Consultation submission cover sheet

This form accompanies a submission on:

The document 'Evidence required to support indications for listed medicines (excluding sunscreens and disinfectants)'	
Name and designation	[redacted]
Company/organisation name and address	[redacted]
Contact phone number	[redacted]

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 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*: Sponsor

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.
There will be a serious financial burden placed on our organisation. It will limit innovation as the analysis required will take a considerably longer time period.
Whether or not you support the revised Evidence Requirements. If not supported, please provide reasons why.
No we do not support the proposed changes to the Guidelines as it is a Prescriptive approach to Low Risk, Low level claim medicine. The level of research required is not balanced with the risk associated with the medicines.
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.
Please see attached comments.

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>.

Comments by Totally Natural Products on the Draft Levels of Evidence Guidelines August 2012

[redacted]

Context:
The TGA has recently had consultations on numerous reforms within the Complementary Medicines (CM) Industry. These reforms which include the Labelling Review, Coded Indications (CI) Project, and ARGCM updates should not be carried independently of the Levels of Evidence (LoE) document. The documents are inter-connected therefore an isolation of these projects should not occur from the LoE Guidelines.

Outside of the Council of Australian Governments (COAG) Principles of Best Practice Regulation:
The COAG has agreed that all governments will ensure that regulatory processes in their jurisdiction are consistent with the following principles:

1. establishing a case for action before addressing a problem;

The intended TGA Reforms are founded on the ANAO Report and the subsequent Blueprint for the Future as published by the TGA. However it is our belief that the ANAO report is based on inadequate non-significant data which would not hold weight in any scientific statistical analysis.

There has been a misrepresentation of the selected information which has lead to the sensationalistion of the data presented. This has then lead to the intended reforms in question. This is not an acceptable method of mathematical calculations and is a demonstration of very poor statistical analysis.

The regulation of Complementary Medicines came to public attention in Australia when the DoHA reported in late 2010 that, based on 2009 – 10 data, as many as 90 per cent of Post Market reviews conducted by TGA were found to be noncompliant with regulatory requirements. These examples of non-compliance are based on the so called 31 randomly selected cases. Of the thousands of CM which can be found on the ARTG, only 110 Product Reviews were used in calculating the figures which resulted in the Blueprint for the Future. However this rate was calculated to exclude the entire numbers of reviews conducted in that same year. Therefore how accurate is this 90% rate of non compliance?

The ANAO claimed that only 3 of the random cases were compliant and did not consider the totality of the information presented ie the other fully compliant "non random" reviews.

As you can see from table 4.2 below, "90% non-compliant" reviews were taken from 110 Medicines of which 79 cases were targeted reviews. The 90% non compliant rate only applied to 31 of these cases. 80% of the random reviews had minor issues, whilst 40% of the targeted products had minor non-compliance problems. Whereas approximately only 10% of the random reviewed cases had significant problems, 48% of the targeted products had significant problems.

This confirms that the sample taken by the TGA is not a representation of the overall sample, because here we can compare two sample populations and they are very different from one another. This is why it is important to get more information why products were

non-compliant. As you can see in Table 4.2, 10.9% of total reviews (targeted and random) were fully compliant and 51.8% of total reviewed products had rectifiable problems. A significant number of products subsequently required removal from the ARTG. However why these medicines were removed is not stated. It is likely that the medicines were on the ARTG but not actually present on the Australian Market.

I would like to stress that the proportion of products that were either fully compliant or had rectifiable non conformances make up the significant body of information even in this very small sample size at 62.7%.

From the data presented, the true rate of non-compliance should be the 12.7% of medicines which the TGA were forced to cancel as a result of Regulatory Breaches.

I would also like to bring to the attention of the TGA, some of the statistics that often make up the "minor non conformances" based upon our own experiences of Post Market reviews. In the time period that this data is extrapolated from, our company had 13 medicines which had Post Market Reviews. Of these reviews, none of the medicines were seen to be "fully compliant". All of the reviews showed minor non conformances which required corrective action. These included:

- The re-wording of sentences which essentially refer to the same indication
- The font size of our company address on the packing
- The insertion of the word "may" as a claim qualifier
- Rewording statements such as "Clinically Proven" to "Clinically trialled/tested"

Most of the "non conformances" were based on opinion as one reviewer who may have carried out a Post Market Review previously had a different opinion than the next Reviewer (as some products had been subjected to Post Market Reviews previously). Unfortunately however, these examples as listed above have become a "statistic of non compliance". However the seriousness and the risk associated with this non compliance rate should have been reported.

