

CMEC 33

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Thirty-third Meeting
15 March 2002

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
ANZFA	Australia New Zealand Food Authority
AQIS	Australian Quarantine Inspection Service
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
BP	British Pharmacopoeia
BSE	Bovine spongiform encephalopathy
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicines Evaluation Committee
DSEB	Drug Safety and Evaluation Branch
ELF	Electronic Lodgement Facility
EP	European Pharmacopoeia
GBR	Geographical Risk of BSE
JHTF	Joint Herbal Task Force
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
OCM	Office of Complementary Medicines
PBS	Pharmaceutical Benefits Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAL	Therapeutic Goods Administration laboratory
TSEs	Transmissible spongiform encephalopathies

The thirty-third meeting of the Complementary Medicines Evaluation Committee was held at the Kingsford Room, Stamford Hotel, Sydney Airport, between 9:30 am and 3.40 pm on Friday 15 March 2002.

Members of CMEC present were:

Professor Tony Smith (Acting Chair)

Associate Professor Alan Bensoussan

Mr Nick Burgess

Dr Colin Duke

Dr Joachim Fluhrer

Ms Val Johanson

Professor Stephen Myers

Mr Kevin Ryan

Professor Bill Webster

Dr Heather Yeatman

Present from the TGA were:

Dr David Briggs

Dr Fiona Cumming

Dr John Hall

Mr Geoff Newman-Martin

Ms Michelle McLaughlin

1. Procedural Matters

1.1 Opening of Meeting

Professor Smith opened the meeting at 9.30 am on Friday 15 March 2002.

1.2 Apologies

Apologies were received from Dr Roberta Chow.

1.3 Conflict of Interest

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

2. Confirmation of Minutes of CMEC 32 (1 February 2002)

The minutes of the thirty-second meeting of CMEC were accepted as an accurate record of proceedings, subject to certain amendments.

Members made the following recommendation:

Recommendation 33.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 32, 1 February 2002), as amended, are a true and accurate record of that previous meeting.

3. *Guidelines on levels and kinds of evidence to support claims for therapeutic goods (the 'Guidelines')*

3.1 Working party

At CMEC 32, it was agreed that CMEC Members would provide amendments or corrections to the draft Industry Guidelines document to the Office of Complementary Medicines (OCM). Members also agreed at CMEC 32 that they would provide comments on the list of additional references proposed by industry for inclusion in the Guidelines. OCM would draft minor modifications to the CMEC Guidelines document for clarification and develop appropriate wording to indicate that the Industry Guidelines were consistent with CMEC's Guidelines document.

4. Stakeholder consultation paper: review of the regulation of herbal medicinal substances

Members were advised that the CMEC Working Party on Herbal Medicine Issues had met on Thursday 14 March 2002. The Working Party is finalising a draft consultation paper as the basis for a comprehensive review of the regulation of herbal medicine substances.

CMEC, in its initial discussions, had originally identified seven core issues to be addressed in the consultation paper. Following further consideration the Working Party subsequently identified another issue relating to standardisation of herbal ingredients. It was noted that there is currently no definition of the term 'standardised' in therapeutic goods legislation in Australia, although a variety of meanings have been attributed to the term both in Australia and internationally. There are currently numerous approaches to the use of the term 'standardisation', resulting in a term which is considered to be confusing and of limited meaning to consumers, industry and regulators. Lack of uniformity in the definition of 'standardisation' has led to a wide variety of 'standardised' ingredients in the marketplace, often resulting in different standards for the same herbal component. CMEC and the Working Party recognized that there was a need to establish a definition of the term 'standardised' so that, when the term is used to describe a herbal ingredient, it has a consistent and agreed meaning. A paper was prepared, and endorsed by CMEC, as an eighth core issue for the consultation paper.

Members recalled that at CMEC 32 (1 February 2002) it was agreed that the issues pertaining to standardisation be discussed at the Joint TGA/Industry Herbal Task Force (JHTF), as had previously been done with the consultation paper. A third meeting was held with the Joint Herbal Task Force on 14 March 2002, to discuss the standardisation proposal. At the meeting it was stressed that the aim of the consultation paper was to facilitate consultation and to explore ways to approach the issues it raised. Under the CMEC proposal, the JHTF noted that

a claim for standardisation should not be made on the label of a herbal ingredient unless a validated analytical method for the ingredient is included in a TGA-recognized monograph (such as a monograph in the *British Pharmacopoeia*).

