Complementary Medicines Australia submission to the Therapeutic Goods Administration

Adoption of the European Union Guidelines – Ethanol & Boron

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Complementary Medicines Australia (CMA) welcomes the opportunity to provide comment on the TGA's consultation on adoption of the European Union (EU) guidelines in Australia for medicines.

The EU guideline proposed for adoption that is relevant for complementary medicines is:
EMA/CHMP/302620/2017 - **Updated Annex to the European Commission guideline** on
'Excipients in the labelling and package leaflet of medicinal products for human use (pdf,130kb);
with respect to:

- Ethanol in medicines for children
- Boric acid (and borates)

The guidelines proposed for adoption are at this time we understand are intended to be mainly applied in respect of registered medicines. Our members represent sponsors of complementary medicines in the listed and registered categories, including the newly available 'listed assessed' category.

There are currently around 42 registered complementary medicines, and over 11,000 listed medicines. The number of 'listed assessed' complementary medicines that will enter the ARTG in the next 3-5 years is not known but might be expected to be in the low hundreds.

In respect of registered complementary medicines, we expect that the EU and ICH guidelines adopted in Australia would be applied during the registration process.

In respect of listed complementary medicines, the use of EU and ICH guidelines adopted in Australia and other Australia-specific guidelines is not mandated (or currently proposed to be mandated) in the legislation in relation to listed medicines. Historically, regulatory changes for registered medicines are often later mandated for listed medicines through the s.26BB Therapeutic Goods (Permissible Ingredients) Determination.

In respect of listed assessed medicines, these are currently a 'hybrid' of a pre-assessed medicine and a listed medicine. Although the requirements of the s.26BB Determination are applicable to this category, it is not clear whether the EU guidelines would also apply to the labelling of these medicines at the pre-assessment phase, which includes the medicine label.

Boric acid (and borates)

We note the TGA Annotation on this item;

> 'The TGA is adopting the European Commission annex to the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' with regard to Boric acid (and borates). The guidelines will help to address dose-related developmental and reproductive risks to children under 12 years of age and unborn foetus', associated with the use of boric acid (and borates).
>
> While the Australian Poisons Standard specifies a Schedule 4 limit of 6mg Boron per recommended daily dose, the EU Guideline entries for Boric acid (and borates) provides lower limits of Boron (B) for children less than 2 years (1 mg B/day), children less than 12 years (3 mg B/day) and unborn infants. The current level of 6 mg/day in people over the age of 12 years (other than pregnant women) will remain.'

CMA does not have any comment or opposition to the additional statements for boron at the stated age groups and limits per recommended daily dose.

However based on the final sentence of this annotation, we query whether there is a review into the dosage limit for pregnant women below 6mg/day. The EU Annex applies the warning statement for pregnant women at a dose at or above 7mg/day.

As for any ingredient changes to complementary medicines including listable medicines, we would like adequate information and consultation prior to proposed changes.

Ethanol in medicines for children

CMA supports the safe use of complementary medicines for consumers including paediatric populations, and we principally support international harmonisation efforts. For the Australian regulatory environment for complementary medicines, the principles of best practice regulation from the Department of Prime Minister and Cabinet must also be applied to ensure practical and effective outcomes in our quite unique context. We have reviewed the proposed addition with the above views to determine whether the proposed changes can be applied to CM categories in Australia.

CMA notes that explanation for the adoption of this Annex: the absence of current guidance in Australia for safe limits for ethanol/alcohol in medicines for the paediatric population.

The updated Annex contains three entries for ethanol as an excipient, with varying label requirements based on the total content of ethanol in the final product. Varying quantities triggering different warning statements on the medicine packing, in particular the product leaflet. These requirements would be applied in addition to the existing TGO 91/92 Schedule 1 requirement that if alcohol is present at 3% v/v, or more, in the final preparation, that the product label must carry a declaration of the total alcohol content expressed as %v/v.

THRESHOLD	INFORMATION FOR THE PACKAGE LEAFLET	COMMENTS
Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
100 mg per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <dose>. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5% vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per <dose>, equivalent to ... ml beer, ... ml wine per <dose>. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	

Our primary concern with the above proposed changes is that many of these changes would not be practical to be applied to Listed medicines (and some to Registered complementary medicines). If Registered medicines (of all kinds) are brought into harmony with the EU guidelines, it will create a regulatory divide between medicines in Australia between Listed and Registered medicines. We believe it is more important to harmonise medicines within Australia that have the same ingredients, than it is to harmonise registered medicines internationally. While we support important and necessary safety measures, if extra information on alcohol in the paediatric population is to be introduced within the Australian context, it should be examined in totality for its ability to applied to different medicine types through a separate review and consultation. Therefore, it appears to us that rather than adopting this guideline, it may be a better to consider a separate review and consultation on this matter. Further information and background on our reasons for this are included below.

