# CMEC6

# Complementary Medicines Evaluation Committee

## Amended Extracted Ratified Minutes

## Sixth Meeting

## Wednesday, 10 June 1998

# Complementary Medicines Evaluation Committee

## Item 1 Procedural matters

### Item 1.1 Opening of Meeting

The sixth meeting of the Complementary Medicines Evaluation Committee was held at the Ansett Golden Wing Lounge, Sydney airport on Wednesday, 10 June 1998.
Members of the committee present were:

Professor David Roberts, Chairperson
Professor Jorma Ahokas
Dr Roberta Chow
Dr Colin Duke
Dr Joachim Fluhrer
Ms Val Johanson
Dr Stephen Myers
Mr Allan Ware

Also present from TGA were:

Ms Laurayne Bowler
Dr Helen Cameron
Dr Judy Cunningham
Dr Barry Fankhauser
Ms Pat Brown

### Item 1.2 Apologies

Apologies were received from Professor Chiang Lin and Dr Anne Tonkin. Professor Lin had a car accident on the way to the airport to attend the meeting.

### Item 1.3 Conflict of Interest

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

## Item 2 Confirmation of Minutes

### Item 2.1 Confirmation

The minutes were confirmed.

## Item 3 Action Arising from Previous Meetings

**Australian Approved Names for New Listable Substances**

The members noted the Australian Approved Names and a minute about the new active listable substances to be added to Schedule 4.

**Item 3.1 CMEC 5 Meeting**

**Item 3.1.1 Shark Cartilage - item 3.1.1.2 of CMEC5 referred**

At CMEC5, members had made three recommendations in relation to the proposal that shark cartilage be declared a therapeutic good. The second round of public comment was delayed until more information was obtained on the use of shark cartilage as a food.

Dr Cameron spoke to the item. She advised that shark cartilage in bulk form, was considered by the Australian Quarantine Inspection Service (AQIS) not to be a food and it is not considered under the Imported Food Inspection Program (IFIP). Raw materials are being imported as therapeutic goods.

Members noted that the safety and quality of shark cartilage were the main issues.

It was agreed that information on the use of shark cartilage powder as a food would be sought from those people who made submissions in response to the first request for comment as well as from an expert from the School of Medicine at Monash University.

This information would be considered by CMEC7 prior to the second round of public comment on the other shark cartilage issues, such as the draft monograph, being sought by TGA.

**Item 3.1.2 Working Party on Priorities for the Review of Herbs - item 3.1.3 of CMEC5 referred**

Dr Myers reported that the Working Party on Priorities for the Review of Herbs would immediately meet after CMEC6. Mr Bone and Mr Clavey would join part of the meeting by teleconference.

There was some discussion about the ways in which the Working Party could proceed with the review of herbs. Some points mentioned included:

- the use and availability of monographs;
- the need for a time line or action plan in reviewing the ten herbs already identified by the Working Party;
- the use of ADRAC reports;

- difficulties in obtaining details of herbal products on the ARTG because of the technical documentation;

- the difference between those products on the ARTG and the actual products (including volume) sold in Australia; and

- the possibility of obtaining details on the volume of products sold in Australia from suppliers - such information may be commercial- in-confidence.

It was agreed that the Working Party would proceed with assistance from the NFAA on the products available in Australia. TGA would provide whatever information was available from ARTG.

**Item 3.1.3 Proposed Schedule 14 - item 3.2.2 of CMEC5 referred**

Members noted the copy of the proposed Schedule 14 included in the agenda papers. They suggested that the definition for complementary medicines included in the Schedule, which stated that 'the schedule defines complementary medicines but does not convey approval for inclusion in any therapeutic good' be amended to state 'the schedule designates active ingredients in complementary medicines'.

**Item 3.1.4 Safety of Ginger - item 3.3.1 of CMEC5 referred**

At CMEC5 members had noted a response from the sponsor of a concentrated ginger product to the request by TGA for information about the methodology by which the company provides the information on the safety of the product in relation to anti coagulant therapy and gastric effects.

