CMEC9

Complementary Medicines Evaluation Committee

Extracted Ratified Minutes

Ninth Meeting

29 October 1998

Complementary Medicines Evaluation Committee

Item 1.1 Opening of Meeting

The ninth meeting was held at the Melbourne Airport, Ansett Golden Wing lounge between 10.00am and 4.30pm on Thursday, 29 October 1998.

Members of the committee present were:

Dr Anne Tonkin (Acting Chairman)
Ms Jocelyn Bennett
Dr Roberta Chow
Dr Fiona Cumming
Dr Colin Duke
Ms Val Johanson
Professor Chiang Lin
Dr Stephen Myers
Mr Allan Ware

Also present from TGA were:

Mr Graham Peachey
Dr Helen Cameron
Dr Judy Cunningham
Dr Leigh Lehane
Ms Pat Brown

Dr Tonkin opened the meeting at 10.00 am and welcomed members.

Item 1.2 Apologies

Apologies were received from Professor David Roberts, Chairman, Professor Jorma Ahokas and Dr Joachim Fluhrer. Apologies for delays in arrival were received from Dr Myers, Professor Lin and Dr Cameron.

Item 1.3 Conflict of Interest

Conflict of interest forms were completed by the members and handed to the Acting Chairperson.

Item 2 Confirmation of Minutes

Item 2.1 Confirmation of Minutes of CMEC6, CMEC7 and CMEC8 (16 September 1998)

The minutes were confirmed.

Item 2.2 Consideration of Draft Minutes

Members noted the item relating to the format of the draft minutes.

Item 2.3 Order of the Agenda

The Chairman amended the order of consideration of the agenda items so that item 3.1.2 Harmala Alkaloids and item 3.1.3 Draft Submission to NDPSC on Selenium were discussed after item 2.

Item 3 Action Arising from Previous Meetings

Item 3.1 CMEC8 Meeting

Item 3.1.1 Working Party on Priorities for the Review of Herbs

At CMEC8, CMEC had accepted the report of the Working Party on Priorities for the Review of Herbs relating to the list of priorities of herbs to be reviewed by the Working Party and the flow chart for longer-term planning.

The Chairman of CMEC asked the Chairman of the Working Party if, in view of the discussion in the item 3.1.2 on harmala alkaloids, the list of priorities for herbs to be reviewed would be amended to include *Tribulus terrestris.* The Chairman of the Working Party said that the list had been based on adverse drug reports and, since there were no adverse reports mentioned for *Tribulus terrestris,* it would not be included in the priority list.

The Chairman of the Working Party provided a verbal report on progress of the Working Party on Priorities for the Review of Herbs.

CMS has provided a list of herbs to the Working Party members that combined information from Traditional Medical Evaluation Committee data on herbs needing possible restriction, or herbs unknown to TMEC, and data in the ARTG on numbers of products containing these herbs. The Chairman of the Working Party thanked TGA for this information, which would be considered by the Working Party at a future meeting.

Item 3.1.2 Harmala Alkaloids ¾ Request by NDPSC

At CMEC3, members were asked to provide advice to TGA on the regulation of herbs containing the harmala alkaloids, in particular harmine and harmaline, which are prohibited imports and contained in Schedule 9 of the *Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)*. CMEC studied a report on harmala alkaloids by a consultant, evaluated the safety of these herbs in reference to harmala alkaloid components, and concluded that the level of the harmala alkaloids in products on the market containing these herbs is of low risk.

The August 1998 meeting of NDPSC considered a submission from CMEC for an exemption from Schedule 9 of the *SUSDP* for dried herbs and extracts containing no more than 10 mg of harmala alkaloids per daily dose of nominated herb species. The harmala alkaloids harmine and harmaline had been included in Schedule 9 (with other hallucinogens) at the August 1985 meeting of NDPSC.

NDPSC resolved to exclude harmala alkaloids from Schedule 9 of the *SUSDP* when in herbs or therapeutic preparations

(a) containing 0.1 per cent or less of harmala alkaloids; or
(b) in divided preparations containing 2 mg or less of harmala alkaloids per recommended daily dose.

Nonetheless, NDPSC requested CMEC to provide comment on the relevance of published papers by Dr CA Bourke concerning neurological effects in animals to the potential for adverse effects with chronic use in humans of preparations containing the harmala alkaloids. In his papers, Bourke describes neurological disorders of sheep grazing the plants *Tribulus terrestris* and *Phalaris aquatica.*

As at 22 September 1998, there were 23 products registered in the ARTG containing *T. terrestris,* some with up to 2 g dried plant per dose unit. Traditionally, the herb was used as a demulcent, aphrodisiac, diuretic, and for the treatment of impotence in males.

Members considered the scientific report based on Dr Bourke's research and the introductory remarks by the TGA evaluator. They noted that harman and/or norharman derived from *T. terrestris* accumulate in the CNS of sheep, target specific neurones of the nigrostriatum, and eventually cause irreversible tribulus staggers, a locomotory dysfunction characterised by limb paresis. They also noted that a number of scientists believe that the same alkaloids are implicated in the pathogenesis of a different disease in humans, i.e. Parkinson's disease, by being metabolised in the human brain to bioactivated methylated β-carboline derivatives with a structure similar to MPP^+, the active metabolite of MPTP, an impurity of synthetic heroin that causes parkinsonism. There is much literature pointing to environmental or endogenous β-carbolines being putative neurotoxic factors in Parkinson's disease.

The evaluator said that, while it looks as if harman/norharman may cause a different disease

in humans compared with that in sheep, because of metabolism of the alkaloids in the human brain, both diseases are irreversible neurological syndromes. These research findings must be balanced against the fact that harman and norharman appear to be produced endogenously in the human body and are also present in brewed dietary products and tobacco. However, as the substances appear to be cumulative in the CNS and have been associated with irreversible pathology, no additional intake in the form of herbal medicines could be assumed safe.

The Chairman questioned whether the alkaloids would be cumulative in sheep after 4 months of high-intensity exposure grazing almost pure stands of *T. terrestris.* This may be very different from years of very low level exposure, where metabolism and excretion would probably prevent the alkaloids from reaching toxic levels. There are numerous examples of drugs that are harmful in animals at high doses, but never reach toxic levels in humans. Members also commented that there were difficulties in extrapolating the evidence from sheep to humans. The evaluator said that the latter may be irrelevant in this case, as research suggested that, in humans, harman and norharman are metabolised to dimethylated derivatives, which may be involved in the pathogenesis of Parkinson's disease. In one study (Kuhn *et al* 1996), harman and nor harman levels were significantly higher in the CSF of patients with Parkinson's disease than in an age- and sex-matched control group. The Chairman suggested that the sheep studies (and extrapolation from them) should be put to one side and members should concentrate on the Parkinson's disease connection. While it is possible that humans may be affected either way (i.e. by unmetabolised harman/norharman causing a disease like tribulus staggers; or by metabolised derivatives causing Parkinson's syndrome), there is no evidence that the alkaloids are not metabolised in humans.

