

CMEC 17

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes

Seventeenth Meeting

10 December 1999

The seventeenth meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Golden Wing Lounge, Sydney Airport, on the 10th December 1999.

Members of CMEC present were:

Professor David Roberts (Chairman)
Mr Nick Burgess
Dr Roberta Chow
Dr Colin Duke
Dr Joachim Fluhrer
Ms Val Johanson
Dr Stephen Myers
Mr Kevin Ryan
Prof Tony Smith (afternoon only)
Prof Bill Webster
Dr Heather Yeatman.

Present from the TGA were:

Dr Susan Alder
Dr David Briggs
Dr Fiona Cumming
Dr Judy Cunningham.

1. Procedural Matters

1.1 Opening of Meeting

Professor Roberts, as Chairman, opened the meeting at 9.30 am and welcomed members.

1.2 Apologies

Apologies were received from Prof Smith for the morning of the meeting.

1.3 Conflict of Interest

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

2. Confirmation of Minutes of CMEC 16 (21 and 22 October 1999)

Members ratified the Minutes of CMEC 16 without amendment.

3. Report of the Working Party on Substantiation of Claims

The TGA advised that the document *Proposed approach of the CMEC to standards for levels and kinds of evidence to support claims for therapeutic goods* had been presented to Senator Tambling for consideration.

The document is an evolving one and two particular areas (aromatherapy and homoeopathy) will be the subjects of further work in the near future.

The positive list of disease manifestations that can be referred to in product indications, without the need for high level evidence, will be incorporated into a later version of the CMEC guideline. This list had begun to be developed at CMEC 16 but requires further refinement.

4. Report of the Working Party on Herbal Medicine Issues

A Working Party had been established at CMEC 16 to review a number of issues relating to the regulation of herbal medicine substances and the classification of low risk herbal ingredients. Its Chairman presented progress in the work of this group to the meeting. The group had focussed its work in three main areas: the inclusion of certain substances in Division 2, Part 4 of Schedule 4 of the Regulations, the definition of a herbal substance and the label expression of strength of herbal extracts.

Nine particular entries (for *Arisaema*, *Arnica*, *Daphne mezereum*, *Lathyrus sativus*, *Prunus dulcis*, *Pseudolarix kaempferi*, *Ricinus communis*, *Robinia pseudoacacia*, and *Semecarpus anacardium*) in Division 2, Part 4 of Schedule 4 were considered. These entries are intended to restrict the manner of use of these herbal substances so that safety is maintained. The wording of these entries had been developed following advice from the Traditional Medicines Evaluation Committee (TMEC) in the early 1990s. While the Working Party considered that TMEC's original recommendations in relation to these substances were sound, it has become clear that the wording used in the Regulations does not accurately reflect the intent of the TMEC recommendations.

The Working Party therefore presented a number of recommendations to CMEC in regard to the restrictions on the use of the above herbal substances. The aim of these recommendations is to clarify the intent of the Regulations for these substances. CMEC members accepted these recommendations, detailed below.

The Working Party has made significant progress towards developing a new mechanism for determining whether or not a specific ingredient derived from a herb could, in fact, be considered to be a herbal substance. The existing definition of a herbal substance¹ contained in the Regulations may not deal adequately with modern production processes associated

¹ "Herbal substance means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

- a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and
- b) that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form."

with herbal ingredients, such as sophisticated extraction and concentration techniques. As such, it is not fully apparent whether such ingredients are automatically of low risk.

Members noted a progress paper outlining the range of processes (traditional and specialised industrial) that may be used in the production of herbal substances and identifying the order of refinement that industrial processes produce. The aim of this paper is to develop a guideline that acts as an 'alert' system to identify when an extract becomes something other than a herbal substance. As far as the Working Party members were aware, such a classification of production techniques has not been undertaken in other countries and therefore Australia's work in this area is unique.