**Recommendation to TGA:**

**1 Further studies are required on the effect of concentrated ginger products on platelet action in humans;**

**2 Until such time that the studies are carried out, concentrated ginger products are to contain the following warning statements:**

**'Individuals taking anticoagulants should seek medical advice before taking this product'**

**'Individuals at risk of bleeding problems, should seek advice from their health practitioner prior to taking this product'**

3. **The company be advised that CMEC is considering the information contained in the Zinax insert with a view to requesting the company to**

**modify it in the light of recommendations 1 & 2 above especially in relation to the statement 'The patented extraction process also ensures that the mucous membranes in the stomach and colon are not irritated'.**

The reasons for the recommendation are as follows:

1. The research that has been conducted to date does not address the effect of products such as Zinax on the platelet cascade coagulation mechanism, nor does it address gastric problems associated with these products, in humans;

2. Zinax is much more concentrated than most other ginger products and is the only ginger product for which adverse reports have been noted;

3. Concentrated ginger products could have the potential to precipitate bleeding problems in at risk patients apart from those taking anticoagulants; and

4. CMEC considers that the statement in the Zinax product information sheet may mislead consumers.

**Item 3.1.5 Kombucha Tea - item 3.3.2 of CMEC5 refers**

At CMEC5 members requested that the safety concerns of kombucha tea be discussed at the next meeting of the foods /drugs interface meeting with a view to discussing the education of consumers to address the safety issues.

Dr Cameron advised that a meeting of the foods /drugs interface was arranged for Tuesday 16 June 1998.

A report will be made to a future CMEC meeting on the outcome of the foods/drugs interface meeting.

**Item 3.1.6 New Substances in Sports and Fitness Aids - item 4.2 of CMEC5 refers**

At CMEC5 it was agreed that CMS, in conjunction with NFAA, would prepare a list of substances that could be evaluated as a package as potential ingredients in sports and fitness aids that would be listable subject to review. CMS would subsequently undertake evaluations of those substances, individually and when used in combination. Examples of such substances are coenzyme Q10, amino acids and chromium picolinate and higher doses.

Dr Cameron advised that information had not yet been received from NFAA. She also advised that progress would be made on this matter and a report would be prepared for CMEC7.

Dr Cameron agreed that a list of herbs that are for use in therapeutic goods only, and which are not used for food, could be discussed at the Foods/Drugs Interface meeting.

A member requested that the TGA document "Guidelines for the expression of herbal

ingredients in ARTG applications and on labels" (dated 1992) be made available for CMEC members. Ms Bowler warned that this document was prepared before the present definition of food was put in the *Therapeutic Goods Act 1989.* It would be considered in the revision of all such guidelines.

Members noted this item.

**Item 3.2 CMEC 4 Meeting**

**Item 3.2.1 Application Form for New Complementary Medicines and Guidelines for Submitting Data - item 3.3.1 of CMEC4 refers**

Members considered a document titled, 'Application for an Evaluation of a New Complementary Medicine Substance'.

It was agreed that members would be provided with a copy of Schedule 10 and the justification guidelines that are used by applicants to NDPSC in assessing which, if any, poisons schedule a substance is likely to fall into.

CMEC agreed that the document titled, 'Application for an Evaluation of a New Complementary Medicine Substance' would now be circulated to stakeholders for comment.

**Item 4 Evaluation of new substances**

**Item 4.1.1 Conflict of Interest on Probiotic Organism**

A member declared a possible conflict of interest in relation to this item. The Chairperson ruled that the member's potential conflict of interest be noted, that he/she not be required to leave the room while the matter was discussed and he/she be allowed to take part in the discussion and vote on the matter.

Another member declared a possible conflict of interest in relation to this item. The Chairperson ruled that there was no conflict of interest for the member.