The purpose of this approach was to provide a practical means of ensuring that a claim for standardisation was verifiable and consistent. Industry agreed that under the approach considered for Australia, standardisation should be determined by an end point quantification of one or more components in a herbal ingredient, as opposed to standardising against process, and that the analytical methods used to claim standardisation should be validated. Industry wished to choose its own methodology (e.g. developed in-house) but disagreed that standardisation be limited to components in ingredients included in a TGA-approved monograph as proposed by CMEC. The industry position presented at the JHTF meeting was that a validated analytical method should exist for a component of the ingredient but that the component should not be limited to TGA-recognized monographs. The problem with this approach was that the analytical method may not be validated against a peer-reviewed standard.

The industry position was that there should be a degree of flexibility in defining what components should be standardised against (partly for the marketing advantages this approach would allow). However, this could create confusion among consumers when attempting to compare products which might potentially contain inconsistent information. Industry representatives had questioned whether there was actually a problem with standardisation. They agreed that there may be disparity between manufacturers in that larger companies were more likely to have facilities to enable them to develop and apply properly-validated standardisation in-house, whilst smaller manufacturers might not be able to do this.

Industry representatives had also raised the subject of exported products and the fact that the listing of a product in Australia is considered to confer a market advantage. In their view, restriction within the Australian market of the term ‘standardisation’ could adversely affect export markets, because the product offered for sale overseas could not be sold in Australia or there would be dual regulatory costs for maintaining an export-only product as well as a product for the domestic market.

Present discussion

Members noted that the CMEC approach required independently-validated, identified analytical methods, whereas the position of industry was that in some cases methods were commercially-confidential intellectual property. Against this it could be argued that analytical methods as such were not intellectual property, but that it was, for example, the extraction of the ingredient from the herb which was the subject of intellectual property considerations. Additionally, it was also noted that the TGA treated data from sponsors as commercially confidential, so that details of analytical methods would not be compromised by making them known to TGA. It was possible to validate all analytical techniques including those using less expensive technology, but the method still needed to be identified for validation to be scientifically acceptable.

Members noted the potential difficulties with external validation for companies which marketed large numbers of products, and the logistical difficulties which could face TGA in attempting to validate analytical methods for all of the relevant products on the Australian market. There were potential difficulties for companies which exported products, if Australia

were to unilaterally introduce a more restrictive system of standardisation than that which operated in the USA and Asia. This could also result in competitive difficulties for Australian companies in an international market where other countries are not bound by the same restrictive conditions. Even if an export-only product is marketed, one of the importation eligibility criteria often applied by other countries was whether or not the same product was available for sale in the country of origin.

Members noted that the difficulty in determining:

1. how many product ingredients on the Australian market currently claimed standardisation;
2. whether there was a problem in relation to claims of standardisation in Australia; and
3. whether the proposed approach would significantly affect the export market.

It was noted that, although it was possible that the number of export products including standardised ingredients might be minimal at this stage, significant resources on the part of the TGA and industry might be needed to determine this information.

The OCM was requested to search the Australian Register of Therapeutic Goods (ARTG) to try to determine how many products (including export-only products) claimed to use standardised ingredients. A TGA officer advised that it could be possible to build into the postmarket system a means of determining such information about products on the market, as a part of the ongoing post market review of products. This would, however, be a long-term means of defining the extent of the problem. The OCM was requested to gather evidence from industry, regulatory sources and consumers of the extent of the problem.

Members requested the OCM to prepare a draft plan for further consideration at the next meeting of the CMEC Working Party on Herbal Medicine Issues, which in turn would refer its deliberations to CMEC. This plan would include suitable reference to standardisation.

There was general discussion as to how well consumers understood labelling of therapeutic goods. A TGA officer advised that a review of the labelling of therapeutic goods was being conducted by TGA. When the report entitled *Review of the labelling requirements for medicines: consumer-focused labelling a way forward? Consultation Report March 2002* was complete it would be provided to CMEC Members for information.

It was suggested that it was not necessary for the discussion paper to canvass all relevant methods of analysis, and that it would be sufficient to outline generic principles to be adopted by companies. In this context it was important to note that companies would not necessarily be required to use analytical methods included in a TGA-approved monograph, but rather a method validated against such a TGA-recognized, or TGA-accepted, method. This would give companies the flexibility to use their own internal analytical methods.