The Chairman asked whether there was evidence of motor system problems in humans exposed to harmala alkaloids over a long period of time. The TGA evaluator replied that there was none, but that the use pattern of *T. terrestris* had changed only recently.

A member mentioned a pharmaceutical drug that caused Parkinson disease-like symptoms (haloperidol). It was metabolised down to a similar cationic form to that of MPTP. The Chairman noted that there are a number of drugs that cause Parkinson's disease as side effects; for example, antipsychotic drugs. Large amounts of such drugs are being used, and their effects are reversible.

Another member suggested that one group in the population — beer drinkers who smoke — would have been exposed to harmala alkaloids over a long period of time and asked about documented side effects. The evaluator pointed out that, despite the fact that tobacco contains harman/norharman, smoking is inversely related to Parkinson's disease. This has been attributed to tryptamines also present in tobacco blocking the effect of the alkaloids. The Chairman noted that since MPTP was found to cause induced parkinsonism, scientists have accepted that toxins in the environment may cause Parkinson's disease.

Members discussed whether the levels of harmala alkaloids ingested (i.e. in herbal preparations and otherwise) would ever become high enough to be likely to cause disease. For example, is it reasonable to compare low levels of harmala alkaloid exposure with taking

a concentrated drug form? In response to this, a member noted that it was not a reasonable comparison: the study reported that the 2,9-dimethylated derivatives were more harmful than harman and norharman, and that the methylating process was much less effective in humans than in animals.

The TGA evaluator, to present an alternative view, pointed out the reference to the research of Matsubara *et al* (1993) in the middle the scientific report, which demonstrated 'bioactivated' 2-methyl-norharmanium and 2,9-dimethyl-norharmanium ions in the substantia nigra, and to a much lesser extent in the cortex, of apparently normal human brains. The Chairman commented that this was reassuring, as methylation apparently occurred commonly and was not associated with harmful effects. A member asked whether the discussion was referring to endogenous or exogenous alkaloids. The evaluator said that it was probably both. It seems likely that these substances can be produced endogenously, but they can be ingested too, even in fried fat material.

The Chairman enquired about long-term effects and the pattern of use of *T. terrestris* in Australia. There were new substances becoming available for use by body builders. The major harmala alkaloid preparation used over recent decades has been *Passiflora*. It has been available for use by dispensers and for sale in health food shops to the public in relatively low dosages. As for the anti-anxiolytic prescription drugs, in the member's training and experience, such herbs are prescribed for short periods only (up to 6 weeks to 3 months). Such herbs are rarely used alone. Within the industry, powdered capsules containing harmala alkaloids are mixed with other powdered herbs considered to have mild anti-anxiolytic activity, and because of this you don't get a large amount of any particular substance in these preparations.

The Chairman asked what levels of harmala alkaloids are present in those preparations, in terms of mg/kg, compared with the *T. terrestris* preparation taken by bodybuilders. The answer to this question is unknown.

A member suggested that CMEC consider the products on the market and the amount of harmala alkaloids in them. The ratification of the NDPSC decision and the date of effect of the NDPSC amendments were also discussed. The NDPSC decision was gazetted in August and would take 6 months to come into effect. There was some concern expressed about the enforcement of the amendment made by NDPSC without knowledge of the amount of harmala alkaloids in products. The Chairman said it was not TGAL's responsibility to do analytical work for sponsors, although it would be useful information for CMEC. The products should be marketed with their content of harmala alkaloids stated, and sponsors need to start thinking about this.

Members noted that there are 23 products on the market containing *T. terrestris*. Their content of harmala alkaloids is unknown. The CMEC Secretary pointed out that there is also no information about the *T. terrestris* products being brought in by personal importation. The Chairman said that the circulated article in *The Bulletin* was disturbing, especially in relation to the claim of a Viagra-like effect. It was noted that *T. terrestris* does not have a long history

on the Australian market and it is certainly not in the common category of herbs prescribed by practitioners.

There are two aspects from the consumers' perspective — freedom of choice versus being exposed to something potentially harmful. Members agreed that it was difficult to assess the possible harmfulness of herbal preparations containing harmala alkaloids at this stage. It would take several months for TGA laboratories to establish the alkaloid content of the products on the market. This information will indicate how much people are getting when consuming recommended daily doses. However, unless the figure was surprisingly high, akin to the doses used in the animal studies, this would be unlikely to help our understanding of the potential risk.

A member said that there have been studies that measure the effects of the methylation that is required to form molecules that will cause Parkinson-like symptoms in pharmaceutical drugs and this data could be considered. The levels of harman and norharman in humans were measured and it was not clear whether they could be metabolised to something that could be harmful. In themselves they are not harmful and will not cause Parkinson-like symptoms unless they are metabolised. Methylation in humans is much less effective than in animals. The TGA evaluator queried this, saying that methylation apparently did not occur in sheep, and again noted the paper by Matsubara *et al* (1993) referred to in the scientific report.

The Chairman suggested that it seemed that members did not want to request NDPSC to change its recommendation on this matter, because there was not sufficient solid evidence. The TGA evaluator said that extrapolation from sheep was probably irrelevant anyway. The Chairman said that without the extrapolation from sheep, then there really is no evidence at all, apart from the chemical similarity. The evaluator replied that there was a lot of scientific literature, which she had barely touched on, suggesting that harman and norharman may be implicated in Parkinson's disease.

The Chairman suggested that the Committee may wish to accept option 1, to say that the committee feels the sheep research is not particularly relevant, but is there human research that is more relevant in terms of neurotoxicity?

The CMEC Secretary said that NDPSC is looking to ratify the decision of the previous meeting and they will be looking for CMEC input on this additional information. Their question was 'Is the sheep work important'? Other issues have been raised in the paper. It is necessary to know how much of the alkaloids are in these preparations, in terms of possible neurotoxicity unrelated to the sheep work. At this stage there is no evidence that 2 mg/day is harmful. This can stand, pending further investigation into the neurotoxicity aspects insofar as what is known in humans, particularly in relation to Parkinson's disease. This can be looked at independently, and referred to NDPSC again if necessary The Chairman agreed that a person with specialist expertise should look at it. The evaluator mentioned a further issue, that *T. terrestris* has three toxic principles (harmala alkaloids, steroidal saponins and nitrate), and should the other mechanisms of possible toxicity be examined. A member noted that lot of plants contained saponins and he is not sure these ones are any different, except perhaps in

very large amounts. Sheep are ingesting an enormous amount of fresh plant material.