**Item 4.1.2 Probiotic Organism**

Members noted the following information contained in the agenda paper:

- TGA has been requested to consider permitting therapeutic goods containing probiotic organisms to be listed on the Australian Register of Therapeutic Goods (ARTG), via an amendment to Schedule 4 of the Regulations. There are currently a number of products containing probiotics on the ARTG; all are registered "grandfathered" products (AUSTR).
- In addition a company applied for an evaluation of the safety of *Bifidobacterium longum* BB536 with the aim of permitting its use in listable therapeutic goods.

- "Probiotic" is a term used to describe certain microorganisms that have beneficial effects when used in a therapeutic manner. The major group of microorganisms of interest is that commonly called the "lactic acid bacteria", which includes certain organisms of the genera *Lactobacillus*, *Enterococcus* and *Streptococcus*. *Bifidobacterium* are also included in the probiotic group, although not strictly considered to be lactic acid bacteria as some members of the genus do not ferment lactose. Probiotics are normal constituents of the human bowel microflora and are widely used in fermented milk products such as yoghurts.

- Probiotic organisms in current use generally have a long history of safe food use in fermented milk products. However, safe food use does not necessarily equate to safe therapeutic use, particularly as probiotics may be used therapeutically in patients who are already ill and potentially vulnerable to additional infection.

- The safety of probiotics may be dependent on the strain of a particular species used, as there appears to be considerable strain-to-strain variation in a number of properties including the ability to aggregate platelets (Donohue 1998).

- Certain probiotic organisms have been documented to be associated with severe infections such as endocarditis. Nevertheless these infections generally occur in patients already ill, or vulnerable as a result of recent surgery or accident. Further, there is no available evidence to indicate whether or not intentional ingestion of probiotics in foods or therapeutic goods is related to the onset of severe infection.

- There is some evidence that lactobacilli are associated with certain dental infections although it is not certain whether the association is causal (Bratthall 1998).

- Questions have arisen over the potential for probiotics to act as a vehicle for the transfer of antibiotic resistance. Many probiotics display resistance to a range of common antibiotics and are often taken in conjunction with antibiotics to counteract any adverse affects of the latter on bowel microflora. However, many or all of the strains likely to be used in probiotic therapeutic goods are already available without restriction in foods.

- The TGA is not aware of any safety-related issues that have arisen from the use of the probiotic products currently on the Australian market.

- In 1994 the TGA Laboratories conducted an assessment of fourteen therapeutic goods containing *Lactobacillus acidophilus*. The species of Lactobacilli present were confirmed and of the numbers of viable organisms enumerated. Three products were found to have counts far below the stated levels, particularly when packed in capsule form. One product contained *Lactobacillus gasseri* as a

contaminant. All products met TGAL guidelines for contamination by pathogens and yeasts and moulds.

- The TGA has also received a letter from the company, regarding the possible reclassification of probiotic products from registered to listed. The company expressed the belief that standards for the quality of probiotics must be developed, in order both to maintain safety and to prevent consumer deception. They note the use of strains of probiotics with resistance to antibiotics, such as vancomycin and streptomycin.

- Since the establishment of the current regulatory procedures in 1991, no new probiotic products have been approved. As probiotics are not permitted in listable goods, all new products have to undergo registration. All applications to the Medicines Evaluation Committee (MEC) have been rejected on the grounds of inability to demonstrate product efficacy. In its most recent evaluation of a probiotic product, MEC concluded that "it has reviewed many ... studies on the effect of various lactic acid bacteria products on gastrointestinal microflora and diarrhoea, but has so far failed to find satisfactory evidence that any combination of lactic acid bacteria is effective in preventing or treating diarrhoea from any cause."

- A brief literature search suggests that there is considerable *in vitro* evidence of the efficacy of probiotics in improving the gastrointestinal microflora, inhibiting pathogen growth and influencing immune function, but this has not necessarily translated into clear demonstration of *in vivo* human efficacy. Many of the human studies have focussed on probiotic administration in the form of fermented milk products, where the food may offer some protection for the microorganisms against digestive processes. As with safety, efficacy, as measured *in vitro*, of probiotics appears to be dependent not only on the species of bacteria, but on the strain (Crittenden et al 1998).