As part of the herbal consultation process Members recognized that the extent of the problem associated with the current usage of the term 'standardisation' will be determined. A request for stakeholder feedback on this matter will be explicitly included in the herbal consultation paper.

5. Action Arising from Previous Meetings

5.1 Condition of Listing requirement for Bach flower and homoeopathic medicines at risk of containing aristolochic acids

At CMEC 29 (September 2001), Members were advised of the implementation of the additional conditions of Listing for medicines containing herbal genera at risk of contamination with *Aristolochia* species. The conditions require sponsors to provide evidence demonstrating the absence of aristolochic acids or *Aristolochia* species for every batch prior to supply. Acceptable evidence is either a certificate of chemical analysis, using an approved method, confirming the absence of aristolochic acids, or a certificate of botanical identification confirming the identification of the raw herbs used in manufacture.

At CMEC 30 (October 2001), it was noted that whilst *Aristolochia* is not used as a Bach flower medicine, there are flower essence medicines incorrectly called Bach flower medicines, which could utilise this genus. There are essentially two methods of manufacture for true “Bach” flower remedies. The first of these was floating selected flowers on the surface of water exposed to sunlight, and the second was to boil the flowers, and sometimes the foliage, for a period of 30 minutes. The OCM has been advised that “flower essences” might also be produced by passing the flower over the water to absorb the “essence” into the water (or water/ethanol mix).

Present discussion

A TGA officer explained the basis of the current conditions of listing in relation to evidence demonstrating the absence of aristolochic acids or *Aristolochia* species, for Bach flower medicines and homoeopathic medicines. CMEC Members noted that in the case of flower essences there are two possible courses of action. An appropriately signed declaration may be provided to the TGA stating that the product is a flower essence, and that there has been no contact between the plant and the solution during preparation of the product. Alternatively, where there is contact between the plant and the solution during the manufacture of the flower essence (such as is the case for Bach Flower remedies), the sponsor may apply for an exemption from the relevant condition of listing, where certain conditions are met. This involves an appropriately signed declaration which will include details such as a complete and detailed description of the manufacturing process of the base flower essence and evidence of measures in place to botanically identify the herbal material.

Where analytical evidence is available to show that the base flower essence is free of aristolochic acids or that botanical source material has been verified, it is proposed that it not be necessary for the sponsor to meet the relevant condition of listing for every batch of the product, providing that the batch of product has been derived from the ‘approved’ batch of base flower essence.

Members were advised that similar information will be required in support of an exemption for the condition of listing for the mother tincture of homoeopathic medicines containing genera with species known to contain aristolochic acid, or at risk of being substituted or contaminated with species known to contain aristolochic acid. Where analytical evidence is available to show that the homoeopathic mother tincture is free of aristolochic acids, or where the botanical source material has been verified, it will not be necessary for the sponsor to

meet the relevant condition of listing for every batch of the product, providing that the batch of product has been derived from the ‘approved’ batch of homoeopathic mother tincture.

CMEC Members noted that *Aristolochia* species for therapeutic use were listed in Schedule C of the *Standard for the Uniform Schedule for Drugs and Poisons*, and as such were prohibited from sale, supply or use. Members also noted that the Office of Complementary Medicines will assess each application for exemption on a case-by-case basis.

5.2 Update on homoeopathic matters

At the CMEC 30, Members recommended that the definition of ‘homoeopathic preparation’ included in Regulation 2 of the *Therapeutic Goods Regulations 1990* be modified in order to more clearly encompass the principles of homoeopathy. It was also agreed that the term “homoeopathic preparation” be amended to “homoeopathic medicine”. At CMEC 31 (December 2001) Members noted that the TGA had received advice from the Legal Unit indicating that the definition of “homoeopathic preparation” in the Therapeutic Goods Regulations could be amended. However, it would be necessary to seek public comment on any proposed changes to the Regulations.

Members recalled that at CMEC 30 (October 2001), members recommended that a definition of ‘homoeopathic proving’ be included in the glossary for the *Guidelines for levels and kinds of evidence to support indications and claims*. Based upon the information provided at the meeting, it was noted that a well-designed homoeopathic proving should follow a recognised set of principles, such as those outlined in the *European Council of Classical Homoeopathy (ECCH) Recommended Guidelines for Good Provings*.