This information was then contained in DoHA's incoming government brief, which was released to the public in late 2010. The information in the brief attracted significant interest and debate and the topic has persisted. However the information as stated above is not a true representation of the rate of compliance for the CM industry.

Table 4.2 – Extract from Audit Office Report (Page 110) Desk-top compliance reviews of listed complementary medicines completed from 1 July 2009 to 31 March 2010

Type of review:	Random	Targeted	Total	%
No. of desktop compliance reviews completed	31	79	110	100%
No. of products where full compliance was found against the regulatory requirements reviewed	3	9	12	10.9%
No. of products that required corrective action and the sponsor corrected deficiencies	25	32	57	51.8%
No. of products that required corrective action and the TGA cancelled the medicine at the sponsor's request	2	25	27	24.5%
No. of products that the TGA cancelled as a result of regulatory breaches	1	13	14	12.7%

Source: TGA advice, 17 May 2011.

2. a range of feasible policy options must be considered, including self-regulatory, co-regulatory and non-regulatory approaches, and their benefits and costs assessed;

The current method of co-regulation is the preferred adopted method for CM. However the new LoE Guidelines may make this level of co-regulation cost prohibitive. It may be a more cost effective action if the TGA was to pre-evaluate the evidence and claims and have Sponsors subsidise this evaluation. This will remove the ambiguity on claims and prevent the costly need for change in packaging and updates to ARTG records which often result after a Post market Review.

3. adopting the option that generates the greatest net benefit for the community;

The intended purpose of the TGA Reforms is so that the broader community and the consumer have access to CM which is safe and of good quality. The intended reforms will mean that Sponsors of CM will no longer be able to educate the consumer on the benefits of their medicines. They will most likely need to remove medicines from the Australian Market as they can not sustain or justify the costs of having the product.

Therefore ultimately the net benefit to the community at large is negative.

4. in accordance with the Competition Principles Agreement, legislation should not restrict competition unless it can be demonstrated that:
    - the benefits of the restrictions to the community as a whole outweigh the costs, and
    - the objectives of the regulation can only be achieved by restricting competition

The limitations which these new Guidelines apply will make the CM market uncompetitive. There is no real benefit to the community by enforcing these new guidelines. The cost to implement the new LoE Guidelines will be much higher than it is currently and we see no beneficial purpose other than to restrict Sponsors, increase costs and limit competition.

5. providing effective guidance to relevant regulators and regulated parties in order to ensure that the policy intent and expected compliance requirements of the regulation are clear;

We do not believe that the expected compliance requirements will be met by the changes to these regulations. It will in fact be more detrimental to compliance rates as Sponsors who do not have the relevant background or training or staff numbers will opt to make claims without having their sources of evidence until they are reported to the TGA. They will then look at other avenues to promote their product which are not connected to or regulated by the TGA (ie as a food) product.

Has the TGA determined how it will review new medicines as per these new guidelines?

6. ensuring that regulation remains relevant and effective over time;
7. consulting effectively with affected key stakeholders at all stages of the regulatory cycle; and

Has there been effective consultation on the impact of these changes to the industry? The level of workload in the area of Regulation will increase significantly. The time to bring new products onto the market will be considerably longer and the innovation of industry will be therefore limited. This impacts all sectors of the industry from the raw material suppliers, manufacturers, sponsors, distributors etc.. This ultimately will result in a decrease in the

size of the manufacturing sector. The impact to all areas of industry should be given consideration before any changes are to be made.

8. government action should be effective and proportional to the issue being addressed.

We believe that the proposed changes are disproportionate to the problems at hand. The requirements as proposed by these guidelines are equivalent to those requirements by medicines making higher level claims than what is intended for use by CM.

The medicines are "low risked" medicines with low/medium listable indications. They are not applicable for the treatment of serious diseases. Therefore the level of evidence should also be proportional to the intention of use. The current document, as proposed, is therefore inappropriate for listed medicines which by definition are low risk.

Complexity of Document:
The document is largely complex and onerous. It is applying a numerical, prescriptive approach to the review of evidence collated for every indication of a medicine which often contains numerous active ingredients which carry different indication. Also the complexity of the document is not warranted as we are only dealing with low risk medicines.

