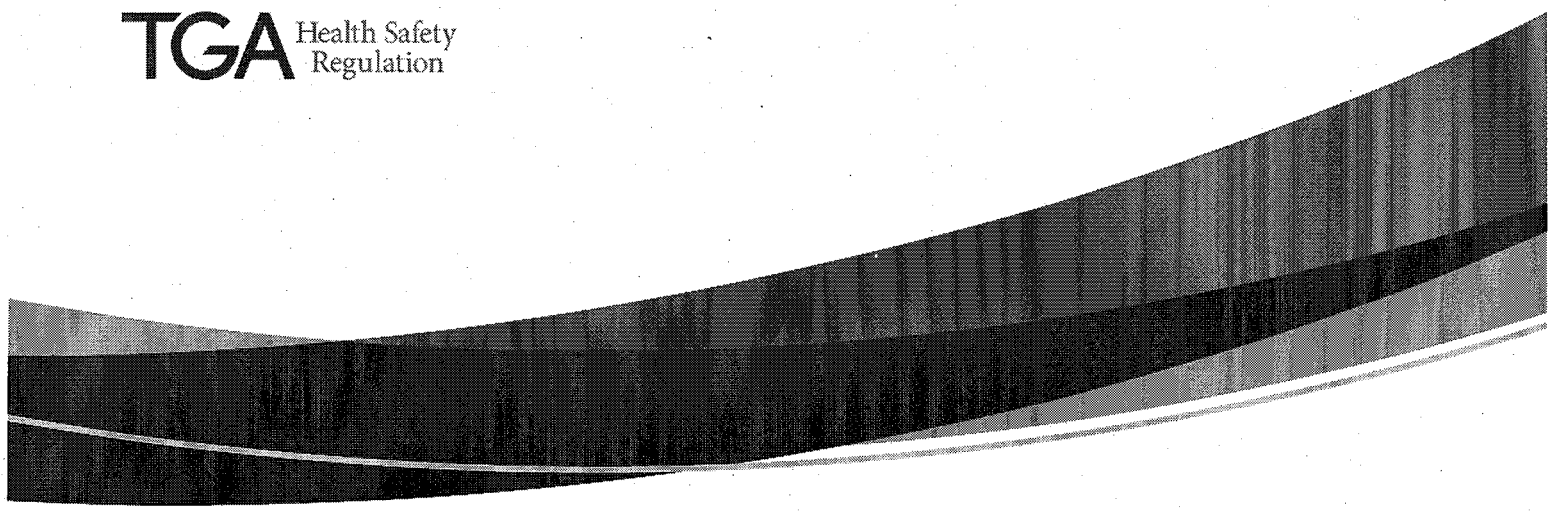
Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 12th Advisory Committee on Complementary Medicines

Ratified Minutes

7th December 2012

TGA Health Safety Regulation



Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
BP	British Pharmacopeia
CMEC	Complementary Medicines Evaluation Committee
CSU	Committee Support Unit
FSANZ	Food Standard Authority Australia and New Zealand
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
MAG	Marketing Authorisation Group
OCM	Office of Complementary Medicines
OPR	Office of Product Review
TGA	Therapeutic Goods Administration
USP-NF	United States Pharmacopeia and National Formulary

The Advisory Committee on Complementary Medicines (ACCM) held its twelfth meeting at the Stamford Plaza Hotel, Mascot from 9:40am to 1:40 pm on 7 December 2012.

Members of ACCM present

Professor Alan Bensoussan (ACCM Chair)

[redacted]

Present from the Therapeutic Goods Administration

Ms Jenny Burnett (ACCM Secretary)
Mr Anton Norder (A/g Head, Office of Complementary Medicines)
Dr Michael Carland (Office of Complementary Medicines)
Ms Judy Develin (Head, Market Authorisation Group)

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9:40am, welcoming ACCM members and TGA staff.

Anton Norder introduced himself to the committee as the acting Head, OCM.

Judy Develin introduced herself as the Head of the Marketing Authorisation Group, noting this was her first attendance at ACCM. Ms Develin outlined the further re-structuring of the TGA Executive, subsequent to TGA 21 and resulting from the retirement of the Chief Regulatory Officer, and provided a summary of the roles and functions of the two Groups within TGA. An update on the process for recruitment of a permanent Head of OCM was also provided.