The third area of activity for the Working Party was clarification of the expression of the strength of herbal extracts on product labels. A variety of means of expressing strength are now available (eg fresh weight equivalents, dry weight equivalents) and this may be confusing for consumers and may not allow direct comparison of product strengths. The Working Party recommended that the strength of herbal extracts should be expressed as mg/g of the equivalent dry weight of the herb.

The Working Party is preparing a final report for a future CMEC meeting. Aspects of this report will be circulated for public comment. The CMEC Chairman thanked the Working Party for their work to date.

CMEC noted and endorsed the approach of the Working Party on Herbal Medicine Issues. CMEC also endorsed the following recommendations of the Working Party to the TGA:

Recommendation 17.1

To amend the entry for *Arisaema*, in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations, in order to infer that *Arisaema* preparations at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose) are eligible for inclusion in listed goods, and to omit the reference to preparations containing cardiac glycosides.

Recommendation 17.2

To amend the entry for *Arnica* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations, in order to infer that preparations of *Arnica* used externally, or those used internally at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose), are eligible for inclusion in listed goods.

Recommendation 17.3

That expert advice be sought (eg from the Chair of the former Traditional Medicines Evaluation Committee and other experts) relating to the issues of:

- a) dermal absorption of the toxic component(s) of *Daphne mezereum*, and whether there is further information (to that available in 1994/5 when TMEC considered this herb) relating to the toxicity of *Daphne mezereum*; and**
- b) possible mechanisms for restricting external dose to a specified amount.**

Recommendation 17.4

To amend the entry for *Lathyrus sativus* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations to omit the reference to “cooked seed”, and to include a reference to preparations containing no lathyrogenic amino acids. The entry is meant to imply that preparations of *Lathyrus sativus* containing no lathyrogenic amino acids AND preparations of *Lathyrus sativus* at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose), are eligible for inclusion in listed goods.

Recommendation 17.5

To amend the entry for *Prunus dulcis* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations to omit the reference to preparations containing cyanogenic glycosides. The entry is meant to imply that preparations of *Prunus dulcis* seed are only eligible for inclusion in listed goods at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose). Preparations of *Prunus dulcis* containing other plant parts remain eligible for inclusion in listed goods at any dose safe for that ingredient.

Recommendation 17.6

To amend the entry for *Pseudolarix kaempferi* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations in order to infer that preparations of the stem bark and root used externally, or preparations of any plant part used internally at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose), are eligible for inclusion in listed goods.

Recommendation 17.7

To amend the entry for *Ricinus communis* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations so that it is clear that the fixed oil of the seed ONLY is eligible for inclusion in listed goods.

Recommendation 17.8

To amend the entry for *Robinia pseudoacacia* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations in order to infer that preparations of the leaf and flower, or preparations of other plant parts at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose), are eligible for inclusion in listed goods.

Recommendation 17.9

To amend the entry for *Semecarpus anacardium* in Schedule 4, Part 4(2) of the Therapeutic Goods Regulations in order to infer that preparations of the seed, or preparations of other plant parts at low doses (equivalent to 1mg or less of dry herbal material per recommended daily dose), are eligible for inclusion in listed goods.

5. Action Arising from Previous Meetings

5.1 CMEC 16 Meeting

5.1.1 Hydroxycitric acid (item 4.2.1 of CMEC 16 refers)

Members were reminded of previous consideration of this matter at earlier CMEC meetings. At CMEC13 a recommendation was made that hydroxycitric acid and its sodium, potassium and calcium salts be accepted as suitable for use as active ingredients in listable goods. At CMEC16 members were advised that the zinc and magnesium salts of hydroxycitric acid are now available overseas and advice was sought on the broad principles that the TGA could follow in considering whether or not to extend an approval to encompass new salts of an approved substance. At its 16th meeting CMEC advised the TGA that one principle that should be followed under these circumstances is that there should be evidence that the anion and cation dissociate rapidly, so that the evaluation can focus on the anion and cation separately.

The TGA has been unable to obtain dissociation data for magnesium and zinc hydroxycitrates or even any dissociation data on the sodium, potassium and calcium hydroxycitrates. Further, it has not been possible for the TGA Laboratories to readily determine comparative dissociation values for these salts due to impurities present in commercially-available products. Therefore it has not been possible to meet the criterion established at CMEC16.