The CMEC Secretary said that the content of saponins could be an issue in relation to making information available to people in what they are taking, especially for those who are going to take it outside traditional uses and who are going to have access to it outside registered products. Often side effects are irrelevant to such people, who take anabolic substances in the hope of short-term gain and hope they will not be detected. Because the steroidal saponins are 'natural', people are increasingly using them and may consider them to be safe. The community should be informed that such preparations may have long-term effects.

Another member said it is not known how much *T. terrestris* bodybuilders are taking for performance enhancement and there is evidence to suggest that some people taking these substances are not concerned about critical long-term health issues. They are taking the preparations for their saponin content, and perhaps the possibility of hepatotoxicity should be assessed. The TGA evaluator said there is a lot of work on the hepatotoxicity of these saponins in sheep, but most of it points to a co-factor being involved. However, there is some South African work in which the pure saponins were demonstrated to produce hepatotoxicity. She said that, with the Committee's approval, she would like to explore this angle.

The Chairman commented that the descheduling of these products from Poisons Schedule 9 is still highly appropriate. The concern now is not related to hallucinogenic properties, but something completely different.

Recommendation 1

CMEC recommends that CMS submit the scientific report on the relevance of Dr Bourke's research to human health to NDPSC and advise NDPSC that Dr Bourke's papers are not relevant to the proposed descheduling of herbs or therapeutic goods containing 0.1% or less, or 2 mg or less per recommended daily dose, of harmala alkaloids.

Reasons for recommendation:

- Sheep develop neurological signs only after 4 months of grazing almost pure stands of *Tribulus terrestris*. The intake of the herb in humans taking complementary medicines would be much lower, it cannot be assumed that harmala alkaloids would accumulate in the brain. It is expected that metabolism and excretion of the alkaloids would prevent them from approaching the CNS levels attained in sheep even after years of consumption.
- It appears that harman and norharman are more likely to be metabolised in the human brain to dimethylated derivatives, which have been implicated by some scientists in the pathogenesis of Parkinson's disease.

Recommendation 2

CMEC recommends that TGA Laboratories Branch analyse herbal products in the ARTG containing *Tribulus terrestris* and other herbs suspected of containing harmala alkaloids for the presence and levels of harman and norharman, at least, as a matter of priority.

Reasons for recommendation:

- The harmala alkaloid content of these herbs is relevant to the issue of scheduling.
- The alkaloid contents of these herbs are unknown and it is possible that they may cause neurological toxicity when consumed on a long-term basis.
- Appropriate regulatory action cannot be taken until more is known about the levels of alkaloids that these herbs contain, and their potential risk.

Recommendation 3

CMEC recommends that TGA contract a consultant neurotoxicologist to review further the possible role of β-carboline derivatives in the pathogenesis of Parkinson's disease, and to examine the safety implications for people taking herbal medicines containing these alkaloids.

Reasons for recommendation:

- It is increasingly believed that an environmental toxin or toxins may play a significant role in the pathogenesis of Parkinson's disease.
- β-carboline derivatives have been implicated by a number of researchers.
- This is a highly specialised area and beyond the scope of Complementary Medicines Section to take further.

Recommendation 4

CMEC recommends that CMS conduct a fuller review of the safety of *Tribulus terrestris*, including its potential to increase testosterone concentrations in the body and to have toxic levels of nitrates, when time permits.

Reasons for recommendation:

- The increased, and possibly long-term, use of this herb warrants a closer examination of its potential toxicity.
- The Chairman of the Working Party on Priorities for the Review of Herbs, recommended that such a review be placed low on the current list of priorities.

Item 3.1.3 Draft Submission to NDPSC on Selenium

Members noted that the report had been amended as recommended at CMEC8 and NDPSC would consider it in a few weeks.

Item 3.2 CMEC6 Meeting

Item 3.2.1 Shark Cartilage

CMEC has considered issues relating to shark cartilage at a number of meetings. Issues discussed include the wording of a proposed section 7 declaration, the content of a draft monograph, and the suitability of shark cartilage for use in listable therapeutic goods.

Shark cartilage was discussed most recently at CMEC7, where the text of a draft letter to industry and to previous respondents from the first round of public comment was considered. Discussion focussed on the question of whether or not to include shark cartilage powder within a revised declaration. Members had noted that if shark cartilage powder was not included in the proposed section 7 declaration, then products containing powder could be either foods or therapeutic goods. Their classification could be decided through the foods/drugs interface on a case-by-case basis. It was agreed to seek comment on the inclusion of powdered shark cartilage and that if considerable criticism was received from either the Chinese community or from exporters, then the declaration could be amended to delete powder.

Following CMEC7, the letter was sent to all previous correspondents, seeking comment on the wording of the revised section 7 declaration, the wording of a warning statement and the content of a draft monograph. More than sixty letters were distributed and only five responses were received. Comment was invited on the following proposed section 7 declaration of goods to be therapeutic goods:

- Shark cartilage in forms such as powders, capsules, tablets and pills.

No objections were received to the proposed declaration. The TGA evaluator had visited a large Asian grocery store in Canberra and did not see any powdered shark cartilage, or indeed any shark cartilage products, available for sale as foods.

Comment was sought on the following warning statement:

> ‘Children, pregnant or breastfeeding women, and those who have recently had a heart attack, surgery or a major accident should not consume this product without medical advice.’ (in 1.5 mm type with consideration of larger type for larger containers) *or words to that effect.*

There was support for the wording of the warning statement.

The draft monograph for shark cartilage was proposed to clearly define the substance and to set limits on its heavy metal content. The limited data on metal contamination of shark cartilage suggested that there might be instances of high metal levels. The draft monograph proposed the existing limits for metal contamination in food products, stipulated in the Food Standards Code. Comment was invited on a draft monograph.

Members noted that there was some use of shark cartilage powder as a food in wholesale use. It is used as a thickener in soups and in fish balls and cakes. Members noted that amending the wording of the declaration to read 'shark cartilage in forms such as powders, other than where labelled as being for food use, tablets, capsules or pills' would clearly indicate that possible food uses of shark cartilage powder (eg as a thickener) are not captured by the declaration. If manufacturers were found to be abusing the intent of the declaration, it could be amended at a later date. Surveillance staff of TGA could monitor the situation and report to CMS.

