CMEC 12

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes

Twelfth Meeting

27, 28 April 1999
The twelfth meeting of the Complementary Medicines Evaluation Committee was held at the TGA, Symonston on the 27th and 28th of April 1999.

Members of CMEC present were:

Professor David Roberts (Chair)
Dr Roberta Chow *
Dr Colin Duke
Dr Joachim Fluhrer
Ms Val Johanson
Dr Stephen Myers
Mr Kevin Ryan
Dr Heather Yeatman
Prof Bill Webster

Members of the CMEC Expert Advisory Panel (CMEC EAP) present were:

Dr Alan Bensoussan
Dr Rajen Cooppan
Ms Robyn Minski
Mr John Lumby**
Mr Rob Santich

Present from the TGA were:

Dr Fiona Cumming
Mr Graham Peachey
Dr Helen Cameron
Dr John Hall
Ms Pat Brown
Ms Judy Cunningham
Dr Harry Rothenfluh

* Unable to attend until day 2 of the meeting
** Unable to attend until the afternoon of day 1 of the meeting

1. Procedural Matters

1.1 Opening of Meeting

Professor Roberts, as Chairman, opened the meeting and welcomed new and returning members of CMEC. He also welcomed members of the new Expert Advisory Panel (EAP) explaining the role the EAP would have in supplementing the expertise of CMEC as required and being involved in CMEC working parties as available and appropriate.

1.2 Apologies

Apologies were received from Mr Nick Burgess.
1.3 Welcome by Senator Tambling

Senator Grant Tambling, Parliamentary Secretary to the Minister for Health and Aged Care, addressed the members briefly and welcomed them to the revised committee.

1.4 Welcome from Acting General Manager

Dr Susan Alder, Acting National Manager, welcomed members and presented an overview of TGA.

1.5 Introduction to TGA

Dr Susan Alder introduced the following members of TGA who outlined the structure and function of their respective branches:

Dr Leonie Hunt, Conformity Assessment Branch
Dr Larry Kelly, TGA Laboratories Branch
Ms Laurayne Bowler, Review of Drugs and Poison Legislation Branch
Dr Udomsri (Toi) Low, International Services Branch
Dr John McEwen, Adverse Drug Reaction Unit
Mr Graham Peachey, Chemicals and Non-Prescription Medicines Branch

1.6 Introduction to Committees

Dr Susan Alder introduced the following TGA staff who gave an overview of the role of the following committees for which they were responsible:

Mr Paul Archer Medicines Evaluation Committee
Dr Brian Priestly National Drugs and Poisons Scheduling Committee

A briefing on the role of the Australian Drug Evaluation Committee is to be provided at future meeting of CMEC.

1.7 Meeting Procedures and Conflict of Interest

The Chairman outlined members’ obligations with respect to conflict of interest as detailed in the Guidelines included in the agenda papers. The appropriate instruments were made available for members to read and sign as required.

One member expressed concerns about affiliations with professional associations which might create a conflict of interest when items being considered by CMEC and which involve consultations with TGA impinge on the interests of that association. The Chair confirmed that such professional affiliations should not preclude that CMEC member from discussions on that item so long as potential conflicts of interest are declared.

The meeting sought further information on sitting fees should the need arise to seek broader expertise and experience than that available through the current membership of CMEC and the EAP or should CMEC and EAP members themselves be involved in additional
consultations such as working parties. A TGA staff member agreed to follow this up and report to the next meeting.

It was clarified that the papers distributed to members prior to and following meetings are confidential in nature and procedures for safeguarding their security need to be adopted by members.

2. Review of the Advertising Code

The Chair outlined the aims of the current review of the Therapeutic Goods Advertising Code (TGAC), including the role of the Therapeutic Goods Advertising Code Council (TGACC) carrying out this role and the timeframes to which it is working.

Members were briefed on the role of the TGAC Task Force which is undertaking this role on the review on behalf of TGAC and were introduced to the consultant assisting the Code Council Task Force.

The consultant addressed the meeting on
- the terms of reference for the review;
- the history of the TGAC and early approaches to regulation of advertising of therapeutics;
- approaches in other countries (in particular USA, Canada and UK) and contrasts with the Australian regulatory environment;
- issues of concern; and
- current progress with the review.

Members were informed that an important role for CMEC in the work of the Code Council would be to carefully consider and advise on the level and quality of evidence needed to support claims for complementary medicines on labels and in advertising.

The need was identified for a CMEC working party to progress this matter and to report back to CMEC and to the TGAC Task Force. Val Johansen, Heather Yeatman and Stephen Myers made themselves available. TGA is to provide the secretariat to the working group.