- Common, minor complaints for which probiotics may be indicated include gastrointestinal disturbance. Permissible claims under the Therapeutic Goods Advertising Code could include:

    - for the relief or treatment of digestive disorders
    - relief of gastrointestinal disturbance
    - aids or assists in digestion
    - helps maintain digestive function
    - aids or assists in the treatment of diarrhoea, provided that this statement is accompanied by a recommendation to seek medical advice if diarrhoea persists

- The application for evaluation of *B. longum* BB536 contains considerable evidence, predominantly from Japanese studies, to support the efficacy of

BB536, when administered in the form of fermented milks, to treat symptoms of gastrointestinal disturbance such as constipation. Evidence is also presented on the administration of a form of BB536 similar to that intended by the sponsor, ie removed from the food matrix and presented in the form of a therapeutic good. An assessment of acute and chronic toxicity of the strain is presented. The manufacturer has supplied information that claims there has been no transfer of antibiotic resistance despite the considerable use of *B. longum* BB536 in Japan for 20 years. This use includes its administration to hospital patients to prevent infection from methycillin resistant *Staphylococcus aureus*.

- Registrable, non-prescription therapeutic goods undergo a thorough evaluation of the safety, quality and efficacy of individual products in the form in which they are intended for sale. Efficacy may be assessed by clinical trial data and/or by literature research substantiating the efficacy of the active ingredients in the same or very similar presentations. Safety will be based on an assessment of the active and excipient ingredients, as well as any safety implications relating to the product presentation (eg dose size, labelling, manner of use). The validity of label claims is examined. Product stability is checked and an assessment made of the shelf life and required storage conditions, based on validated laboratory data.

- In contrast, listable goods are accepted for inclusion on the ARTG on the basis of the sponsor certifying that evidence relating to efficacy is available. Applications are generally submitted electronically and the sponsor has lists of specific, low-risk ingredients from which to choose. Licensing of manufacturers is checked electronically and the system alerts sponsors and the TGA to the need for appropriate warning statements. Label claims that can be made are limited by the Therapeutic Goods Advertising Code. A proportion of applications are checked in detail. Sponsors do not have to provide evidence to the TGA of product stability for the duration of the claimed shelf life. Listed goods do not, therefore, undergo the same rigour of assessment of efficacy nor the same detailed checking of label claims.

- An Australian Register of Therapeutic Goods down-load identified 54 products containing *Lactobacillus acidophilus*, in some cases mixed with other microorganisms such as *L. casei*.

- Of the 54 products identified, eleven had at least one component produced by a manufacturer who was either not licensed by the TGA or who did not have evidence of pharmaceutical GMP. Of these eleven products, only six manufacturers were involved as some manufacturers supply materials for several products. Five of these six companies were non-Australian; one was listed as being the Victorian Department of Employment, Education and Youth Affairs. All companies who do not have GMP evidence have been contacted by the TGA and given three months to produce this evidence. If the evidence is not

forthcoming the products in question will be de-registered.

- All manufacturers of therapeutic goods produced in Australia, whether these goods are listed or registered, are in inspected to ensure compliance with the *Australian Code of Good Manufacturing Practice for Medicinal Products 1990*. Factors examined include the state of the buildings and grounds, equipment, personnel including their training, quality control procedures and validation procedures. There are no inspection conditions specific to probiotic products and these products would be regarded for GMP purposes in the same way as other non-sterile oral products. Where a product is imported, each nominated overseas manufacturer is expected to comply with the equivalent standard of GMP as would be required of an Australian manufacturer.

Members were reminded of the late paper tabled at the meeting relating to information on the licensing and GMP status of manufacturers and asked if members had any specific issues relating to *Bifidobacterium* and the nature of evidence provided that could assist TGA in assessing the application.

CMEC agreed that if probiotic organisms are to be permitted in listed products, then in relation to safety and GMP, the requirements for a final product would be a viable culture, presence of a consistent strain and absence of contamination. These requirements could also be incorporated into a monograph.