Members noted that the TGA had not yet sought public comment on a proposed change to the definition of ‘homoeopathic preparation (medicine)’ as the OCM has been awaiting comment from the Australian Register of Homoeopaths (AROH) on another homoeopathy matter (see below) which will be also put forward for public comment at the same time.

At CMEC31 (December 2001) members noted that the TGA had contacted the AROH to seek their views on the recommended definition of ‘homoeopathic proving’. The AROH was also requested to advise as to whether it endorsed the European guidelines for homoeopathic proving, or whether there was an appropriate set of Australian guidelines. Members noted that the Secretary of the AROH had recently contacted the OCM indicating that the requested information had been circulated to members for comment. Comments had been received from two homoeopathic practitioners for the consideration of the CMEC.

Members were advised that the OCM has recently updated a template letter outlining the current regulation of homoeopathic medicines in Australia, which is sent out in response to inquiries relating to homoeopathic matters. The specific updates are in relation to implementation of the new labelling order *Therapeutic Goods Order No. 69 – General requirements for labels for medicines*.

Present discussion

A TGA officer advised that the OCM was awaiting further responses from the AROH. It was noted that the material used in provings is serially diluted, rather than the crude substance. A

number of comments were made on the procedures set out in the International Council of Classical Homoeopathy (ICCH)/ECCH recommendations.

6. Evaluation of new substances

6.1 Lutein

CMEC Members noted that an application had been received for listing of lutein in the form of purified crystalline lutein (PCL) as a complementary medicine substance.

Members noted that the lutein application had been considered at CMEC 32 (February 2002) CMEC. At CMEC 32, Members had noted that no specific toxic effects had been shown in *in vitro* and *in vivo* toxicity studies with PCL. Formulated PCL was not demonstrated to be mutagenic *in vitro*. It was noted that most of the data for lutein consumption by humans is for lutein found in foods. No apparent ill effects are associated with the highest reported dietary intake of lutein. However, no clinical safety data have been presented in support of use of lutein at recommended doses. CMEC Members had also noted the lack of long-term animal toxicity and carcinogenicity studies on lutein.

At CMEC 32, Members agreed that further consideration of this item should be deferred pending acquisition of further information on reproductive toxicity from the sponsor, and its assessment by the OCM.

Present discussion:

Members noted that the evaluation report had been updated to take into account a preliminary report of a reproductive study which had been commissioned by the sponsor, together with additional information on the process used to manufacture purified crystalline lutein. The data suggest that administration of PCL up to 1 g/kg/day during gestation (days 6-20) had no effect on reproductive parameters and foetal development and morphology in rats. Members noted that there was little to suggest that PCL is a substance which represented a risk of reproductive toxicity and that it had been administered in a quite high dose during the study. It was noted that it was intended to include antioxidants in PCL which inhibited the production of potentially mutagenic compounds which could be produced by degradation of the parent compound.

Members noted no safe upper limit for lutein had been determined and that the exposure of Australians to products containing lutein, including food, was not known. It was also noted that no adverse reactions to lutein have been reported in Australia. Members also noted that most of the lutein consumption by humans was in foods, and that no clinical safety data had been presented in support of the use of lutein for therapeutic purposes at recommended doses. However, there was no scientific evidence that levels of lutein would have adverse effects different from lutein found in foods. It was also noted that long-term animal toxicity and carcinogenicity studies had not been presented, but that *in vitro* and *in vivo* toxicity studies with PCL had not shown specific toxic effects, and a one-year study had been conducted in monkeys which did not demonstrate any significant adverse effects.

Members noted that lutein is prone to breakdown by oxidation, and therefore considered that any recommendation to recommend that lutein was suitable for use as an active substance in

listed therapeutic goods should be subject to a condition of listing that it be stabilised to minimise degradation.

CMEC Members made the following recommendation:

Recommendation 33.2

CMEC recommends to the TGA that lutein is suitable for use as an active ingredient in listable therapeutic goods, provided that it is stabilised to minimise degradation.

7. Safety reviews

There were no matters for consideration under this agenda item

8. Registration applications

One recommendation was made under this item.

9. Variation to a registered product

There were no matters for consideration under this agenda item.

10. Matters referred from within the TGA

10.1 Report from the 258th meeting of ADRAC

A TGA officer provided an update to CMEC Members in relation to a report of a patient who had experienced a sudden onset of acute, non-chronic renal failure after taking two Chinese medicines.