1.2 Apologies

[redacted]

1.3 Meeting declaration of interest

Members submitted conflict of interest declarations, specific to agenda items for this meeting, to the Chair.

2. Minutes of previous meetings

2.1 Ratification of ACCM 11th minutes

The minutes of the previous ACCM meeting were ratified out of session.

3. Action arising from previous meetings

Nil

4. Evaluation of New Substances

4.4 Sucrose as an active ingredient in listed medicines

Background

A TGA officer introduced this item, advising members that an application had been received to approve sucrose as active ingredient in listed medicines, broadening its current availability from use as an excipient.

Currently, there are no products on the ARTG containing sucrose as an active ingredient. Approximately 2,300 products contain it as an excipient, some at high levels, and sucrose is also a common food component and additive, again occurring at high concentrations in some foods.

There appears to be an established use of sucrose to manage procedural pain in newborns and infants in the clinical/hospital setting. Although dosing studies have not been performed, and there is a conflicting evidence base for efficacy, three examples of Australian clinical guidelines for the use of sucrose in procedural pain relief were provided to the committee.

Data provided in the application to support the use of sucrose as an active ingredient in listed medicines included that obtained from two clinical trials. These trials reported that sucrose calmed and reduced crying in young infants in the absence of parental intervention and it appears that these trials would be used as the evidence base for the therapeutic indications associated with listed medicines. The applicant has indicated that the proposed medicines would make claims that sucrose as an active ingredient would maintain or increase the general wellbeing of infants by calming them and reducing their crying time.

The committee was asked to note that no systematic reviews on the calming effect of sucrose on infants not undergoing procedural pain have been located; that the mechanism of action for the analgesic effect of sucrose was poorly understood; and that no studies have focussed on possible adverse effects in infants as a result of long-term sucrose dosing.

ACCM was asked to advise on any possible therapeutic benefit if sucrose is made available as an active ingredient in listed medicines, particularly as efficacy data for sucrose has been generated under specific clinical conditions.

The officer also brought to the committee's attention a typographical error in the briefing paper, noting that 'Aust R' on page 1 should be corrected to 'Aust L'.

Discussion

Clarification was sought by the committee as to whether it was being asked to advise on the efficacy or safety of the substance. The TGA officer responded that advice on the risks and benefits of approving the substance was being sought and therefore evidence of both the safety and efficacy was presented for consideration.

One member queried whether the application proposed to limit the age groups within the target population. The TGA officer responded that no age groups, nor any other conditions, were defined by the applicant. It was likely that the substance would, if approved, be available for all age groups, noting that the proposed indication for medicines containing this substance as an active ingredient would be for 'increasing general well-being of infants' and that appropriate evidence needs to be held in support of any claim. Concern was raised over the broadness of the proposed therapeutic claim, particularly given the target population, and the potential for unrealistic expectations and inappropriate use that may arise. It was considered that appropriate restrictions would need to be applied, but that the evidence supplied did not allow these to be defined.

Members discussed the quality of the evidence submitted to justify the proposed indications. One member considered the trials presented in support of the application to be sound and on that basis it be approved with some caveats regarding age of patient population, intended purpose and warnings regarding the effect of development on teeth. Another member raised concerns over the 'weight' that could be given to the two trials, noting that both were conducted by the same research group, that the research took place a significant number of years ago and that there was a lack of reproduced studies supporting the findings of the original paper. However, one member did note that there had been a Cochrane review published in 2010 (Stevens, Yamada and Ohlsson: "Sucrose

for analgesia in newborn infants undergoing painful procedures") which reviewed 44 studies enrolling 3496 infants and concluded that "*Sucrose is safe and effective for reducing procedural pain from single events. An optimal dose could not be identified due to inconsistency in effective sucrose dosage among studies*".

Further discussion noted that there was no evidence of use outside a clinical setting and it was unclear that a therapeutic benefit would be achieved when the substance was provided by parents. Additionally, it was proposed that the risk of inefficacy could be considered a safety risk. Several members concurred that concerns remained over the context of its use and were in favour of its approval only if the dosage was appropriate.