A member advised that, as dissociation and dissolution are linked for true salts (ie those salts where complexation between the anion and cation does not occur), measurement of dissolution (solubility) would satisfy CMEC's previously stated requirements for true salts. These measurements should take place under simulated gastric conditions, for example using the method outlined in the US Pharmacopoeia. These data could be provided by a sponsor seeking approval to use magnesium and zinc hydroxycitrate in listable goods, rather than the TGA expending further resources on this matter.

Members agreed that they did not hold any other specific safety concerns for magnesium and zinc hydroxycitrate, based on current evidence and noting that dosages of zinc salts are already controlled under the *Standard for the Uniform Scheduling of Drugs and Poisons*. Members therefore made the following unanimous recommendation (with two absences) to the TGA:

Recommendation 17.10

CMEC advises the TGA that it does not hold any significant concerns related to the safety of zinc hydroxycitrate and magnesium hydroxycitrate additional to those for the hydroxycitrates already approved for listing, noting that the use of zinc salts in listed medicines is subject to the requirements of the *Standard for the Uniform Scheduling of Drugs and Poisons*. Consistent with its previous recommendation, CMEC advises that solubility data, determined in simulated gastric juice (as per the method outlined in the US Pharmacopoeia), need to be provided before these salts are recommended for use as active ingredients in listable therapeutic goods. If these data are provided, then zinc hydroxycitrate and magnesium hydroxycitrate would be considered for suitability for use in listable therapeutic goods.

6. Evaluation of new substances

6.1 Bovine lactoferrin

The TGA evaluator introduced this item and outlined the reason the evaluation had been conducted. It was noted that some sponsors wished to use bovine lactoferrin as an excipient ingredient while other sponsors wish to use it as an active ingredient.

No matter how a substance is classified, safety needs to be assessed. Members requested that the TGA prepare a paper for the next meeting outlining regulatory issues relating to excipient ingredients compared to active ingredients.

Excipient ingredients are not generally required to be declared in the labels of therapeutic goods containing them, unless required to do so under the second schedule of Therapeutic Goods Order (TGO) 48 - *General requirements for labels for drug products*. Members discussed the need for consumers to be clearly informed that a substance derived from cows' milk is contained in a therapeutic good. It was considered to be important for consumers to be advised of the cows' milk origin of bovine lactoferrin for safety reasons (eg for those consumers who may suffer from cows milk allergy) and for cultural reasons. Members therefore recommended the inclusion of bovine lactoferrin in the second schedule of TGO 48. The use of the descriptor 'bovine' may not be sufficient to fully inform consumers that lactoferrin is derived from cows' milk, and therefore a further descriptor (eg "from cows' milk") may be required.

Members noted that Australians already have significant dietary exposure to bovine lactoferrin from an early age, via consumption of cows' milk products. They also noted that the TGA had been unable to find any reports of adverse events associated with bovine lactoferrin. All members considered that bovine lactoferrin is of sufficiently low risk as to be suitable for use in listable therapeutic goods.

Recommendation 17.11

CMEC recommends to the TGA that bovine lactoferrin be accepted as both an active ingredient and an excipient ingredient suitable for use in listable therapeutic goods. Where bovine lactoferrin is used as an active ingredient, the label should advise that the substance is derived from cow's milk. A request for consideration should be made to the Therapeutic Goods Committee that bovine lactoferrin be included in the second schedule to Therapeutic Goods Order No. 48 - *General requirements for labels for drug products*.

7. Safety reviews

7.1 Valerian (*Valeriana officinalis*)

A member declared a conflict of interest in relation to this agenda item

The Committee agreed that the member could participate in the deliberations and vote on the recommendation to go forward to the TGA.

Valerian (*Valeriana officinalis*) was selected for review as part of a program of reviewing the safety of commonly used herbal substances. The original CMEC committee established this process in 1998.