Labelling products 'for food use' may not be satisfactory, as products could be so labelled, but still be promoted inappropriately for therapeutic purposes, as has occurred to date. Another option could be to include provision that all products labelled without a dosage and frequency are therapeutic goods.

Another member commented that if powder were excluded shark cartilage powder would be sold as a food, without labelling with dosage and frequency. Information on therapeutic use would then be available on the Internet. A solution could be that all shark cartilage be labelled either for food or therapeutic use. Appropriate labelling and compliance may be difficult to enforce. The alternative was to declare all shark cartilage preparations to be therapeutic goods.

Recommendation 5

CMEC recommends that the following declaration be made under section 7 of the Therapeutic Goods Act, of goods to be therapeutic goods:

- **Shark cartilage in forms such as powders, capsules, tablets and pills.**

Reasons for recommendation:

- Wide public comment has been sought and only one objection has been received to this declaration.
- Inclusion of powdered shark cartilage would provide greater clarity for regulators and sponsors.

It was agreed that the option to progress the draft monograph for shark cartilage be deferred

until more information is available on the metal content of shark cartilage from TGA Laboratories.

The option to endorse TGA's approach of establishing specific conditions of listing, where necessary for safety reasons, may be reconsidered by CMEC at a later date if necessary.

Item 3.2.2 Probiotic Organisms

At CMEC6, members considered whether or not probiotic organisms were likely to be suitable for use in listed therapeutic goods. Although there is a considerable number of therapeutic goods containing probiotics in the ARTG, they are all grandfathered and registered. CMEC recommended that strains now in these grandfathered products, of the following three bacterial species, be permitted in listable therapeutic goods: *Lactobacillus acidophilus, L. casei* and *Bifidobacterium bifidum*. CMEC requested that CMS obtain information on current strains from the sponsors of products in the ARTG that contain probiotic organisms. CMEC agreed that strain specification was necessary, as different strains within a species may have different efficacy and safety profiles.

At CMEC7, members noted that TGA had a poor response to its request for information on strain identity, with only two strain names being supplied for the above bacteria. CMS advised that another search of the ARTG showed that *L. acidophilus* and *B. bifidum* are the most used species, *L. delbrueckii* subspecies *bulgaricus* is the next most used strain, and *L. casei* is present in far fewer products. The CMEC recommendation was therefore extended to include an identified strain of *L. delbrueckii* subspecies *bulgaricus*.

Members also agreed at CMEC7 that further specialised microbiological input was required on:

- the need to specify strains;
- whether there had been any safety concerns with the strains mentioned; and
- whether these probiotics are usually sold by strain.

Subsequently, CSIRO's Food Science Australia provided specialist advice on the issues identified at CMEC7. The CSIRO report notes that species within the genera *Lactobacillus* and *Bifidobacterium* (other than *B. dentium*, which is potentially pathogenic) are regarded as safe. On that basis, CMEC was invited to reconsider its recommendation and permit all *Lactobacillus* and *Bifidobacterium* that are currently used in Australia to be permitted to be used in listable products.

Members noted that the US probiotic supplier Natren, in correspondence to TGA, suggested that *Bacillus coagulans* (also called *Lactobacillus sporogenes*), *Bacillus laterosporus*, *Enterococcus faecium* and *Enterococcus faecalis* should not be permitted in therapeutic goods on safety grounds. Natren claims that *E. faecium* is able to acquire antibiotic resistance and is a common opportunistic pathogen in US hospitals. *E. faecalis* is present in four products in the ARTG.

The TGA evaluator mentioned that the safety of probiotics has not been established in immunocompromised and seriously ill patients. There has been a number of studies where probiotics have been administered to neonates to treat gastroenteritis, under medical supervision. She asked if members considered that there was a need for therapeutic goods containing probiotics to carry some form of label warning. A member suggested that a warning statement might actually prevent people taking the preparation who would benefit from it.

Members agreed that a warning statement was not necessary.

Members discussed the ability of manufacturers to identify species and strains of probiotics. The CSIRO report considered this matter. The evaluator said that the identification of genus was not difficult, according to the CSIRO report.

Members considered it was not necessary to be prescriptive. The evaluator commented there were reports of *Enterococcus faecium* and *Enterococcus faecalis* being common pathogens in US hospitals, and *Enterococcus faecalis* was in grandfathered products in the ARTG. If all species and strains were included, there was a possibility that pathogens could be included.

If strains were accepted, then documentation could be required from sponsors to show they had already been used in Australia. If a list could be prepared by TGA of strains/species which had been supplied over the past 5 years in Australia could be more generally known. New manufacturers would not be disadvantaged as they could then produce new products using these strains. The following wording in the amendment to the regulations was suggested: 'Including those strains/species on a list maintained by TGA, but not necessarily excluding other strains/species subsequently shown to be in use in Australia.' Members noted that new strains would be evaluated on a case-by-case basis.

Recommendation 6

CMEC recommends that all species and strains of probiotic bacteria currently in use in products included in the ARTG as at 31 July 1998 be permitted in listable therapeutic goods, other than *Bifidobacterium dentium*, *Bacillus coagulans* (also called *Lactobacillus sporogenes*), *Bacillus laterosporus, Enterococcus faecium* and *Enterococcus faecalis,* for which significant safety concerns exist.

Reasons for recommendation:

- Major taxonomic changes are occurring within the genera *Lactobacillus* and *Bifidobacterium,* making it difficult to specify species within Regulations. A strain that has a safe history of use, but which has been reclassified within a different species, may no longer be able to be used, if only specific species and strains are identified.
- Owing to the poor response to TGA's request for information on the identity of strains in current use, there are likely to be strains used that have not been specifically identified. Wording the regulations so that only specific strains are permitted could therefore disadvantage some manufacturers.

- Sponsors would be required to provide evidence to demonstrate that the strain they wish to use has been supplied previously in therapeutic goods in Australia.
- Owing to safety concerns with *Bifidobacterium dentium, Bacillus coagulans* (also called *Lactobacillus sporogenes*), *Bacillus laterosporus, Enterococcus faecium* and *Enterococcus faecalis*, these species are excluded from the general permission.
- This recommendation would provide the greatest flexibility to industry.
- This arrangement could be monitored closely and reviewed after 2 years of operation, or earlier if a need to do so was identified.