Further discussion focussed on whether appropriate expectations were being raised by the proposed indications, especially with regard to pain management. If medicines containing the substance as an active ingredient were used for the management of pain, then conditions around its safe use would be required. One member considered the therapeutic action to be about modifying behaviour, not pain management. It was noted that the mechanism of action is poorly defined and that artificial sweeteners appeared to convey a comparable effect.

Concern of the potential impact on the development of teeth was discussed further and it was noted that information in the attachment provided with the briefing paper suggested there was no issue with adverse dental consequences. It was also noted that this impact may be comparable to that of fruit juice consumption.

A member noted that sucrose has been available as an excipient in medicines for a long time and there was little doubt regarding the safety and quality of the substance, given that both the USP and BP contain relevant monographs. From this perspective, there were no grounds for refusing to allow its use in listed medicines and consideration by the committee was only needed with respect to determining appropriate conditions or restrictions.

Whether the substance should be considered a medicine, because it is also recognised as a food, was discussed. It was noted that the argument that 'as quality and safety were established, approval should be automatic' could be applied to any food and a number of examples, including that of chocolate, were put forward. Members agreed that this should be approached with caution and that the *need* to regulate a substance as a medicine must be identified. Potential use of a substance as an active ingredient in a medicine should be considered with regard to wider safety concerns, beyond the toxicity of the ingredient *per se*. It was noted that both sucrose and honey are used as 'home remedies' to calm infants, however there was a significant difference between a home remedy and a medicine 'endorsed' by a national regulatory body.

A TGA officer brought to the committee's attention that where a substance is regulated as a food, it is excluded from regulation as a medicine (when subject to a standard under the *Food Standards Australia New Zealand Act 1991* or has a tradition of use as a food in Australia or New Zealand), while noting that numerous substances span the food-medicine interface. Members noted that an important consideration is dose, as foods are not subject to dose restrictions, and that use of some foods needs to be defined such that they can be identified as therapeutic goods in certain circumstances. Further, consideration should be given to consumer perceptions as to what constitutes a medicine; the definition of 'therapeutic use' as defined in the Act was read out and members considered whether the proposed use of sucrose met this definition and noted the recent rejection of water as a 'hydrating agent' in Europe on the basis that while this could be considered a therapeutic use, it was inappropriate to regulate water as therapeutic goods.

It was queried whether TGA had any additional guidance in regard to the food-medicine interface. A TGA officer noted there were no prescriptive guidelines relating to this topic and assessments often had to be made on a case-by-case basis. One member noted the existence of a guideline document on the TGA website (an archived document later identified as http://www.tga.gov.au/archive/anztpa-121127/meds/gt-food-medicine.htm)but it was suggested that a 'guiding principles' document on the food/medicine interface be drafted and members expressed willingness to be involved in this process.

A vote was taken and a majority of the committee was of the view that sucrose should be permitted as an active ingredient in listed medicines with conditions, but that there was no consensus that there is adequate evidence to establish those conditions. One committee member wished it to be noted that the view to approve sucrose was not unanimous.