1. Micro residues in solid herbal extracts (all categories of complementary medicines).

Almost all medicines containing herbal extracts, of which there are many thousands, include a step of manufacture that involves ethanol/water extraction. The processing of the liquid extract to solid extraction removes the majority of ethanol but some very small amount may remain in micrograms or the low milligrams per dose. In this instance, the warning statement applicable at under 100mg could be

required to applied to thousands of herbal medicines, when there is no appreciable risk to the paediatric population. This does not appear to be a risk-commensurate or useful regulatory outcome by the government best practice principles. Should such guidance be implemented without appropriate thresholds it could negatively impact the public view of herbal traditional medicines preparations and practices. If there is to be warning statements introduced for ethanol in child populations, there must be a reasonable and evidence/risk-based threshold before a statement applies.

2. Label space

Listed complementary medicines are not required to and in almost all cases do not include a package leaflet in the form of a product information (PI) or Consumer Medicine Information (CMI). Therefore, it is the primary label that must carry any required warning statements set out within:

- The TGO 92;
- The s.26BB Therapeutic Goods (Permissible Ingredients) Determination;
- The Poisons Standard.

The warning statements included under 'information for the package leaflet' would be exceptionally lengthy and generally not possible in their existing form for the relatively small labels of most complementary medicines. They would not be able to be added to the s.26BB Determination and would create regulatory differences between products containing ethanol in Australia.

3. Restricted representations

The second two categories contain warning statements with advertising 'restricted representations'; alcoholism liver disease, and epilepsy. If warning statements were to be applied to primary labelling, sponsors would require restricted representation approvals for their labels. This would likely prevent addition to the s.26BB Determination and create another difference between medicines.

4. Uncertainty as to the appropriateness of the proposed labelling scheme

The proposed limits are to establish ethanol labelling thresholds to avoid exceeding blood alcohol concentrations (BAC) of 0.125g/L (0.0125%) in children.

The Questions and Answers (Q&A) accompanying the Annex, contains data considered in support of the decision for the thresholds, and quotes various standards recommended across countries, as well as those recommended by the World of Health Organisation (WHO). The WHO limits quoted in the Q&A are presumably for the amount of ethanol in the finished product, not a single dose, although this is not explicitly stated:

5g/L or 0.5% (<6yo)
50g/L or 5% (6 – 12yo)
1g/L or 10% (12yo>)

The Q&A does not translate these medicine percentages into minimum blood alcohol concentrations, nor are they related back to the desired maximum BAC of 0.125g/L.

Furthermore it is not explained in the Q&A how the limits of <100mg, 100mg and 3g were arrived. That is, these quantities are not translated into the expected rise in BAC in any age group.

Nor are the EU guidelines for alcohol content age dependent, like the WHO.

We raise the following concerns with respect to complementary medicines.

- **Ethanol content expression and threshold limit.**

The content limits in the Annex are calculated per dose, which is far more conservative limit than that in the existing labelling orders which are expressed according to the percentage of ethanol in the final product. The labelling order requirements and the EU guideline requirements are not in alignment.

- **First threshold: Less than 100mg**

If this threshold were to be applied it would capture any medicines that has an alcohol residue which would capture traditional complementary medicine preparations, as well as any medicine that may have an alcohol residue, even in trace amount. The label warning statements attached to this threshold: "This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per <dose>" is unlikely to appease parents as the numerical value is not meaningful information to the average consumer and more likely to raise alarm than offer reassurance.

- **Second threshold: 100mg/dose**

This quantity cannot be expressed as a concentration as doses can be different, therefore the percentage volume of alcohol cannot be calculated, making it difficult to determine to what degree 100mg of ethanol would raise blood alcohol.

Should the equivalent volume of beer and wine be a requirement for labels of paediatric medicines, this may cause confusion and unnecessary parental distress. It is also difficult for parents to understand the meaningfulness of this measure when the safe or non-safe amounts of ethanol for children in different age groups is not commonly understood in the same way that it is for adults.

- **The 3rd threshold: 3g dose**

Again, this quantity cannot be expressed as a concentration, as doses can be different, therefore the percentage volume of alcohol cannot be calculated, making it difficult to determine to what degree 3g of ethanol would raise blood alcohol.

The references to alcoholism liver disease, epilepsy, and driving machines in the label warning statements could be unusual for medicine intended for children and perhaps confusing.

Conclusion

CMA thanks the TGA for the opportunity to be involved in the consultation on the adoption of the EU Guidelines. CMA supports the safety in use of medicines and supports methods of introducing changes that is best for consumers and industry. We do not believe the proposed Boron adoption poses any major difficulties and supports the safe use of Boron. However, for ethanol products, there is a mismatch in content and label warning statements between the Orders and the Annex, and between what can be reasonably imposed on Listed medicines and many complementary medicine preparations. The proposed limits also do not appear to be of particular use and possibly confusing to parents, and introduces regulatory impact on the manufacture, supply and sale of complementary medicines (both listed and registered) should they be adopted in their current form for all medicine categories. However, if significantly different requirements for different categories are introduced, it is also confusing to have different information on various preparations with the same excipient of concern, unless those differences are specifically examined and accepted within the Australian context (for example, a shorter statement for listed medicines and perhaps an expanded statement, if warranted, for Registered medicines). It appears to us that it is preferable in this context to have harmony between categories within Australia than harmony between Australian and international standards, for the purposes of clarity for Australian consumers. An Australian risk-based assessment and consultation on this particular issue (and depending on the outcome, a regulatory impact assessment) would be preferable to adopting to the EU guidelines at the current time to obtain the best regulatory outcome.