Recommendation 12.1

That a Working Party be established, to deal with the levels, types and quality of evidence needed for substantiation of claims made in labelling and advertising of therapeutic goods, consisting of the Chairperson Professor Roberts, Ms Heather Yeatman, Dr Stephen Myers, Ms Val Johanson and Mr Graham Peachey.

Recommendation 12.2

That the Working Party holds three meetings before the next CMEC meeting to formulate a draft submission on behalf of CMEC to the review of the Advertising Code.
Item 3  **Subcommittees and Working Parties**

### 3.1 Working Party on Priorities for the Review of Herbs

The Chairman outlined for the purpose of newer CMEC members the background to this item in that, previously, CMEC had established a working party to compile a priority list of herbs for safety reviews by CMEC. The Chairman of the Working Party tabled a report on the progress of the working party and this formed the basis of a verbal report he presented to the meeting.

The Chairman of the Working Party concluded that while the group had been able to make considerable progress on identifying those herbal substances to which CMEC and Office of Complementary Medicines resources should be directed, further work would need to be done. He suggested that the new CMEC develop a mechanism to advise the OCM on priorities for safety evaluation.

The following motions were put and agreed:

**Recommendation 12.3**


**Recommendation 12.4**

That CMEC requests TGA to prepare a paper on the initiative on the regulation of products containing herbal substances for discussion at the next meeting.

Item 4  **Herbal Substances – ARTG Requirements**

A TGA officer introduced this item explaining that the Project Advisory Committee overseeing the redevelopment of the new Electronic Lodgement Facility (ELF) sought advice from CMEC on type and detail of information that may be needed by CMEC on the nature and specification of herbal substances when making safety assessments.

One member declared a potential conflict of interest on this item. The Chair indicated, and members agreed, that the member could take part in discussion and any decision making on this item.

Members heard that the issue becomes particularly important where, following the listing of a herbal substance and the issuing of an Australian Approved Name (AAN, which fully identifies that substance for purposes of the Australian Register of Therapeutic Goods (ARTG), including its preparation), the formulation of that substance changes. An example of such a change could be where the extraction ratio or extraction process is varied as a result of a change in manufacturing process, the sourcing of product from another manufacturer or for other reasons.
Members discussed at length the advantages and disadvantages of continuing to collect the full set of information on herbal substances.

Members were not prepared to make a decision on this matter without a more thorough understanding of the current and future information requirements as they pertained to the existing and proposed new mechanisms for the lodgement of notifications to list a therapeutic good and using the Electronic Lodgement Facility (ELF).

The Chairman put the following recommendation which was carried with one abstention:

**Recommendation 12.5**

That any decision on the type and detail of information needed by CMEC regarding the nature and specification of herbal substances when making an Electronic Lodgement Facility (ELF) listing application be deferred until after a viewing of the current and new systems at the next meeting.

**Item 5  Action Arising from Previous Meetings**

**Item 5.1 Proposed Consultancy Regarding the Regulation of Probiotic Bacteria**

One member declared a conflict of interest in relation to this item. However the Chairman proposed, and members agreed, that this should not prevent that member from joining in the discussion and any decision making process arising.

A TGA staff member gave a brief background to this item referring to a previous CMEC recommendation that the only probiotic bacteria permitted in listable therapeutic goods were those strains present in grandfathered registered goods.

A draft consultancy brief presented with the agenda paper for this item seeks to obtain expert information on the strains most likely to be present in existing probiotics, on any safety or other concerns which might arise from their use and information on other strains likely to be used in probiotic substances.

Members commented favourably on the draft consultancy brief and agreed it be the basis for an approach to the consultant to gain the required information.

The following recommendation was put and agreed:

**Recommendation 12.6**

That the consultancy brief be acceptable in the form drafted without amendment.
Item 6  Evaluation of New Substances

6.1 Squalene

The TGA evaluator provided members with an overview of the agenda paper, the main points being that squalene:

- had been the subject of a section 7 declaration and declared to be a therapeutic good
- occurs in a wide range of oily foods and is used in cosmetics
- is found in high levels in commercial shark liver oil products and is extracted from this source
- acts as a cholesterol precursor in animals and man
- has a low toxicity profile
- has inconsistent effects on cholesterol levels in human studies
- while being promoted as an antioxidant and promotant of general well being, has no evidence in support of any specific therapeutic claims.

Discussion

Members discussed at length the conflicting results from the two human studies reported in the evaluation in which effects on cholesterol were studied. Discussion centred around the methodological differences and the mechanisms of action which might account for these results.

Members briefly considered the need for the labelling of squalene products to indicate the fact that it was derived from animal sources (for the benefit of vegetarians) but it was agreed to take this matter on notice as a more general issue to be addressed at a later time.

