



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 47
Complementary
Medicines
Evaluation
Committee

Extracted Ratified Minutes
Forty-seventh Meeting
13 August 2004

Abbreviations:

ADEC	Australian Drug Evaluation Committee
ADRAC	Adverse Drug Reactions Advisory Committee
ADRU	Adverse Drug Reactions Unit (of TGA)
AQIS	Australian Quarantine Inspection Service
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
BP	British Pharmacopoeia
BPC	British Pharmaceutical Codex
BSE	Bovine spongiform encephalopathy
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicines Evaluation Committee
DSEB	Drug Safety and Evaluation Branch
ELF	Electronic Lodgement Facility
EP	European Pharmacopoeia
FSANZ	Food Safety Australia and New Zealand
LOAEL	Lowest Observable Adverse Effect Level
MEC	Medicines Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
NOAEL	No Observable Adverse Effect Level
OCM	Office of Complementary Medicines
PBS	Pharmaceutical Benefits Scheme
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TGA	Therapeutic Goods Administration
TGAL	Therapeutic Goods Administration Laboratory Branch
TSE	Transmissible spongiform encephalopathies

The forty-seventh meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in the Wangaratta Room, Hilton Hotel, Melbourne from 9.30 a.m. to 4.30 p.m. on Friday 13 August 2004.

Members of CMEC present were:

Professor Tony Smith (Chair)

Dr Vicki Kotsirilos
Associate Professor Douglas Moore
Dr John Ryan
Mr Kevin Ryan
Professor Gillian Shenfield
Dr Iggy Soosay
Professor Bill Webster
Associate Professor Heather Yeatman

Present from the Therapeutic Goods Administration (TGA) were:

Dr David Briggs
Dr Richard Hill
Dr Bogdan Sikorski
Mr Karl Skewes
Mr Terry Slater

Observer from MedSafe (New Zealand)

Ms Kathy Daly (items 1 – 10.5)

1. Procedural Matters

1.1 Opening of Meeting

The Chair opened the meeting at 9.30 a.m. and welcomed CMEC Members and TGA staff.

1.2 Apologies

The Secretariat received an apology from Professor Stephen Myers.

1.3 Conflict of Interest

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

2. Confirmation of Minutes of CMEC 46 (11 June 2004)

Members accepted the minutes of the forty-sixth meeting of CMEC as an accurate record of proceedings, subject to a number of minor amendments.

CMEC Recommendation:

Members made the following recommendation:

Recommendation 47.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 46, 11 June 2004), as amended, are a true and accurate record of that previous meeting.

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

CMEC did not consider any matters under this agenda item.

4. CMEC Working Party on Herbal Medicine Issues

CMEC did not consider any matters under this agenda item.

5. Action Arising from Previous Meetings

5.1 *Morinda citrifolia* (Noni) fruit juice powder.

The Committee considered one outstanding issue with respect to its evaluation of this substance at the previous meeting.

5.2 The Committee made one recommendation under this agenda item.

6. Evaluation of New Substances

6.1 Enzymes:

- **amylase, tilactase, protease derived from *Aspergillus oryzae*;**
- **cellulase derived from *Trichoderma longibrachiatum*; and**
- **lipase derived from *Rhizopus oryzae***

Background

The specific enzymes amylase, lactase, protease (all derived from the fungus *Aspergillus oryzae*), cellulase (derived from the fungus *Trichoderma longibrachiatum*) and lipase (derived from the fungus *Rhizopus oryzae*) are currently ingredients that can only be used in registered medicines. The enzyme name, tilactase, is the Australian Approved Name for lactase. An industry association requested that OCM evaluate the suitability of these enzymes for use in Listed complementary medicines via a 'switch' application.

This evaluation has been conducted to establish whether or not the above enzymes meet the quality and safety requirements for use as ingredients in Listed medicines on the Australian Register of Therapeutic Goods (ARTG).