CMS would consider the safety and GMP requirements. A member would provide the names of companies that have data to assist CMS. The requirements would be considered at CMEC7. CMS would obtain information about other strains of organisms listed of the scientific report and a recommendation could be considered on them. Sponsors of these products could be requested to provide information on volume of sales.

**Recommendation to TGA:**

- **that existing strains of *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum*, subject to information on what strains are currently in use in therapeutic goods, should be suitable for use in listable therapeutic goods.**

The reasons for the recommendation are as follows:

- current use of many years both in therapeutic goods and food;
- the risks are low with existing strains;
- but, nonetheless, safety rating is strain specific.

**Recommendation to TGA:**

- **that other probiotics could be suitable for use in listed products**

The reason for this recommendation is as follows:

- This would facilitate the development of new products.

As a result of these recommendations CMS will conduct a full evaluation of the application for *B. longum* BB536 which is likely to be suitable for use in listed therapeutic goods.

**Item 4.2.1 Conflict of Interest on Fibre, including chitosan**

A member declared a possible conflict of interest in relation to this item. The Chairperson ruled that the member participate in the discussion and vote on the matter.

**Item 4.2.2 Fibre, including chitosan - issues arising from comment on a possible section 7 declaration**

Members noted the following information contained in the agenda paper:

- In December 1997, following advice from the External Reference Panel on Interface Matters (ERPIM), public comment was sought on a proposal to declare goods containing fibre in capsule, tablet or pill form, to be therapeutic goods. In formulating this proposal ERPIM was particularly aware of the sale of chitosan as a fibre supplement.

- Declaration of goods as therapeutic goods is possible under section 7 of the *Therapeutic Goods Act 1989* (the Act). Under this section, the Secretary of the Department may declare certain goods to be, or not be, therapeutic goods when used, advertised, or presented for supply in a particular way. Public comment closed in late March 1998. Section 7 declarations do not change the requirements of the legislation. They are intended to provide greater clarity and certainty for sponsors and regulators by resolving the status of certain products at the food/drug interface.

- The rationale provided for the proposal was as follows:

  - The recommended daily intake of dietary fibre is at least 30 grams per day. Where a product is consumed in amounts that contribute only small amounts of fibre, the goods clearly do not have a principal food use. Fibre supplied as tablets, capsules and pills provide relatively low levels of fibre.

  - These products are likely to be perceived by consumers to be therapeutic goods because of the dosage form and recommended dosage regimen. These products are likely to be ingested with the anticipation that they

would have a therapeutic effect, i.e. the modification of a physiological process.

- Chitosan is a product derived from chitin, a polysaccharide found in the exo-skeletons of shrimp, crabs and other shellfish. It is indigestible by humans and therefore functions as a source of fibre in the intestine. Chitosan adsorbs lipids or fats, at a claimed rate of 5 to 10 times its mass, and is therefore also being promoted for weight loss. Chitosan's adsorbent properties have led to its use in controlling environmental damage, such as oil spills, and in purifying water.

- Chitosan products available contain 250 - 300 mg chitosan per capsule or tablet. Recommended administration may be three times per day, for example before meals. Therefore likely daily intakes are in the range of 1 to 2 grams per day. As a source of dietary fibre they would appear to be of little value, as most adults would need approximately 30 g fibre per day for efficient bowel function.

- In terms of fat-binding, a dose of 2 g chitosan may have the potential, in theory, to bind 10 to 20 g fat per day. Many Australians consume fat intakes of 60 to 80 g per day so would still consume enough fat to provide sufficient fat soluble vitamins. Chitosan's fat-binding properties may be of concern in consumers who also have a very low daily fat intake (20 - 30 g per day). However, numerous studies have found that only very motivated individuals are able to maintain such a low fat intake in the long term.