Members agreed that the grandfathered products containing the strain of *Enterococcus faecalis*, which were excluded in the above recommendation, be reviewed as a matter of priority. In addition, a TGA staff member commented that the general question of antibiotic resistance was still to be addressed, although it was not necessarily a high priority. It was also agreed that the US supplier, Natren, be asked to provide supporting evidence to its statement that *Bacillus coagulans* (also called *Lactobacillus sporogenes*), *Bacillus laterosporus, Enterococcus faecium* and *Enterococcus faecalis* should not be allowed in therapeutic goods because of safety concerns.

Members noted that ANZFA is developing a standard for novel foods, which is to be completed in about 3 months. Some probiotics are included in the definition of novel foods. As part of the development of the standard, a safety assessment framework will be considered. This work could be useful in developing a draft standard for the production of therapeutic goods containing probiotic bacteria. It was agreed that the option to develop a draft standard for the production of therapeutic goods containing probiotic bacteria, which will be adopted as a condition of listing once finalised, be deferred until ANZFA completes its work on novel foods.

Item 4 Evaluation of New Substances

Item 4.1 Glucosamine

CMEC is requested to evaluate the safety and efficacy of glucosamine, glucosamine sulfate and glucosamine hydrochloride and to advise TGA on their suitability for use in products.

The TGA received an application in July 1998 for a scientific evaluation of glucosamine and its sulfate and hydrochloride salts, to have them approved for use in listable products. Another application was received in June 1998 for an evaluation of glucosamine sulfate to have it approved for use in a registrable product. This application was subsequently amended to have glucosamine sulfate evaluated for use in listable products. Glucosamine is proposed for use as a treatment for the relief of pain associated with osteoarthritis.

Glucosamine hydrochloride is currently an active ingredient in three products in the ARTG. One of these is a grandfathered registered product that was included in the ARTG in 1991, while the other two are export-only listed products. Neither glucosamine nor its hydrochloride or sulfate salts have been evaluated for safety by TGA.

The first sponsor indicated that the glucosamine and its sulfate and hydrochloride salts that it wishes to include in therapeutic goods are prepared synthetically. The glucosamine that the second sponsor wishes to supply is isolated from the chitin in crab or shrimp shells. There may be a risk of allergic reactions in consumers who suffer from seafood allergies in the second sponsor's product. At CMEC7, the possibility of seafood allergies was addressed in relation to chitosan, also obtained from seafood. In approving chitosan for use in listable products, CMEC members advised that a statement advising of the seafood origin be included.

Product specifications appear to be satisfactory, and at this stage there does not appear to be a need for TGA to establish an additional monograph.

The intended therapeutic claims to be made by the sponsors are not acceptable according to the TGA Advertising Code, and should be modified along the following lines:

'Glucosamine may reduce pain associated with osteoarthritis'
'Temporary relief of symptoms of osteoarthritis'
'Temporary relief of joint pain associated with osteoarthritis'
'May improve range of motion of osteoarthritic joints'

Members were advised that no serious adverse effects of glucosamine are known. There are no drug interactions, specific contraindications or precautions recommended in the literature. Long-term feeding trials show that rats and dogs can consume >2000 mg/kg glucosamine sulfate without suffering immediate or overt adverse effects. These levels are much greater than human recommended doses of around 20 mg/kg.

A TGA officer advised members that although methods of manufacture were not given, it was considered that the substance specifications established adequate quality of glucosamine from both synthetic and shellfish sources in regard to impurities and contaminants.

Glucosamine was ineffective in inhibiting the inflammatory response to known endogenous mediators histamine, bradykinin and serotonin, and was ineffective in inhibiting proteolytic enzymes associated with inflammation. However, it slightly reduced inflammation to certain foreign agents (e.g. *Mycobacterium butyricum* adjuvant, kaolin, carrageenin, croton oil, formalin and dextran). This was called 'cyclo-oxygenase-independent, membrane-stabilising anti-reactive activity'. Glucosamine rated poorly when compared with ibuprofen in reducing symptoms of arthritis in clinical trials, and was not analgesic when tested against writhings in mice provoked by IP phenylquinone.

Glucosamine is quickly and almost completely absorbed from the gastrointestinal tract following an oral dose. However, it is unclear whether the molecule is absorbed intact. After absorption, most is removed by the liver in the first pass, resulting in a low bioavailability. It is not known how much, if any, glucosamine gets to articular cartilages and whether it is utilised there.

Members were advised that, while it is claimed that glucosamine taken orally is utilised in the body to stabilise membranes and improve the structural integrity of joints, there is no scientific evidence to support this at present. Although evidence exists from European trials that glucosamine sulfate may modify symptoms (mainly pain) in some patients, no double blind, placebo-controlled trial of adequate length has been conducted to establish claims of structural improvement of articular cartilages. If glucosamine does afford relief from pain, the mechanism is not understood.

Animal toxicity studies with glucosamine are scarce, and although the toxicity of the substance would appear to be low, based on summarised results of 6- and 12-month studies in rats and dogs respectively, this cannot be assumed for long-term dosing without further supporting studies. The repeat-dose toxicity studies were not available for evaluation. The results were simply referred to in another paper. The main adverse effects in clinical trials were mild gastrointestinal disturbances, but no trial lasted longer than 2 months. It has been postulated that glucosamine ingestion may interfere with carbohydrate metabolism, but there is no evidence that this has happened. Glucosamine from shellfish may lead to allergy in some people, and shellfish-derived products may require a warning statement.

A member noted that the products may be taken for long periods of time, but safety data for humans was based on 4 weeks' use. Members noted in the scientific review, the details of the repeat-dose animal toxicity studies and clinical trials with doses similar to those proposed in the application. The Chairman noted that none of the clinical trials showed any adverse reactions of concern. She suggested that the information provided was sufficient for members to conclude that the substance was suitable as an ingredient in listed products.

There was discussion as to whether or not glucosamine is an endogenous substance. In the pharmacokinetic studies it is understood that dosed glucosamine was being measured (this was radiolabelled glucosamine in most of the studies). Glucosamine-6-phosphate is formed from a reaction of fructose-6-phosphate and glutamine in cartilage, and probably glucosamine does not exist as a free substance in plasma.

A member discussed the clinical trial that compared glucosamine sulfate with ibuprofen (referred to in the evaluation report). He noted that the trial was carried out over a relatively short period, but said that this is not unusual for trials of anti-inflammatory drugs. The way that ibuprofen is expected to work in arthritis is that of an analgesic/anti-inflammatory agent. Most people would derive benefit within a fortnight. So extending a trial up to 6 weeks is giving any agent used as a positive control some significant period of time for comparison. While ibuprofen seemed to perform better and act much faster than glucosamine, there was no significant difference between the two substances in terms of the clinical symptoms. The dose of glucosamine was 500 mg tid (1500 mg/day). The use of a preparation (shark cartilage) that contains chondroitin sulfate, which is the end product of glucosamine, had already been approved. It would be interesting to know the glucosamine content of shark cartilage, because if someone is taking 10 g of shark cartilage/day they may actually be getting a full supplement of glucosamine.