Characterisation of the substances

The enzymes considered in this evaluation with their particular activity include:

- amylase, or more specifically α -amylase, is a carbohydrate-degrading enzyme obtained from *A. oryzae*;
- lactase (tilactase) is specific for lactose, the primary disaccharide found in dairy products. Lactase obtained from *A. oryzae* is involved in the breakdown of lactose to glucose and galactose;
- protease enzymes (containing both endopeptidase and exopeptidase) obtained from *A. oryzae*, hydrolyse polypeptides to yield peptides of lower molecular weight;
- cellulase obtained from *T. longibrachiatum* breaks down plant fibre. The human body does not produce cellulase and cellulose passes through the digestive system providing no nutritional value; and
- lipase obtained from *R. oryzae* is a lipid-degrading enzyme, characterised by its ability to hydrolyse triacylglycerols (the main lipid found in the diet) into diacylglycerols, monoacylglycerols, and free fatty acids and glycerol.

Manufacturers produce these enzymes by growing non-toxicogenic and non-pathogenic strains of microorganisms in an aqueous suspension in large vessels by submerged fermentation. Surface culture (i.e. semisolid fermentation) of microorganisms accounts for less than 10 % of enzymes commercially produced. During the recovery phase of production, the manufacturers destroy the microorganisms before removing the nonproteinaceous material away from the enzyme preparations. Enzymes recovered from fermentation broth are usually present in an aqueous solution or processed to a dried state. When used in oral medicines, commercially obtained digestive enzymes are formulated with appropriate stabilisers and excipients.

There are no specific pharmacopoeial monographs to describe any of these enzymes. However, TGA has developed draft compositional guidelines for these fungal-derived enzymes.

History and patterns of use

Cellulase produced by *T. longibrachiatum* has a history of safe use in the food, animal feed and pharmaceutical industries. For example, in Japan fungal cellulases (including from *T. longibrachiatum*) have been manufactured commercially on a large scale since the 1960s. Cellulase has been used in digestive aids without any evidence of toxicity. Enzymes from *Rhizopus* species have also been used in food production for many years. *R. oryzae* has been used in the production of fermented foods and alcoholic beverages in Indonesia, China, and Japan. However normally, the enzymatic food production processes include an enzyme inactivation or removal step, via the use of processing aids. Consequently, the exposure to food-processing enzymes in the diet is likely to be minimal, if at all. In contrast, lipase derived from *R. oryzae* and cellulase derived from *T. longibrachiatum* has been consumed for many years as digestive aids without apparent adverse reactions.

All of the enzymes considered in this evaluation report have been available in a multitude of enzyme products marketed for minor digestive disorders in many countries, including Australia. Other enzymes such as papain, bromelain, and pepsin are also often included in these products. Nevertheless, the physiological benefit of including cellulase in human nutrition, be it as a supplement or as a therapeutic agent, does not appear to have been established. Importantly, the risks associated with the long-term, relatively high-dose intake of cellulase are unclear. This is in contrast with the potential risk associated with the use of the other fungal-derived enzymes in this evaluation that essentially have the same activity as those produced by the human body.

At the time of evaluation there were twelve Registered products on the ARTG containing enzymes similar to those considered in this evaluation; nine were in tablet form and three in capsule form. Eleven products contain amylase, three contain lipase, two contain protease, and cellulase and tilactase appear in two products each. The amount of amylase in formulations varies from 20 to 131 mg with an average of 56 mg. Lipase in two products has an average content of 24 mg, protease 131 mg, cellulase 15 mg and tilactase (as a single active) at 110 mg.

Biological activity

Each of the enzymes considered in this report, except cellulase, has a specific digestive role in human nutrition. Amylase, found in the saliva and pancreatic digestive juices, breaks down polysaccharides with α -1,4-glucan bonds, e.g. starch. Protease, found in the stomach as well as pancreatic secretions, facilitates the breakdown of proteins into oligopeptides and amino acids. Lipase, produced mainly by pancreas, but also in stomach mucosa, breaks down lipids (triacylglycerols) into diacylglycerols, monoacylglycerols, and free fatty acids and glycerol. In contrast, cellulase, which is not present in human body and therefore has no known digestive role, breaks down polysaccharides with β -1,4-glucan bonds, e.g. cellulose which yields β -dextrins (i.e. shorter glucose polymers with β -1,4-glucan bonds).