- The effectiveness of chitosan to inhibit fat digestion *in vivo* is uncertain. Digestion of fats begins in the mouth and it is likely that at least partial digestion of fats would occur even if they were loosely bound to chitosan. For efficient binding of fat, chitosan would probably need to be mixed with foods prior to eating, rather than before or after fat consumption. Shils & Young (1988) report that increased faecal fat loss has been observed in high fibre diets but that these have seldom been above 7 g more than normal faecal fat loss.

- Chitosan may present a health risk to consumers who have an allergy to shellfish. Therefore products containing it should also carry a warning statement.

- As with all seafood-derived products, there is a possibility of heavy metal contamination depending on the area from which the product is derived. We do not have any data on the heavy metal levels in chitosan. If sold as a food, chitosan would be required to comply with the general limits for foods stipulated in the Food Standards Code.

- There are a number of fibre supplement products are already included on the Australian Register of Therapeutic Goods. Many of these contain approximately 35 - 50% psyllium husk and may or may not contain other fibre sources. Products such as this would supply far greater levels of dietary fibre

(approximately 10 - 15 g per day) than are present in chitosan capsules.

- Only two substantial responses were received in relation to the proposal. Neither respondent opposed the proposal, but both recommended that chitosan be included in Schedule 4 of the Regulations, so as to permit its use in listed therapeutic goods. One respondent recommended a 6 month lead-in time to allow producers of fibre products currently sold as foods to apply for listing as therapeutic goods.

- Other significant issues raised were:

– The form of presentation of goods is only one of several criteria used at present to decide whether goods are foods or therapeutics. Other factors include the presence of a defined dosage regime, whether or not the product has a principal function as a source of nutrition and whether or not it is covered by a standard in the Food Standards Code. If the proposed declaration is made this will not prevent the sale of other foods in such modes of presentation.

– Action can already be taken to control the sale of illegal foods and therapeutics, although this is a costly process for regulatory authorities. The intention of the proposed declaration is to provide certainty to regulators and sponsors as to the appropriate regulatory category of fibre supplements. In this way, the need to take enforcement action and to spend resources assessing individual products may be minimised.

– The intent of the proposal is to include all sources of fibre when presented in the form of capsules, tablets or pills. As noted above there are already many fibre supplements included on the ARTG, some of which are in these forms. Products presented in these forms are generally not suitable for use as a food ingredient, in contrast to fibre forms such as wheat or oat bran sold as loose powders, where the fibre can easily be dispersed into a meal.

It was agreed that CMS would investigate the concerns expressed by members about safety and provide information for CMEC to consider at a future meeting.

**Item 5 Safety review**

**Item 5.1.1 *Echinacea* - review, Conflict of Interest**

A member declared a possible conflict of interest in relation to this item. The Chairperson ruled that he/she participate in the discussion but when the final decision is being made, members may need to discuss his/her position with him/her absent from the room.

Another member declared a possible conflict of interest in relation to this item. The Chairperson ruled that the member participate in the discussion but the matter may need to be considered when the decision is being made.

**Item 5.1.2 *Echinacea* - review - progress report**

Members noted the following information in the progress report:

- Echinacea was reported in the *Medical Observer* (Rachel Sharp, 8/9/97) (Attachment 1) as a potential hazard for asthmatics, based on the *in vitro* observation that Echinacea increases the production of a cytokine which enhances inflammation undesirable during an asthmatic attack. The Chief Executive Officer of the National Asthma Campaign wrote to the TGA in August 1997 asking what action the TGA intends, in response to the article.

- The President of the National Herbalists Association, Mr Nick Burgess, published a refutation in *Access* (10/9/97), also at Attachment 1, claiming that the polysaccharides used in the *in vitro* tests are not present in significant quantities in commonly used Echinacea preparations and are poorly absorbed in any case. Isolated polysaccharides do not behave pharmacologically in the same way as herbal extracts containing multiple components. Mr Burgess points out that the behaviour of the herb *in vivo,* rather than in cultured cells, is important.