There was discussion about the apparent uniformly positive results of glucosamine in clinical trials in regard to relief of pain. The Chairman questioned whether or not the confidence limits were narrow enough to avoid Type 2 errors, saying that it is difficult to show a difference between two things if there is a lot of variability. Another member said that osteoarthritis research is fraught with difficulties of obtaining objective markers over short-term studies. One is obliged to deal with subjective measures, but there are now some exceedingly well-developed scales used in this sort of research. He has discussed glucosamine with a colleague in the osteoarthritis research group at the University of Queensland, who believes that there is evidence that glucosamine has some activity when compared with positive controls, as opposed to placebo controls. This activity remains ill defined. It is not via cyclo-oxygenase, which is a potentially significant benefit, because gastrointestinal haemorrhage associated with NSAIDs is avoided. Members agreed that the clinical trial results for glucosamine appeared to be favourable.

A member expressed concern about seafood being present in the substance after it is processed. What level of purity is obtained in the manufacturing process? If a person is allergic to seafood, only a few molecules are needed to produce a reaction, and reactions are potentially fatal. A member said if the sea product is broken down enzymatically, there might still be an allergy problem, but it may be broken down chemically. It was agreed that CMS would request the applicants to provide details of the manufacturing process. Members agreed to a warning unless CMS obtained information from the sponsor that indicated it was not necessary. If there is any possibility that protein remains in the product, it is essential that it has a warning.

Concern was also expressed about the amount of potassium in the glucosamine tablets and its possible effect on the potassium levels of people taking potassium-sparing diuretics or angiotensin-converting enzyme inhibitors. It was noted that the average daily intake of potassium for adults was around 60 mM. Fruits contain around 2.5–10 mmol (100–400 mg) potassium/serve and Slow K tablets contain 300 mg (8 mmol) of potassium. The amount of potassium in the recommended daily dose of glucosamine sulfate (1.5 g) is about 190 mg or 5 mmol. Considering these figures, members agreed that it is not necessary to have a warning for people taking drugs that tend to retain potassium.

Members also decided that there was no need for a warning for diabetic people. The risk of glucosamine causing an upset in carbohydrate metabolism is theoretical and predicted to be low.

Recommendation 7

CMEC recommends that glucosamine, and its hydrochloride and sulfate salts, are suitable for use in listable therapeutic goods, provided the appropriate warning statements are included.

Warning statements may include:

- Seafood origin of glucosamine sulfate (in cases where it has been extracted, not synthesised).

This warning statement is to be included if it is considered necessary by CMS after information is provided by the sponsor on the method of manufacture.

Members noted that the sponsors would need to label the products containing glucosamine and its hydrochloride and sulfate salts in accordance with the Australian Approved Names (AAN) requirements. If the salts contain potassium this may have to be included in the AAN.

Item 5 New Product Registration Evaluation

Item 5.1 *Kunzea ambigua* **Essential Oil**

In the absence of the TGA evaluator, the A/Head, CMS, introduced the application. She advised that the application is to allow inclusion of the product in the ARTG. Although the sponsor would prefer to list the product, it is a new herbal ingredient and the current situation is that it would have to be registered first.

TGA requested advice from CMEC on whether there is sufficient data to decide that the product is of suitably low risk to be a listed ingredient; and even if it is of sufficiently low risk, is there enough information to register the product and look into moving it to a listed status later? Alternatively, if CMEC does not consider the product is low risk, or if there is not enough data to decide this, and the product may end up being scheduled, could CMEC decide to register the product? This involves looking at quality, safety and efficacy.

There are recognised deficiencies in the application, owing to the small size of the company and the limited use and novelty of the product. However, it has the advantage of having had limited human use, having been used under the State limitations system in Tasmania. It has also had the benefit of some chemical analysis. However, there is a lack of data on stability and toxicity. CMS has looked at the individual components and what can be said about them (e.g α-pinene).

TGA received an application in July 1998 for registration of *Kunzea ambigua* essential oil. The use of the oil has been designated for 'aromatherapy only'. The oil would carry the following claims:

- temporary relief of the pain of arthritis
- relief of muscular aches and pains
- relief of the symptoms of colds.

The essential oil is obtained from the leaves, small stems and seed bolls of *K. ambigua* by steam distillation. The product is manufactured, and has been available, in Tasmania for use

by practitioners for almost 2 years.

K. ambigua had two recorded uses by Australian Aborigines:

- moist leaves were placed onto hot coals and the vapour inhaled; and
- the pulped leaves were used to relieve toothache.

A chemical analysis of *K. ambigua* oil was supplied. It consists mainly of α-pinene and 1,8-cineole at about 50% and 14%, respectively. Other components between 9% and 12% concentration include globulol, viridiferol, and unidentified sesquiterpene alcohols.

The product is similar to other aromatherapy oils in regard to constituents, but the proportions are different. None of the levels of the constituents makes it immediately eligible for scheduling in the *SUSDP*, and it is not on the list for examination by the Essential Oils Working Party of NDPSC. NDPSC has never looked at *K. ambigua* oil.

The CMEC Secretary said that main danger with essential oils is their inappropriate use. The risk of ingestion was the main concern, but this could be addressed by the type of container used and the requirements for warnings on the label.

There were statements from practitioners who had used the oil. Although they did not report irritation to skin, a warning about possible skin irritation may still be advisable. First aid instructions would be necessary on the label, in line with requirements for scheduled essential oils.

A member commented that the testimonials were from practitioners who had mostly used it for massage and their patients had not inhaled the product. Another member suggested that inhalation would occur during massage and that the oil would be absorbed through massage and any irritation to the skin would have been known in the period of use. Another member expressed difficulty with the testimonials because of their uncertain quality. The use of testimonials does not fulfil requirements for efficacy in products being assessed for registration. It was noted that although the herb has been used traditionally, it has not been used in the way the sponsor was now proposing.

The Chairman said that if CMEC is looking at the product for registration, the Committee must examine efficacy. There would be a credibility issue if testimonial data is accepted. It would be better to decide if the product is of sufficiently low risk to be listed, and then wait until the legislation changes, and not have to go through the registration process. In response to a query as to how long this might take, the CMEC Secretary, said that the legislative basis for the requirement to register the first product, even though the recommendation from CMEC was that they could be Listable, was being reviewed.