In introducing this item the TGA evaluator noted that valerian is a widely used herb in Australia but that since 1993 there have been only nine adverse reactions reported to the TGA for it. Short-term clinical trials have reported few reactions associated with its use. The incidence of reported adverse reactions is likely to be lower than for echinacea, for which a CMEC review concluded that no changes were required to its regulation at this time.

Some of the reported adverse reactions for valerian have been of hepatotoxicity and it was suggested that these events were most likely to be due to concurrent use of *Scutellaria* spp. Substitution of *Scutellaria* with the hepatotoxic herb *Teucrium* spp has occurred in the past. The meeting was advised that there is little potential for hepatotoxicity from valerian and also that the rate of allergic reactions to valerian is very low. The following recommendation was made:

Recommendation 17.12

CMEC recommends to the TGA that *Valeriana officinalis* (valerian) appears to be of sufficiently low risk as to continue to be suitable for use in listable therapeutic goods, with no additional restrictions imposed.

7.2 Ginkgo (*Ginkgo biloba*)

A member declared a conflict of interest in relation to this agenda item. The Chairman ruled that this member could participate in the debate and vote on the outcome of the deliberations.

Ginkgo (*Ginkgo biloba*) was selected for review as part of a program of reviewing the safety of commonly used herbal substances. The original CMEC committee established this process in 1998. Ginkgo is the last of its priority list of herbal substance safety reviews.

There have been relatively few reports of adverse reactions in association with the use of ginkgo in Australia and ginkgo is believed to be one of the most widely used herbs in Australia. Some reports in other countries have identified serious bleeding events but these have tended to involve patients with significant pre-existing conditions. However as ginkgo is likely to be used by an older patient group, the small number of adverse reaction reports does not necessarily mean that few adverse reactions have occurred, as reaction reporting in older, sicker, patients may be lower than for younger patients.

Members noted research that suggested that ginkgo may interfere with the action of Platelet Activation Factor (PAF). However a member advised that PAF has only a weak effect on platelets and therefore any interference with its action by ginkgo is unlikely to lead to serious bleeding problems. The meeting was advised that, if ginkgo did have a significant effect on the ability of blood to clot, then there would be a substantial number of reports of bleeding problems following its consumption, given the high level of usage of ginkgo in Australia. It is not possible to establish causality in the overseas reports of bleeding events associated with ginkgo and it is possible that these incidents could be unrelated to the use of ginkgo. Aspirin is known to effect platelet function, and is used therapeutically for this purpose, but is not

required to carry label warning statements about bleeding potential. Therefore, based on current evidence, members considered that it is not necessary to require any label warning statements about any potential for medicines containing ginkgo to cause bleeding.

There are also reports of human poisoning in association with consumption of ginkgo seeds, but these cases have involved consumption of large quantities of seeds in famine times. The majority of ginkgo products listed in Australia contain leaf extracts and these reports are considered to have little relevance to the therapeutic use of ginkgo in Australia.

Ginkgolic acids are a class of acids (also known as anacardic acids) found in the leaves and seeds of ginkgo. Related compounds are known to be allergens. Members were advised of a proposed European limit (5 ppm) for ginkgolic acids in certain ginkgo leaf extracts but noted that as this limit is not compound specific, it may not in fact be limiting the amounts of the substances that may be exerting an allergenic effect. At this time, members did not consider that there is a need to establish a limit for ginkgolic acids in Australian therapeutic goods containing ginkgo.

Recommendation 17.13

CMEC recommends to the TGA that *Ginkgo biloba* (ginkgo) appears to be of sufficiently low risk as to continue to be suitable for use in listable therapeutic goods, with no additional restrictions imposed.

CMEC recommends to the Office of Complementary Medicines that advice should be sent to the Drug Safety and Evaluation Branch of TGA regarding the possibility of an amendment to warfarin labelling or product information, to the effect that patients be advised not to take complementary medicines while on warfarin therapy without medical advice. CMEC noted that this advice is being prepared and will be considered at CMEC's 18th meeting.