- Adverse reactions are being reported to the Adverse Drug Reactions database and in the press. Publicity was given in the press earlier this year to a report in the Medical Journal of Australia (Mullins, February 1998) of a patient who experienced anaphylaxis after taking Echinacea (among other dietary supplements) (Attachment 2). The patient exhibited a positive skin test to Echinacea challenge, supporting a conclusion of an allergic reaction. Dr Mullins arranged for testing of stored sera from atopic patients and found Echinacea-binding IgE at moderate to strong levels in 20% of these. Dr Mullins is concerned that members of the community could have antibodies that cross-react with proteins in Echinacea and subsequently experience severe reactions, even on first time use of the drug.

- Subsequently, defence of Echinacea appeared in the press, including a challenge to the conclusion of Dr Mullins that high numbers of susceptible (with cross-reacting antibody) individuals are taking Echinacea (Dr Iggy Soosay, The Age 26/2/98)(Attachment 3). Mr Burgess noted the widespread and popular use of Echinacea relative to the small number of reported reactions.

- Echinacea is a native North American plant of the 'Compositae' family (related to daisies) used to improve immune function and stimulate wound healing. The Indians used it for snakebite, infections, toothache, sexually transmitted diseases and blood purification. It was introduced into the European culture late last century. It is currently promoted as a non-specific immune system stimulant, often recommended for recovery from colds and flu.

- There are three species recognised as having therapeutic value: *Echinacea*

*angustifolia, Echinacea purpurea, and Echinacea pallida,* predominantly the first two. Differences between these species, macroscopically, microscopically and chemically, assist in accurate identification. An early history of substitution for Echinacea root with *Parthenium integrifolium* (Missouri snakeroot) led to a confused documentation of distinguishing constituents.

- The variety of Echinacea products is widened by the possible plant parts chosen, the preparation methods and the final dosage forms such as tablets, capsules or liquid extracts. Root extracts, whole plant extracts and expressed juice have been used. Administration modes include topical, injectable, homoeopathic and oral. Herbalists recommend combinations of above the ground preparations of *E. purpurea* and the roots of *E. angustifolia.*

- The chemistry, pharmacology and clinical effects of Echinacea have been studied, but have been marred by misidentification of species. Most clinical work has been done with the injectable form in Germany. The active components responsible for immunomodulation have not been identified, although support can be given for polysaccharides and alkylamides as active.

- The characteristics of efficacious products have not been defined in that it is not clear which of the constituents are the active components and what dosage is really required.

- Echinacea products are listable in the Australian Register of Therapeutic Goods, which means that they are regarded as low risk. The products are not standardised, so that they do not have to comply with a minimum level of any ingredient (even if actives known) and there are no limits for adulterants. Echinacea could be present as the prime ingredient or as a minor ingredient.

- Evidence for the ability of Echinacea components to act as immunomodulators is being reviewed.

- A total of twenty-eight reports had been received by the Adverse Drug Reactions Advisory Committee since 1990, many associated with allergic responses such as bronchospasm and skin rashes. There are 11 reports of bronchospasm, dyspnoea or oedema, five of hepatic dysfunction, seven involving skin reactions, three of malaise and two each of arthralgia, dizziness and fatigue.

- Compared to the usage of Echinacea this number of reports is small. The potential for harm caused by the Echinacea products on the Australian market should be estimated, however, because:

    - the reporting rate does not have a direct relationship to the number of reactions occurring; and

- the reported reactions are of significance to the people involved, even if the reactions are rare.

- A summary of the 779 products in the Australian Register of Therapeutic Goods containing Echinacea was included as an attachment to the agenda paper. Further searching on the ARTG is required to try to reveal the formulations and species used in these products.

- This review is of Echinacea products being used by Australians. It is not a review of Echinacea *per se,* although reports of adverse reactions to overseas products are relevant.