Sources of Evidence:
Page 27 of the Draft LoE Guidelines states that indications and information may be gathered through either:

- the identification of evidence linking an indication to an ingredient, group of ingredients or product described in an authoritative source of information recognised by the TGA as a SEE as described in Section 3.1, OR

- by a thorough review and assessment of the available literature certified by the sponsor (Evidence Report) as outlined in Section 3.2 of this document.

These approaches apply to both scientific and traditional indications. Consideration then needs to be applied to the sources which the TGA has listed in Section 3.1 pg 66-71.

The sources listed are well established authorities in the use of CM; however, often these sources may not contain all of the information required as per page 29 of the Document such as method of preparation etc...

Also it is the active herbal ingredient which contributes to the efficacy of the product or the standardised component within the product as is often described in an SEE. However we may not have access to the exact same ingredient with the exact same extraction ratios as described in the SEE. Therefore often we will have access to herbal ingredients with different extraction methods yet yield the same standardisation on a raw material. Therefore this requirement as proposed will limit the use of ingredients to those which may be available **only to specific clinical trials.**

The therapeutic use may be listed and described in the SEE however the details that are required by the Draft Guidelines may not be present or available. Therefore I propose that this point is removed from the Draft Guidelines.

The specific concerns that we have are related to the *"Relevance to context of use"*. Both Scientific and Clinical evidence often may not contain all of the required details as to the population which either traditionally used the medicine or the diet/lifestyle of the population

in the clinical study. Therefore finding evidence which satisfies the new requirements may not be possible.

Assessing study relevance for scientific indications:
All literature that is gathered as Evidence texts need to be assessed for relevance. This is standard practice for any good regulatory team working on formula development. However the new Draft Guidelines intends to *rate the relevance* of studies in order to achieve a numerical value, rather than examining the total body of evidence present. This is a prescriptive approach to the evidence, and it would be better to examine the entire body of evidence rather than rate each individual trial independently.

The "Relevance to the context of use" examines whether the evidence can be applied to an Australian population. This is a very limiting requirement as not all studies are conducted in Australia. In fact there are few studies which are conducted in Australia. The Australian population is very Multicultural therefore to assume that there is a "one size fits all" is unreasonable. Therefore I would like to see this parameter removed from the "Assessment for relevance" on page 16.

I am also concerned that this requirement goes above and beyond the requirements for prescription medicine. OTC products and Prescription medicines rely on Clinical evidence to justify their claims as we know. However Sponsors of OTC/Prescription Medicines certainly do not conduct all clinical trials in Australia.

Studies are conducted in all areas of the world, and the information is then submitted as part of evidence to the TGA. Therefore to limit the evidence for CM to what is applicable only to an Australian population is not just. Quite frankly it is an unreasonable expectation.

In the past we were asked to examine the totality of the body of evidence which was seen to be adequate. Now the new "Assessment of Relevance" or ARS will determine if the study is considered suitable for a listable indication.

Algorithms:
There are numerous algorithms specified in the Draft Guidelines. I can not comprehend why such algorithms are necessary if there is an established "SEE". If the proposed SEEs are acceptable sources for the TGA, then they should be completely acceptable for use with no question.

Therefore there are appears to be a disproportionate level of requirement in calculations for low these types of low risk medicines.

The "Evidence Report" both Traditional and Scientific also requires a mathematical calculation for:

- Assessing relevance of evidence
- Assessing level and quality of evidence
- Assessing the Health benefit:
    - Experimental studies
    - Observational Studies
    - Estimate of Clinical impact
- Assessment of the Balance of Evidence

This appears to be a formal literature review for low risk and low/medium indication products. Again there is a disproportionate requirement for evidence.

Biomarkers:
The requirements for Biomarkers such as weight, blood sugar, blood pressure, cholesterol etc have been given defined and set parameters on which the evidence can be based. This is a positive move in order for Sponsors to collate accurate evidence.

However, I have some concerns on the *"Relevant Study population"* limits which are below:

Total Cholesterol: The Upper limit of Cholesterol levels required in the population group is approximately 15% above the healthy limit of cholesterol. There are some studies on ingredients which have used population groups within these cholesterol levels.

However, the accuracy of Cholesterol testing shows that there is about 10% margin for error in any given study and that seasonal levels vary from person to person with no restriction of diet or medicinal intervention. Fasting and non fasting cholesterol levels also vary in the same person by 10-15%. Often Good Clinical Practitioners will assess Blood Cholesterol levels trend results before making a final diagnosis.