While members were generally supportive of squalene becoming available as a listable good, there was concern over the unpredictable effects of squalene on serum lipids and how this could impact upon its safe use in certain population groups. While there was interest in alerting consumers about the potential effects on cholesterol, there were difficulties in determining the precise information to be communicated. On the one hand members were reluctant to devise a warning concerning cholesterol effects which may be unnecessarily discouraging of the use of the product, particularly when there is exposure to squalene from other dietary and environmental (eg cosmetics) sources. On the other hand the variability in effect on cholesterol levels represented a potential safety issue in those consumers for whom monitoring and management of serum lipid levels are important.

Members adopted the following recommendation with one abstention from the vote:

Recommendation 12.7

CMEC recommends that squalene is suitable for use in listable therapeutic goods subject to consultation by TGA as to the wording of an advisory/warning labelling requirement with respect to its effects on serum lipids.
This recommendation was proposed for the following reasons:

- Squalene appears to be of low toxicity, based on current information.
- Consumers and practitioners may not be aware that ingestion of squalene may, in some cases, lead to increases in serum lipids.
- Advice such as letters to practitioner organisations could be considered.
- A label statement such as the following could be considered:

  *Squalene is a precursor of cholesterol – those with cholesterol problems should have their cholesterol levels measured regularly.*

### 6.2 Bifidobacterium longum

The TGA evaluator provided members with an overview of the agenda paper, the main points being that probiotic bacterium *Bifidobacterium longum*:

- is the first example of a new strain within the genera *Lactobacillus* and *Bifidobacterium* to be considered for listing since amendment of the Therapeutic Goods Regulations to permit the listing of certain probiotics;
- is appropriately identified by methods considered acceptable by the evaluation team and within limits for pathogenic and heavy metal contamination;
- is not associated with any safety concerns over and above those related to probiotics in general, where issues of potential transfer of antibiotic resistance and virulence factors may need to be considered; and
- has demonstrated capacity to assist in the normalisation of bowel flora following antibiotic use and can slightly increase stool frequency in mild constipation.

Members adopted the following recommendation for the reasons that:

- The substance is unlikely to present a safety risk above that presented by bacterial strains already permitted in listable therapeutic goods. Strains of bacteria within the genera *Lactobacillus* and *Bifidobacterium* are now permitted in listable goods, provided these strains were used in grandfathered registered goods.
- There is no available evidence to support any specific labelling requirements in relation to products containing this substance. No specific conditions of listing have been established for other listable probiotic bacteria.
- The quality of the substance is considered to be acceptable.
- There is some evidence to show that may be efficacious in treating minor conditions such as constipation.

**Recommendation 12.8**

CMEC recommends that *Bifidobacterium longum* is suitable for use in listable therapeutic goods with no additional conditions over and above the standard conditions.
6.3 Calcium Beta-hydroxy-beta-methylbutyrate (Ca-HMB)

The TGA evaluator provided members with an overview of the agenda paper, the main points being:

- The External Reference Panel on Therapeutic Goods/Foods Interface Matters (ERPIM) had considered Ca-HMB to be a therapeutic good not a food and suggested that a safety evaluation be carried out. Ca-HMB has been gazetted to be a therapeutic good in line with this recommendation.
- While Ca-HMB is known to be an intermediary in the minor pathway of leucine metabolism, no metabolic function has been attributed to it.
- The claimed benefits of Ca-HMB, which relate principally to increasing the positive effects of weight training (including increasing muscle mass), remain insufficiently substantiated on the basis of the data evaluated.
- None of the animal or human studies evaluated had suggested toxic effects of Ca-HMB.

Discussion

Members noted the fact that Ca-HMB was becoming widely used by virtue of its use as an ingredient in a number of sports foods. While holding the above concerns about the mechanism of action, the committee agreed that those using Ca-HMB for its purported ‘anabolic’ effect could do so without harm.

Since the toxicity data for Ca-HMB were based on relatively short term studies, some members were concerned about its long term safety given that it could be consumed for considerable periods of time. There was also consideration about potential use in pregnancy, lactation and by children although one porcine study found no toxic effects on the piglets via sow’s milk and subsequent reproductive cycles were not affected. Members were reluctant to impose advisory statements about the lack of information with respect to longer term safety on labelling and advertising of Ca-HMB, but considered that, because HMB is an endogenous amino acid metabolite whose position in a metabolic pathway has been identified, this could not be justified.

Members discussed the implementation of an upper daily dosage of Ca-HMB but in the absence of long term efficacy and safety studies considered that there was insufficient information to be in any way certain about what this limit should be.

Members adopted the following recommendation with one abstention from the vote:

**Recommendation 12.9**

CMEC recommends that Ca-HMB is suitable for use in listable therapeutic goods with no additional conditions.