[Secretarial Note: Subsequent legal advice is that a specific category for substances of herbal origin in Part 5, Schedule 4 of the Regulations, would obviate the need for Registration of the first product.]

A member suggested that a method or framework needs to be developed for sponsors to use when submitting observational data (which is what testimonials are) in support of applications. It is the sponsors' responsibility to prepare the data. Members noted that, in some situations, CMEC might have to rely on anecdotal or observational data, but that such data is lowest in the hierarchy of evidence. Another member suggested that CMEC might obtain more information by considering safety barriers in traditional use of complementary medicines. An example may be the use of pulp leaves for toothache — did users realise they need to rinse their mouth five times after use? The examination of such practices could be useful.

The Chairman suggested that the NDPSC Working Party on Essential Oils could be requested to provide advice on *Kunzea ambigua* oil in terms of the need to schedule it in the Poisons Schedule because of its constituents.

The Chairman summarised CMEC considerations of the product as follows:

- CMEC could not accept that the oil be registered;
- Rejection of the application is an option; and
- Other similar oils are scheduled and they could continue to be scheduled as a result of the deliberations of the NDPSC Working Party on Essential Oils. This particular oil might be scheduled if the Working Party examined it.

A member suggested that the sponsor could be asked to provide more information. Alternatively the decision could be deferred until the NDPSC Working Party on Essential Oils has reported on other oils. The Chairman suggested CMS write to the sponsor explaining the situation and saying that the company should supply the safety data required to evaluate the substance and efficacy data for the registration of the product.

A member suggested that CMS prepare draft guidelines to assist sponsors in providing satisfactory anecdotal or testimonial data to support their applications. CMEC would consider the guidelines at a future meeting.

Recommendation 8

CMEC recommends that CMS write to the sponsor, requesting efficacy and safety data to allow the evaluation of *Kunzea ambigua* essential oil for registration.

Item 5.2 Melaleuca Oil

A sponsor applied in June 1998 for registration of a melaleuca oil drug product for the proposed indications of minor cuts, minor burns, abrasions, pimples, athlete's foot, insect bites, stings and nasal and chest congestion (temporary relief).

The product comprises 100% melaleuca oil obtained from the leaves and twigs of *Melaleuca*

alternifolia (maiden et Betche) Cheel. The product is to be packed in glass bottles, each of 15 or 25 mL capacity.

This product must be labelled as a Schedule 6 product, and packed in a child-resistant closure. It should carry the following first aid instructions on the label: *If poisoning occurs get to a doctor or hospital quickly. If swallowed, do NOT induce vomiting. Give a glass of water.*

The product's proposed label and outer carton meet the labelling requirements of the *SUSDP*.

The major constituents of melaleuca oil are terpenoid compounds. The chief constituent of melaleuca oil is 30+% terpinen-4-ol. The oil also contains 15–41% terpinenes and a variety of other compounds including p-cymene, α-pinene and α-terpineol.

Various brands of 100% melaleuca oil, registered in the ARTG and quoting similar indications, are freely and legally available in pharmacies and supermarkets in bottles ranging in volume from 10 to 25 mL; they are equipped with child-resistant closures, and labelled in accordance with the requirements of the *SUSDP*.

The product must be classified under Schedule 6 of the *SUSDP*, since it is stated to contain in excess of 25% melaleuca oil. Therefore the product must be evaluated for registration (quality, safety and efficacy).

A TGA officer explained that there are some limitations to the stability data provided by the sponsor, which in fact applied to another (similar) product and supported a shelf life of 5 years. However, the sponsor provided a chemical analysis of the product for registration, which showed that there would be little difference between it and the one tested for stability.

The TGA officer said the application was not supported by clinical trials. The indications are similar to those for other similar products on the market. In view of the small volume of product (15–25 mL), the child-resistant closure and the proposed method of use, there may not be a major risk of ingestion.

A member considered that the sponsor had compared the product to the standard for melaleuca oil, which was a quality standard, but not to other products on the market. He suggested that he takes the chemical analysis of the product to the Australian Tea Tree Oil Research Institute on the campus of his university and asks them if it was equivalent to other products on the market. It was agreed that the member could take this action.

Recommendation 9

CMEC recommends that the product be approved for registration, providing that:

1. It is labelled in accordance with the requirements of the *SUSDP* and *Therapeutic Goods Order No. 48*.

2. The indications and directions proposed for use on the label and product carton not be amended or extended without prior approval.

3. The sponsor provides further information on stability test data as outlined in the product evaluation, in order to confirm the tentative shelf life of 5 years.

4. The sponsor to provide analytical data on the first batch to show that that the composition is within the Australian standard.

Item 6 Safety review

No items

Item 7

Withdrawn

Item 8 Matters Referred from Within TGA

Item 8.1 Advice on Proposed Amendments to the Therapeutic Goods Advertising Code Council Relating to the Cholesterol-Lowering Effects of Psyllium Fibre

In September 1998, CMS received a request from the Therapeutic Goods Advertising Code Council (TGACC) to evaluate a proposed amendment to the Therapeutic Goods Advertising Code (TGAC). The amendment would be in respect of the prohibition relating to 'cardiovascular system diseases, ailments or defects', to facilitate consumer advertising of the cholesterol-lowering qualities attributed to psyllium.

The TGAC is designed to ensure responsible advertising in promoting the sale of non-prescription therapeutic goods, including listed medicines. The Code notes that advertisements to the general public relating to goods for therapeutic use should:

a) Help people make rational decisions on the use of medicines legally available without prescription.
b) Take into account people's legitimate desire for information concerning their health.
c) Not take undue advantage of people's concern for their health nor misrepresent or mislead the consumer into unwisely relying on medicines to solve physical, emotional or mood problems.

A TGA representative informed members that, in the United States, the Food and Drug Administration (FDA) had accepted that there was considerable evidence to show that psyllium fibre had a mild cholesterol-lowering effect. The FDA permits certain health claims on foods and dietary supplements. Foods containing psyllium and oat fibre are able to carry the claim that consumption may lower the risk of coronary heart disease (CHD), provided

certain criteria are met. These criteria include a minimum soluble fibre content per dose or serve of 1.7 g of soluble fibre derived from psyllium, together with a requirement that foods containing psyllium must also comply with the requirements for a low fat, low saturated fat and low cholesterol food. The FDA recognises that a minimum psyllium-derived soluble fibre intake of 7 g per day is required to have an effect on the CHD risk. Dietary supplements containing psyllium fibre are also able to claim ability to lower CHD risk.