Members noted a report from the 258th meeting of the Adverse Drug Reactions Advisory Committee (ADRAC) on recent consideration of adverse reactions associated with the use of complementary medicines. Members noted several adverse reaction reports.

A TGA officer advised that the OCM was continuing work on a review of the labelling of caffeine-containing herbal preparations reviewed with a view to indicating the presence of caffeine on labels (Recommendation 31.5).

10.2 Availability of Bulgarian tribulus (*Tribulus terrestris*)

A TGA officer provided an update to CMEC Members on TGA action following consideration by CMEC 32 of a report of hepatotoxicity in a twenty-nine year old male approximately four weeks after commencing a product, which was stated to contain Bulgarian tribulus (*Tribulus terrestris*), phyto-sterol and wild yam. It was noted that there

was a possibility that an infection may have influenced the hepatotoxicity reaction. The product appeared to have been purchased over the Internet as it had no AUSTL number, and CMEC had requested OCM to investigate the availability of this product. Members were advised that a search of the Australian Register of Therapeutic Goods (ARTG) had confirmed that there were no references to this product and it is not an exempt good. However, the OCM had found there were numerous internet websites which advertised this product. A number of those advertising appeared to be Australian sites. Extracts from the sites were provided to members. Members were also informed that the Advertising Unit had advised the OCM that the advertising material was representing the product for a therapeutic use. It was noted that the matter had been referred to TGA's Surveillance Unit for investigation and action as appropriate.

Present discussion

Members noted the update and the action taken. A TGA officer pointed out that it was not illegal to import this product for personal use providing that certain conditions are met, so long as it is not proscribed under the *Customs (Prohibited Imports) Regulations*. One of the problems for persons importing substances for personal use was that they could unwittingly attempt to import a product with a similar name which actually contained a prohibited substance or substances, such as anabolic steroids and androgenic substances.

10.3 Kava

At CMEC 32 (February 2002) Members noted reports from Germany and Switzerland which linked kava-containing products with 30 serious cases of hepatotoxicity and the actions taken by regulatory agencies worldwide. Members were also informed that TGA had written to sponsors of kava-containing products on the Australian Register of Therapeutic Goods requesting that sponsors remain vigilant and forward any adverse reaction reports to the TGA.

At CMEC 32, it was recommended that the TGA undertake a number of initiatives, including contacting hepatologists to ask them to review cases of acute hepatic necrosis occurring in recent years, issuing an alert to health professionals, including advice to consumers and the media on kava on the TGA website, continuing to gather information on products containing kava, consult with the New Zealand health authorities, and continuing its dialogue with international regulatory bodies (Recommendation 32.4).

Present discussion

Members were provided with an update on international developments, including details of regulatory action on kava undertaken in the USA, the UK, Ireland, Portugal and Singapore.

10.4 Aristolochia

A TGA officer advised that TGA had completed some of the recall procedures for products containing aristolochic acids. It had been nearly six months since botanical identification and chemical analysis had been introduced as a condition of listing for products containing

Aristolochia. It was anticipated that there would be ongoing surveillance of at-risk products in order to monitor the effectiveness of these arrangements.

10.5 Review of evidence to support indications on the ARTG for a complementary medicine

One recommendation was made under this item.

10.6 Review of evidence to support indications on the ARTG for a complementary medicine

One recommendation was made under this item.

11. Recommendation record

CMEC Members adopted the following as a summary of the recommendations made at its 33rd meeting.

Item 2 Minutes of CMEC's 32nd Meeting

Recommendation 33.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 32, 1 February 2002), as amended, are a true and accurate record of that previous meeting.

Item 6.1 Lutein

Recommendation 33.2

CMEC recommends to the TGA that lutein is suitable for use as an active ingredient in listable therapeutic goods, provided that it is stabilised to minimise degradation.

Item 8.1 Registration applications

One recommendation was made under this item.

Item 10.5 Review of evidence to support indications on the ARTG for a complementary medicine

One recommendation was made under this item.

Item 10.6 Review of evidence to support indications on the ARTG for a complementary medicine

One recommendation was made under this item.

12. Information items

There were no items for consideration under this agenda item

13. Other business

It was noted that the terms of membership for members of CMEC were nearing completion and that new appointments were under consideration.

The meeting closed at 3.40 pm. It was agreed that the 34th meeting of CMEC would be held in Sydney on Friday 3 May 2002.