Therefore the relative clinical significance requirements which are required by the algorithms discussed above would not be applicable as true clinical significance can not be defined.

It would be a more accurate measure if the limits on Cholesterol levels were increase to up to 25% above normal healthy limits in order to capture the seasonal variation and standard testing errors.

Overweight/Weight Loss: The requirement for evidence with 6 months of clinical trial data may be difficult to achieve with CM. This is due to most weight loss studies being of short duration as the use of any Medication for weight reduction is not recommended in the long term.

The FDA only has 2 drugs which is recommended for long term use (1 very recent), and the clinical studies associated with that drug are not of long term use (up to 1 year for Orlistat) as is for other prescription medication. Most drugs for weight loss only recommend use for up to 12 weeks.

Therefore to expect CM to have clinical evidence for long term use is not practical or reasonable. The safety data and the effects on metabolism needs to be established for the medicine, therefore most Sponsors would probably be unwilling to recommend their product for long term use. This would be beyond the recommendation even for Pharmaceutical products.

The studies conducted should therefore reflect this intended use of the product and the evidence should reflect this intended use. There will be no benefit to the consumer if a clinical study has been conducted for 26 weeks if the intended duration of use is no more than up to 12 weeks.

The required evidence should therefore be parallel to the recommended product use. This will also be consistent with the "Study relevance assessment" as per the Table 2 on page 16 of the Draft LoE Guidelines.

Therefore I propose that the length of trial duration be re-examined and recommendations should only be based on the intended duration of use of the medicine.

Possible Amendments to Document:

- As discussed previously I believe that the document needs to be developed in conjunction with the Coded Indications (CI) Project. If the CIs are set and operational, then some of the concerns with the wording and the Indications of a Medicine will no longer exist. Therefore the matters of non compliance which are usually based on the wording of claims/indications will be rectified by default. I think this is a really important point to consider.

- Also as a set SEE is being proposed then the claims being made will only be available from these documents. Therefore I propose that at the time of Listing, our Evidence Table be submitted to the TGA for a basic examination of the evidence to ensure that the document has been collated from SEE. This will ensure that the Sponsor has used SEEs to gather their evidence and that the doses are the same as proposed in the SEE (as per the evidence table). However the strict requirements as set out as per page 29 will need not apply.

- We propose that the Relevance for context of use be deleted (page 42) as this is beyond expectations for OTC/prescription medication.

- We propose that the need for an identical herbal extraction process and identical extraction ratio be removed as part of the requirements for herbal raw materials. As long as the ingredient, plant part and dose used in the SEEs are comparable then the extraction ratio or methodology is irrelevant.

Other Matters:

- Our observations have determined that the document is limiting, difficult to manage and disproportionate to the low levels of indications for low risk listed medicine.

- The document is not a proactive approach to Regulatory Reform but a reactive approach to misrepresented, inadequate statistical analysis.

- The document itself is against the COAG Principles of best practice as outlined above.

- The detail and analysis that is required will hinder innovation and progress for the industry which will ultimately negatively affect the consumer by limiting their right to choice an alternate pathway to managing their health.

- The Government, with the assistance of the Regulator, should be focusing on preventative care of the Australian Public, rather than making it more difficult for consumers to gain access to information on the benefits of Complementary Medicines. Attached is a Research Article on the direct beneficial economic cost with the use of Alternative Therapy.

- The lack of an adequate consultation and assessment period has hindered the analysis of a proper economic impact to our organisation and the overall industry. We have so far analysed and determined that the proposed changes to the Coded Indications (Indications for Omission) will impact 63% of our business.

- We need clarification on the future of current Medicines which are on the ARTG:
    - How will these changes affect current product?
    - Will there be a Grandfathering process?

- Indications made currently are within the current Regulations as set by the TGA. Will these medicines need to be updated? If so when and who will cover that cost?
- What is the status of Medicines which have already been subjected to a Post Market Review under the current system?
- In order to make a transition to the "new" guidelines we will need a period of 3-5 years in order to sell out of stock and current packaging, make changes on all current Evidence Tables, Review and assess current Evidence literature. What time frame is the TGA proposing for the implementation of these new Guidelines?

We at [redacted] thank you for the opportunity to respond to the new Draft LoE Guidelines. If you have any further queries, please contact me on [redacted]