8. Registration applications

8.1 Tea Tree Oil

A member submitted a conflict of interest declaration in relation to this item. The Committee agreed that the member could participate in discussions for this item but not vote on the outcome.

CMEC considered an application to register a medicine composed of uncompounded *Melaleuca alternifolia* oil. A member advised that there is a general consensus that melaleuca oil is an effective mild antiseptic. Members agreed that specific product efficacy data are not required for medicines such as this that consist solely of uncompounded *M. alternifolia* oil, provided that the indications are in line with the oil's use as a mild antiseptic for minor skin conditions. Other indications would require specific efficacy data.

Members considered that boils and burns were not minor skin conditions. Boils are closed infections and therefore do not necessarily respond to topical treatment. They can also lead to the serious condition of septicemia. Burns should be treated by immediate cold water application and medical attention should be sought for all but minor burns. The use of

melaleuca oil in the treatment of minor burns is really as an antiseptic to treat any minor infections that may develop around the burn site.

The use of melaleuca oil in the treatment of pimples was discussed. One controlled trial of the use of melaleuca oil with acne had been published and had suggested that the oil may be beneficial in removing transient undesirable skin flora.

Members discussed the potential for melaleuca oil to cause skin irritation. The Australian standard for this oil, to which the product in question conforms, limits cineole content to 15%. At this cineole level, one member advised that the oil could cause a burning sensation in susceptible individuals. However members noted that the National Drugs and Poisons Schedule Committee (NDPSC) had recently reviewed the safety of melaleuca oil, as well as a range of other essential oils, and had not made any recommendations that related to the cineole content of this oil.

Members (other than that member who had declared a conflict of interest) unanimously adopted the following recommendation:

Recommendation 17.14

CMEC recommends to the TGA that a tea tree oil product be accepted for registration.

9. Variation to a registered product

No matters were considered under this agenda item.

10. Matters referred from within the TGA

10.1 Tea Tree Oil - policy on evaluation reports

A member submitted a conflict of interest declaration in relation to this item. The Committee agreed that the member could participate in discussions for this item but not vote on the outcome.

Members considered a proposal from the TGA that future registration applications for un-compounded *Melaleuca alternifolia* oil, where the product has indications for minor conditions of a first aid nature and is intended for topical administration, that the application not be referred to CMEC for detailed consideration. CMEC would be advised that a particular registration application had been approved by the TGA. However if the indications were for non-minor conditions, involved a route of administration other than topical, or if the TGA held any other significant concerns about the product, the application would be referred to CMEC for detailed consideration.

Members supported this proposal and made the following recommendation:

Recommendation 17.15

CMEC recommends to the TGA that, in future, registration applications for uncompounded *Melaleuca alternifolia* oil products, intended for topical use and with low level claims of a first aid nature, can be approved by the TGA without requiring prior consideration and recommendation by CMEC.

10.2 Draft compositional guideline for calcium hydroxy methyl butyrate (HMB)

CMEC members noted a draft compositional guideline for calcium hydroxy methyl butyrate (HMB), prepared by the TGA. Calcium HMB had been approved as a listable active substance earlier in 1999. At that time, compositional guidelines had not been developed for new listable actives, but it is now TGA policy that such guidelines be prepared at the time of evaluation of the new substance.

Members endorsed the draft guideline and supported its release for comment, making the following recommendation:

Recommendation 17.16

CMEC advises the TGA that it endorses the draft compositional guideline for calcium hydroxy methyl butyrate and supports its release for broad comment.

10.3 Risk assessment model for new substance evaluations

The history of approval of new complementary medicine substances was outlined. Since 1998 a process has been in place to allow the evaluation of new complementary medicine substances and this process has been refined over the last two years. The question has now arisen as to the appropriate level of evaluation for complementary medicine substances. Any approach to the evaluation of the safety of new complementary medicine substances should be streamlined and appropriate, but must still deliver safety.

The TGA had prepared a document outlining a draft risk assessment framework, for discussion purposes. The document had been developed in part based on a submission from the Complementary Healthcare Council of Australia (CHC).