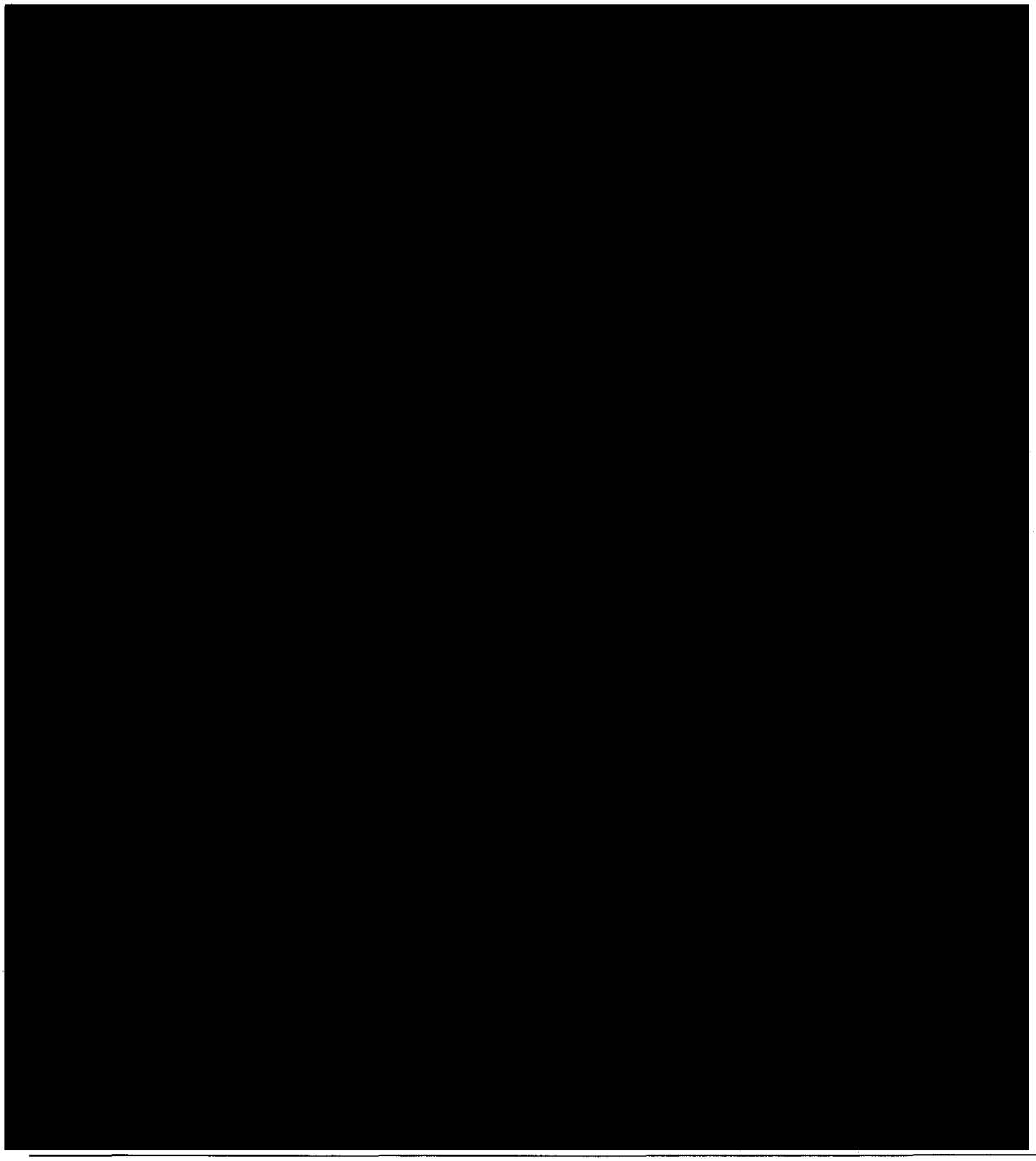
Recommendation 12.1

ACCM advises that, in principle, sucrose is suitable as an active ingredient in listed medicines with restrictions to ensure its appropriate use. However the evidence presented does not allow the conditions to be adequately defined at this time.

Recommendation 12.2

ACCM requests the committee be provided with TGA guidance documentation on food/medicine interface issues for comment and to inform future committee discussions. It was proposed that development of a 'guiding principles document' may be appropriate and that ACCM should provide assistance in its development.

5. Registration Applications



6. Regulatory Activity

6.1 Complementary medicines regulatory reforms update

This item was discussed in conjunction with item 8.1

7. Papers for Information

Item 7.1 ACSOM ratified minutes 13th meeting

Outcome

Members noted the ACSOM September 2012 minutes

8. Other business

Item 8.1 Comments on the role of ACCM

Background

A TGA officer provided the committee an overview of the reforms underway in relation to the role and outputs of the TGA advisory committees. Members were briefed on the nine statutory advisory committees currently managed by the TGA, their role in providing advice to inform delegates making decisions under the provision of the *Therapeutic Goods Act 1989* and how clarification for all stakeholders on this role was necessary to ensure that the legislative processes are robust and

transparent. It was noted that this issue would be covered in more detail in the members' induction program which is scheduled for early 2013.

The committee was also informed of changes to the way committee deliberations and decisions are made public, that are to be implemented in 2013. This work will be conducted as part of the 'TGA Blueprint implementation plan', fulfilling Recommendation 8 to provide clear information on the role of the statutory advisory committees and adopt a consistent and transparent approach to the publication of information from those committees.