A member spoke in detail about the letter published (written jointly by Stephen Myers and Hans Wohlmuth) in the Medical Journal of Australia (MJA) on 1 June 1998 (vol 168). The letter was in response to the earlier article by Dr Mullins in the MJA. A copy of the letter was tabled at the meeting. The article and the letter were titled 'Echinacea-associated anaphylaxis'. Comments in the letter included the following:

- A systematic review of trials concluded that echinacea preparations can be efficacious immunomodulators although further clinical evidence is needed;
- The recent report by Dr Mullins of a case of echinacea-associated anaphylaxis had caused widespread community concern and was one of the first such cases reported in medical journals;
- The likely cause of the immediate pharyngeal irritation was the isobutyl amide constituent, echinacein which causes marked pharyngeal tingling and increased salivation;
- They did not believe the association between echinacea and anaphylaxis has been clearly established in this case.
- Based on the end point of anaphylaxis only, there appears to be few reported cases in proportion to the extent of the use of echinacea.

A member also mentioned their work in relation to sunflowers, the seeds of which do not appear to be allergenic.

Members were asked:

- If more product specific information is required before any regulatory decision such as warning statements can be made.

- If more laboratory investigation should be performed following a survey by TGA of twenty Echinacea products available in Australia that found that the surveyed products contained the herb stated on the label. The amounts of each species were not estimated because an appropriate dose for Echinacea is not prescribed. Contaminants were not investigated. Should further laboratory analysis be requested? For example should protein content and analysis be performed?

- Should the ARTG search be performed in detail, perhaps in a similar manner to the ginger investigation of products available for supply in Australia?

Members noted that submissions on Echinacea are still being received by TGA and will be evaluated for presentation to CMEC at a later date.

Members suggested that a request for specific information about Echinacea being implicated in adverse reactions, be put in the next Australian Adverse Drug Reactions Bulletin.

A member commented that there is information on the constituents of echinacea, in vitro activity and in vivo activity but there is no cohesive information about the connections between all three areas.

Members discussed Dr Mullin's paper on the adverse reactions (attached to the agenda paper). The paper was based on eleven reports of adverse reaction to Echinacea products from July 1996 to September 1997. These reactions could be associated with toxicity or could be idiosyncratic reactions to the product. Members needed to consider these factors when the Echinacea was presented to them.

It was agreed that the following information would be useful in considering Echinacea:

- information on the protein composition of Echinacea;
- details of the formulation of the products on the ARTG similar to those obtained by CMS for ginger could be obtained on Echinacea products from two or three suppliers; and
- polysaccharides content of cold pressed.

It was agreed that information on the concerns raised by members would be obtained and included in the review of Echinacea.

Members noted the progress report on the safety review of Echinacea.

**Item 6 Decision Record**

Decisions were made on the following items:

item 3.1.4 - Safety of Ginger
item 4.1 - Probiotic Microorganisms

**Item 7 For Information**

Members noted the following matters:

- WHO, Report from Working Group on Herbal Medicines - Conclusions and Recommendations;
- extracts of the Minutes of the 27th Adverse Drug Reactions Advisory Committee Meeting of 27 March 1998;
- Australian Adverse Drug Reactions Bulletin, May 1998;
- Evening Primrose Oil - Letter from Amanda Donovan;
- extracts of the Minutes of the 27th Adverse Drug Reactions Advisory Committee Meeting of 15 May 1998; and
- fax from the Victorian Drug Usage Advisory Committee about a seminar titled, 'Different Worlds? Orthodox and Complementary Medicines - Philosophical, Cultural and Economic Questions' to be held on 25 September 1998 in Melbourne.

**Item 8 Other Business**

**Item 8.1 Appointment of Members to CMEC**

Members noted information on the appointment of additional members to the committee. Arrangements would be made to replace the member with expertise in consumer affairs.

The Chairperson requested that a standing item be included on agendas for future CMEC meetings about appointments.

**Item 8.2 NDPSC**

Members were advised the meeting that at the last NDPSC meeting the recommendation from CMEC on kava had been accepted.

**Item 8.3 Chair of CMEC**

Professor Roberts advised the committee that he would be on sabbatical leave in England from July 1998 until December 1998. Arrangements were being made for an acting Chairperson while he was absent. He wished to have CMEC papers sent to him while in England.

The meeting closed at 4.00 pm.