycle). By trialing only on men you are more likely to generate significant results due to a reduction in confounding factors. If women were to be included the population size would need to be much larger and this significantly increases the cost of an already expensive clinical trial. Therefore, Comvita suggest single sex studies should be acceptable as evidence if justification can be provided by the sponsor.

Re: Page 29: Health status
Comment: Most research is either carried out on ill subjects or those with serious conditions. Not being able to use research carried out on sick subjects will greatly affect the size of the body of evidence available to support indications and as such will prevent the use of a large proportion of existing evidence. Comvita recommend that TGA outline specific requirements for biomarkers in a separate section and that trials using healthy population group with elevated biomarker levels in otherwise healthy populations should be acceptable to use as evidence if justified.

Re: Page 29: Health status; The table includes an addition "All must be otherwise healthy"
Comment: Issues can be expected around defining this definition.

Re: Page 31: Ethnic, cultural and social factors; "....studies conducted in homogenous ethnic populations may be limited in their relevance..."
Comment: How can complementary medicines deal with this? Clinical trials typically recruit a homogenous ethnic population to reduce the risk of confounding factors in research. Pharmaceutical companies are able to undertake multicenter studies in order to make it relevant to the population but they have IP protection and market exclusivity for research and claims which allows them to recover costs once products are on the market. These incentives do not exist for listed products (complementary medicines) so trials are done based on a calculated number of participants to reach significance and generally no more due to the high cost of trials. Therefore, these factors should have less of a bearing on low risk complementary medicines.

Re: Page 39: Number of participants
Comment: Power calculations are not uniformly used or reported. Such requirements will have the effect of disqualifying a large body of previously acceptable evidence.

Re: Page 39: Analysis; post-hoc analysis
Comment: Please clarify if sponsors can use indications that are a result of post-hoc analysis. Alternatively, the sponsor should be able to present justification to support the use of evidence derived from post-hoc analysis.

Re: Page 41: Clinical significance; "For some health benefits the parameters used to determine clinical significance may be prescribed by the TGA.
Comment: 'May' is ambiguous, please specify if TGA will prescribe parameters. And when these will likely appear.

Re: Page 43: 3.2.1.9 Assessing the balance of evidence; "Only if the balance of high quality evidence..."
Comment: What if sponsors have no high quality evidence, can we submit an indication based on lower quality studies?

Re: Page 43: 3.2.1.9 Assessing the balance of evidence; "...scores of at least C..."
Comment: Where do these scores come from? They've not been mentioned in the guidance document previously.

Re: Page 43: 3.2.1.9 Assessing the balance of evidence; "As the body of evidence...tips the balance"
Comment: How are sponsors expected to keep up to date on the latest research? It will no longer be practical to monitor research updates due to the large amount of work required should we wish to add a paper to our evidence. We would have to start from scratch with the literature review. This is extremely time consuming and provides an onerous task for reviewing and updating evidence and indications for use. You discuss here 'unsupported' claims, but just as likely is research they disputes the current balance of evidence and this will need to be justified.

3.2.2 Assessing evidence to establish a traditional of use
Re: Page 45: "...starting material and method.... Not significantly different from the classically produced ingredient or product."
Comment: How could sponsors know their ingredient is not significantly different? We cannot access chemical or chromatographic fingerprints from traditional materials. This is not a practical requirement.

Re: Page 45: 3.2.2.4 Identification of evidence; "Evidence held... certified transcript..."
Re: Page 47: 3.2.2.4 Identification of evidence; "Using primary sources of information..."
Comment: This will potentially add huge costs to supporting evidence for traditional medicines. Many historical texts are in languages that only very few specialists can translate. Further, Comvita don't understand why a certified transcript would be required if the ingredient is in a pharmacopoeia or other authorative text as proof it has been traditionally used for the given indication. Comvita question the real benefit of spending time tracing back to primary sources in terms of costs in both time, access to materials and translations.

Re: Page 48: 3.2.2.5 Relevance of evidence of traditional use; Relevance to medicine; "..traditional indication for a product the method of preparation of the active ingredient(s) must be those traditionally used."
Comment: This may make traditional medicines more expensive. Hypothetically, if there is some modern technology that can produce exactly the same end product in a more cost

effective manner than the traditional medicine (proof from chemical profiles etc) – why would you manufacture using the traditional method?

Re: Page 51: 3.2.2.5 Relevance of evidence of traditional use; Determining which sources of evidence of traditional use are relevant; Fail to understand the usefulness of the ARS value.
Comment: Given all studies have previously received a satisfactory and no ARS value will 'fail' as use in evidence, why does time need to be taken to calculate this figure?

Re: Page 52: 3.2.2.8 Assessing the balance of evidence of traditional use; "Traditional references that do not contain.... Do not constitute negative evidence."
Comment: This statement does not make sense, given any reference that didn't contain the indication would not be used as evidence.

Appendix 1: Sources of Established Scientific Evidence
General comment: Again, Comvita would like to raise the issue that access to the latest pharmacopoeia is not always achievable. They are costly and sponsors don't update their access with every new version published. Since the list specifies the latest issues does this mean the SEE list will be updated each year a new version is printed? And further, if sponsors are expected to use the latest pharmacopoeia how does this impact the relevance of the evidence report once the new version is available?

Re: Page 56: Title "Sources of Established Scientific Evidence".
Comment: The title does not provide a provision for traditional SEE's in the list, even thought page 22 states "..approaches apply to both scientific and traditional indications."

Requested changes/updates to the SEE list:
Changes: Move the below references out of "Homeopathic" sources, OR include in the general list:
Cochrane reviews
Medline Plus: Drugs, Supplements & Herbal Information
Natural Standard
Update to include:
EU Register on nutrition and health claims. Authorized claims.
European Medicines Agency. Community Herbal Monographs.
Micronutrient Information Centre, Linus Pauling Institute.
FSANZ P293 Approved Health Claims for food.

Appendix 3: Evidence Report (Scientific)
Re: Page 68: Clinical Significance
Comment: The requirement to calculate the clinical significance of every relevant study, even when this has not been reported in the research paper is unreasonable. For no apparent reason, the template demands the addition of the numerical d-value, itself theoretical, untested and rarely provided by researchers. If the sponsor were to calculate the d-values they could be accused of altering the data. Further, discussion of the requirement of the d-value seems to be lacking from the clinical significance section on pages 40-41.

Finally, the document fails to provide any guidance on implementation and enforcement activity.

Overall, Comvita do not support the current consultation document. We believe it imposes high pharmaceutical standards onto 'low risk' medicines, will add additional unnecessary costs to compliance, stifle innovation and is not proportionate to the complementary medicines industry.

Thank you for the opportunity to submit comments to this consultation.

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