The TGA conducted a preliminary analysis of relevant research, but it was not comprehensive, because of the urgency with which the TGACC expected an answer. This analysis was supportive of the FDA conclusion.

A member commented that one-third of people having heart attacks do not have high cholesterol.

The TGA officer advised that TGAC prohibits any reference in advertisements or labels to cardiovascular disease. An advertisement or label claim that a psyllium-containing therapeutic good can lower cholesterol would be prohibited under the TGAC at present, because of the implied association with cardiovascular disease. Sponsors can apply for an exemption to the requirements of the Code under the *Therapeutic Goods Act 1989*. However the change being considered by CMEC would amend the Code and would apply to registered and listed products.

CMS is aware that a sponsor had recently applied for an exemption for a registered non-prescription product containing a fibre similar to psyllium fibre. The Medicines Evaluation Committee (MEC) evaluated the sponsor's proposed claims for the product and agreed to allow the following indication for this product only, 'a natural product that has a mild cholesterol-lowering effect in persons with mild to moderately raised cholesterol'. The TGA officer provided further details of MEC's deliberations. For example, MEC was concerned about the effects of drug binding, in particular to warfarin, and required a warning on the product. The product has not yet been included in the ARTG.

The TGA officer explained that the consequences of the amendment to the Code are far reaching. A range of food-derived substances other than psyllium also have cholesterol-lowering effects, and permission for psyllium products to claim cholesterol-lowering ability is likely to lead to a spate of requests for other products to be so labelled. In terms of therapeutic goods, similar requests may arise for products containing guar gum and oat fibre, and for soy extracts and garlic products. If claims about cholesterol lowering are allowed, requests may follow to permit claims about other risk factors of serious disease. For example, sponsors of bulk-producing fibre supplements may wish to claim that their products reduce the exposure of the bowel wall to carcinogens by decreasing stool transit time.

The TGA officer suggested that, as psyllium fibre and other non-synthetic cholesterol-lowering substances are derived from foods, any advertising changes adopted by TGA are likely to have a major impact on food advertising and labelling.

A member advised that ANZFA has been reviewing the prohibition of health claims on foods labels since late 1997, and the review is likely to be completed by the end of 1999. A pilot program is being conducted on one health claim being used on certain foods. The program will consider public health outcomes and regulatory efficacy to see if an overall program for claims could be managed in a reasonable manner. Her concern was that, if CMEC agreed to the proposed claims for therapeutic goods, it would be without a framework for substantiation. By contrast, sponsors wanting to make such claims in relation to foods will need to provide substantiation to a defined level of evidence, select suitable foods to carry the claims, demonstrate that education will be provided, and that they will contribute to the monitoring of the claims. From a regulatory point of view, it would be preferable for TGA to act in concert with ANZFA.

A member expressed concern about delays based on this need to act in concert with ANZFA in the approval of new claims with substantiation for therapeutic goods. It was then noted that ANZFA may have substantiation criteria available within 6 months. There was some discussion on the enforcement of the advertising and labelling requirements for therapeutic goods and the illegal claims being made on food products due to lack of enforcement.

A member was surprised that there was no industry submission accompanying the Advertising Council request. Perhaps more information on the intended products and doses for which products are to be promoted would be useful. Any information or promotional material likely to accompany the products would also contribute to understanding of the form the claims would take. Sponsors of Registered products could apply for an exemption to the requirements of the TGAC under the *Therapeutic Goods Act 1989*. It was agreed that industry could be requested to provide more information through TGACC. Such data could also be used by ANZFA in developing the guidelines.

Recommendation 10

CMEC recommends that any amendments in regard to health claims for food-derived substances should be taken in conjunction with action by ANZFA. CMEC requests that industry be asked to provide information that could be used for substantiation of this amendment through TGACC.

Reasons for recommendation:

- Coordinated activity by ANZFA and TGA will provide consistent advice to industry.
- Coordinated activity will reduce the resource cost of progressing health claims.

Item 9 Decision Record

Item 3.1.1 Working Party on Priorities for the Review of Herbs
Item 3.1.2 Harmala Alkaloids – Request by NDPSC refers
Item 3.1.3 Draft Submission to NDPSC on Selenium
Item 3.2.1 Shark Cartilage

Item 3.2.2 Probiotics Organisms
Item 4.1 Glucosamine
Item 5.1 *Kunzea ambigua*
Item 5.2 Melaleuca Oil
Item 8.1 Advice on Proposed Amendments to the Therapeutic Goods Advertising Code Council Relating to Cholesterol-Lowering Effects of Psyllium Fibre

Item 10 For Information

Item 10.1 Article from the *American Journal of Medicine*

Members noted an article by Edward Ernst in the *American Journal of Medicine*, February 1998, Vol. 104, entitled 'Harmless herbs? A review of recent literature'.

The Chairman commented that there could be products in Australia containing substances such as diazepam or NSAIDs. A TGA officer explained that the Surveillance Section of TGA did check such products. The committee discussed the regulation of raw herbs.

A TGA officer commented that powers relating to the dispensing of such preparations were in State and Territory law.

A member said he would obtain copies of the traditional Chinese medicine report prepared by Alan Bensoussan and Stephen Myers entitled 'Towards a safer choice' to give to members of CMEC. The report was commissioned by the Victorian Department of Human Services, NSW Department of Health and Queensland Department of Health.

Item 10.2 Extract from the Adverse Drug Reaction Advisory Committee Meeting of 25 September 1998

Members noted an extract from the Adverse Drug Reaction Advisory Committee (ADRAC) meeting of 25 September 1998.

Item 10.3 Review of CMEC

Mr Peachey informed members that TGA staff had recently met with Mr Grant Tambling, Parliamentary Secretary to Dr Michael Wooldridge, Minister for Health and Aged Care, about the review of CMEC. Mr Tambling will be sending letters to members of CMEC and other interested groups inviting comment on the operation of the committee. Terms of reference for the review will be included with the letters.

The terms of reference set out the areas for comment. These areas include the membership and the mix of the expertise of CMEC, the terms of reference of the committee itself, the timeliness of the decision-making process, and areas for improvement. There will be 1 month to comment. The comments will be examined by TGA in December and January. In the meantime, Mr Tambling will be extending the current membership of members to the end of January 1999.

Members noted that the information provided on the review. Members noted that they were free to make submissions and provide information on the review to other interested people.

Item 11 Other Business

Item 11.1 Meeting Dates for 1999

Members noted proposed meeting dates for 1999.

The meeting closed at 4.20pm.