Members supported the general approach of the TGA on this matter. A member pointed out that foods, with the exception of novel and genetically modified foods, do not undergo an evaluation of safety in Australia. Further, people use foods and medicines differently so that direct extrapolations of safety in food use to safety in therapeutic use as suggested by CHC cannot be made.

Supply of a complementary medicine substance in the United States should not be automatic grounds for allowing its supply in Australia as the US does not have a comparable regulatory environment, nor does it have a strong adverse reaction monitoring system for complementary medicines. Nevertheless consideration of the US experience does provide some information to incorporate into an evaluation.

An ongoing problem in the evaluation of new complementary medicine substances is the lack of complete data sets to support safety. The next step in the development of the risk assessment framework is to identify the data sources that can be used to assist with streamlined evaluations. Another approach that could be used to develop the principles for streamlined evaluations is to trial the framework with some new substances. Members supported the concept of trialing the framework using some substances that are currently permitted only in grandfathered, registered medicines and it was agreed that this should be undertaken in time for the next meeting of CMEC. Members made the following recommendation to the TGA:

Recommendation 17.17

CMEC endorses the general approach outlined by the TGA in the draft paper *Risk assessment framework for new substance evaluations*. CMEC looks forward to the development of principles to support the framework outlined and notes that the approach will be trialed with some substances currently permitted only in grandfathered, registered goods, and referred to the 18th CMEC meeting.

10.4 Bioavailability data in registration applications

Consideration of applications for inclusion as new registrable complementary medicines involves consideration of safety, quality and efficacy. One parameter that influences each of these aspects is bioavailability. The TGA is concerned that sponsors who wish to submit applications to register complementary medicines carrying high level claims may not have the type of bioavailability evidence required to support registration. The TGA has therefore sought advice from CMEC on this matter.

Some members believed that dissolution studies are the minimum requirement for such medicines, although they acknowledged that in multi-component preparations dissolution data may not be appropriate. However if a medicine is making high level claims it is important that the active ingredients are delivered in a reproducible manner to maintain efficacy. Another member advised that little is known about the bioavailability of herbal medicines, which typically contain a large number of compounds. The only meaningful bioavailability studies of herbal medicines are likely to be for medicines containing only one herb where the manufacturer has the financial resources to undertake these studies.

An alternative to a requirement for dissolution could be for sponsors to demonstrate that their medicine is of the same formulation as that used in published clinical trials where efficacy had been demonstrated. However if the formulation was not exactly the same then the sponsor would be required to demonstrate bioequivalence. Bioequivalence demonstration has been a stumbling block for the complementary medicines industry.

Members acknowledged that when dealing with products used to treat serious conditions, where efficacy must be demonstrated, comparable standards must be applied to both complementary and mainstream medicines. Because this issue has major implications for the complementary medicine industry it may be premature to release a paper for comment, until CMEC has further considered the issues involved in determining bioavailability. The following recommendation was made to the TGA:

Recommendation 17.18

CMEC recommends to the TGA that, where a medicine presented for registration is of the same formulation and same form as one for which clinical trials were conducted, then bioavailability data may not be required. However if the medicine is presented in a different form to that used in clinical trials, bioequivalence must be established.

CMEC notes that an approach to determining bioequivalence will be trialed by consideration of future applications to register medicines with indications relating to serious conditions. This will allow further refinement of a discussion paper on the matter, after which industry consultation should be undertaken.

10.6 Report from the Adverse Drug Reactions Committee

An extract of a report from the 240th ADRAC meeting was provided for members. Of particular interest was the item about possible interactions between *Hypericum* (St John's Wort) and antidepressants. This is likely to form the subject of an article in ADRAC's bulletin. Members also noted five reports of adverse events in connection with glucosamine. The events were of varying nature. The TGA agreed to discuss this matter with the ADRAC secretariat.

12. For Information

No matters were considered under this agenda item.

13. Other business

There was no other business.

The meeting closed at 4.30 pm on Friday 10 December 1999. The next meeting is to be held on Friday 18th February 2000.