**Please note:**
While the CMEC review process established that CaHMB was of low risk, a corollary to that decision was CMEC’s conclusion that current evidence does not support any therapeutic claims for CaHMB associated with lean muscle mass increase.

**Item 7 Matters from within TGA**
7.1 Section 7 proposals - update

Members considered a paper providing an update on section 7 declarations (under the *Therapeutic Goods Act 1989*) declaring certain goods to a therapeutic good. Details of recent declarations were presented for information. Members noted the item.

**Item 8 Decision Record**

The following is a composite of the decisions made by CMEC at its twelfth meeting on 27 and 28 April 1999.

**Item 2 Review of the Therapeutic Goods Advertising Code**

*Recommendation 12.1*

That a Working Party be established, to deal with the levels, types and quality of evidence needed for substantiation of claims made in labelling and advertising of therapeutic goods, consisting of the Chairperson Professor Roberts, Ms Heather Yeatman, Dr Stephen Myers, Ms Val Johanson and Mr Graham Peachey.

*Recommendation 12.2*

That the Working Party holds three meetings before the next CMEC meeting to formulate a draft submission on behalf of CMEC to the review of the Advertising Code.


*Recommendation 12.3*


*Recommendation 12.4*

CMEC requests TGA to prepare a paper, indicating future directions, for discussion at the next CMEC meeting.
Item 4 Herbal Substances ARTG Information Requirements

Recommendation 12.5

That any decision on the type and detail of information needed by CMEC regarding the nature and specification of herbal substances when making an Electronic Lodgement Facility (ELF) listing application be deferred until after a viewing of the current and new systems at the next meeting.

Item 5 Action Arising From Previous Meetings

5.1 Proposed Consultancy Regarding the Regulation of Probiotic Bacteria

Recommendation 12.6

That the consultancy brief be acceptable in the form drafted without amendment.

Item 6 Evaluation of New Listable Substances

6.1 Squalene

Recommendation 12.7

CMEC recommends that squalene is suitable for use in listable therapeutic goods subject to consultation by TGA as to the wording of an advisory/warning labelling requirement with respect to its effects on serum lipids.

6.2 Bifidobacterium longum

Recommendation 12.8

CMEC recommends that *Bifidobacterium longum* BB536 is suitable for use in listable therapeutic goods with no additional conditions over and above the standard conditions.

6.3 Ca-HMB

Recommendation 12.9

CMEC recommends that Ca-HMB is suitable for use in listable therapeutic goods with no additional conditions.

Please note:
While the CMEC review process established that CaHMB was of low risk, a corollary to that decision was CMEC’s conclusion that current evidence does not support any therapeutic claims for CaHMB associated with lean muscle mass increase.

Members agreed this was the sum total of the decisions made.
Item 9 For Information

No issues for this item

Item 10 Meetings Schedule 1999

The following meetings of CMEC were proposed for 1999:

Friday June 11
Friday August 6
Friday September 24
Friday October 22 and
Friday December 10

As a matter of urgency, TGA is to advise the EAP members of these dates.

Item 11 Other Business

11.1 Profiles of Members for TGA Internet Site

CMEC members agreed to provide photos and a short paragraph, including postnominals, to the TGA for inclusion in the Internet site but were concerned that the EAP be canvassed for their own views on this matter.

11.2 Facsimile Arrangements

A member asked that the facsimile arrangements be investigated to ensure multiple copies of documents are not received.

The use of electronic mail was also raised as a possibility for despatching papers but confidentiality was mentioned as a problem. The possibility of encrypted documents would be investigated by the TGA.

11.3 Consultation

A member asked about the policy which applies when a CMEC member needs to consult with external parties in the process of deliberating on decision papers sent to them. A TGA member of staff offered to prepare guidelines on this aspect.

The possibility was also raised of arranging a time for acquainting CMEC members more fully on the evaluation and administrative processes being put in place as the Office of Complementary Medicines develops.

11.4 Broader use of CMEC evaluation papers

One member requested that CMEC develop a policy on broader dissemination of evaluation papers where they are of an appropriate standard and relate to appropriate subject matter eg. in peer reviewed journals. It was agreed that this be placed on the agenda for the next meeting.
11.5 General comments on evaluation papers

Members commented favourably on the high standard of papers presented to the meeting and made the following suggestions for future papers:

- **Sample size:** One member commented that small sample sizes need not necessarily be a reason for regarding published research results as being of less importance than those with higher sample sizes – this depends very much on study design and the degree of variability of the sample and smaller sample sizes may be valid in many cases; and

- **Statement of hypothesis:** One member suggested that it would be helpful if, when reporting on a published study, the hypothesis being tested in the study be clearly stated in the evaluation paper.

The meeting closed at 4.00pm.