It was noted that the proposed changes to the publishing of ACCM minutes and recommendations, to harmonise all committees' processes, will result in a decreased level of detail being reported from this committee in the short term. However, in the first instance, TGA is seeking to ensure consistency across the committees and ACCM members were asked to note Recommendation 12 (that the TGA explore mechanisms for providing explanations on its various regulatory processes, and the TGA adopt publication principles on the outcomes of application assessments using as an exemplar the Australian Public Assessment Reports (AusPAR).

Discussion

With regard to the 2013 induction process, members noted that they would appreciate receiving guidance on the types of recommendations that advisory committees can make and also asked that feedback be provided on the outcomes of decisions that are made in light of committee recommendations.

One member queried the liability of committee members in providing advice to the TGA. A TGA officer noted that the Act indemnifies individuals, including statutory committee members, from liability when acting in good faith to provide advice or make decisions.

One member queried the impact of ANZTPA on the role of the statutory committees and the possibility of New Zealand representation on committees. A TGA officer informed members that NZ is aware of and agree with the Australian model, however changes to business processes are in the early stages of development. A paper on the intent of the new joint agency was soon to be published although members were reminded that, at this time, the New Zealand equivalent to 'complementary medicines' will not be subject to joint agency regulation.

With regard to the publication of an outcome statement, in place of the existing publication of ACCM extracted ratified minutes and recommendations, a member stressed the importance of publicising the rationale behind decisions being communicated to stakeholders. It was noted that complementary medicine stakeholders regard the publication of ACCM meeting minutes as an important information source and members asked that the TGA advise industry peak bodies of the effects of the new approach, suggesting also that a statement on the TGA website may also be useful.

The Chair invited members to offer thoughts on the role of ACCM and the following issues were raised:

- Recent focus on specific issues and technical details of applications: this limited the ability of the committee to comment on broader issues.
- Concern that the committee was not being asked to comment on all aspects of a medicine - safety, quality and efficacy, but on one aspect only: it was requested that a summary statement be included in briefing papers to cover those aspects not under specific consideration.
- Full data dossiers were not being provided to the committee: this could result in members not being fully informed.
- The importance of seeking and providing advice with full context, including consumers' and practitioners' perspectives: ensuring 'quality use of medicines' approach.
- Connections with the wider context of regulation of complementary medicines: the possibility for closer involvement with current regulatory reforms.
- Closer links with other statutory committees: this would allow exchange, and better use of, specific expertise.

- Apparent focus on risk assessment of medicines: this potentially leads to limiting the value of the committee's considerations if the benefits are not also assessed and gives rise to a concern that appropriate safety assessments cannot done in the absence of knowledge of efficacy.
- With regard to listed complementary medicines: on-going concern with the assessment of evidence held in support of claims and consumer awareness of the regulatory status of these medicines in comparison with registered medicines.
- The importance of transparency of TGA processes for all stakeholders: clarity on how advice was sought from committees and the apparent lack of feedback mechanisms to inform the committee of decisions subsequently made within the TGA.
- The ability for members to table items under 'General business'

A general discussion on the outcomes of the on-going TGA review of the advisory committees, and the work of the Committee Support Unit within the TGA, in addressing some of the issues raised by members was held.

Actions

TGA should advise CHC, ASMI and the general public through a website statement of the effect that changes under the Blueprint reforms will have on the publishing of ACCM minutes and recommendations. The Office will keep ACCM informed about progress of outstanding issues and follow up activities, for example the revision and creation of regulatory and technical guidelines and documents.

[redacted]

[redacted]

9. Recommendation record

Recommendation 12.1

ACCM advises that, in principle, sucrose is suitable as an active ingredient in listed medicines with restrictions to ensure its appropriate use. However the evidence presented does not allow the conditions to be adequately defined at this time.

Recommendation 12.2

ACCM requests the committee be provided with TGA guidance documentation on food/medicine interface issues for comment and to inform future committee discussions. This may include assistance in the development of a 'guiding principles document'.

[redacted]

Chair's certification

I certify that this is an accurate record of proceedings of the meeting.

Professor Alan Bensoussan

ACCM Chair

December 2012