Pancreatic enzyme supplements that provide proteases, amylases, and lipases derived from porcine pancreas have been used in cases of pancreatic enzyme insufficiency: cystic fibrosis,

pancreatectomy, pancreatic duct obstruction, chronic pancreatitis, and steatorrhea that are secondary to pancreatic enzyme deficiency. Despite their widespread use, the use of pancreatic enzymes as therapy or supplement is associated with some inherent limitations. Pancreatic enzymes are susceptible to being destroyed by gastric acid and pepsin. A pH sensitive enteric coating designed to dissolve above a pH of 5.5 to 6.0 has been applied to various forms of pancreatic enzymes in an attempt to protect them through the acid environment of the stomach. Yet, in clinical studies the coated supplements were often less effective than those uncoated. In contrast to pancreatic enzymes, some microbial enzymes possess high stability and activity throughout a wide pH range. Because in terms of biological activity fungi-derived enzymes are essentially the same as animal-derived ones, they appear to offer certain benefits due to their stability advantages.

It should be noted that TGA would not consider therapeutic claims for treatment of pancreatic enzyme insufficiency as appropriate for Listed medicines containing digestive enzymes.

Toxicology

A summary for each of the enzymes is as follows:

Amylase derived from the fungus *A. oryzae*:

- α -Amylase has a low acute oral toxicity in rodents.
- No signs of toxicity were observed in rats given 7 g/kg/day for 90 to 94 days.

Tilactase (lactase) derived from the fungus *A. oryzae*:

- Tilactase has a low acute oral toxicity in rodents.
- The lowest published toxic dose (TDLo) for subcutaneous exposure in the rat is 26 g/kg administered over 30 days.

Protease derived from the fungus *A. oryzae*:

- A ninety-day study in rats did not reveal any adverse effects.
- Level causing no toxicological effect in the rat: 10% in the diet, equivalent to 7 g/kg/day.

Cellulase derived from *T. longibrachiatum*:

- It has low acute oral toxicity in laboratory animals.
- Three 13-week studies in rats and one in dogs showed no treatment-related effects up to a dose of 4 g/kg/day.
- There were no treatment-related signs or treatment-related effects on reproductive parameters in male and female rats up to 7000 mg/kg/day.

Lipase derived from *R. oryzae*:

- It has a low acute toxicity in laboratory animals. The oral LD₅₀ value of lipase in rats of either sex exceeds 5000 mg/kg.
- In three sub-chronic toxicity studies in rats conducted up to 13 weeks with doses up to 2000 mg/kg/day there were no deaths or adverse clinical signs.
- There was no indication of mutagenicity in both *in vitro* and *in vivo* studies.
- Lowest published toxic doses indicate that high doses of lipase are required to result in adverse reproductive effects.

Clinical trials

Only five clinical studies could be found that used microbial enzymes. No conclusions can be drawn on possible adverse reactions to the enzymes from these clinical studies because only reduction or elimination of symptoms was investigated, and none of these trials looked at the safety aspects of long-term use.

Adverse reactions

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) Secretariat has received three adverse reaction reports for products containing amylase, protease, and lactase other than those containing porcine pancreatic enzymes. In two of these adverse drug reaction reports, other medicines taken concurrently are most likely the causative agents. Lactase supplementation in a 5-month old female may have been the causative agent leading to vomiting, pallor and hypotonia, although lactase maldigestion can also lead to these symptoms. The causative agent could not be determined from the adverse reaction report.

No adverse drug reaction reports could be found for the consumption of enzymes produced by the fungi *A. oryzae*, *T. longibrachiatum*, and *R. oryzae*. Authors of safety studies and reviews indicated that they could find no reports of adverse reactions for oral consumption of microbial-derived enzymes in humans.

Present discussion

A CMEC Member made the following general comments about the quality of amylase, tilactase, protease derived from *A. oryzae*; cellulase derived from *T. longibrachiatum*; and lipase derived from *R. oryzae*:

- although the enzymes would contain a certain amount of residual components, such as protein and salt material from their separation and purification, the defining measure of quality would ultimately be their enzymatic activity. The measurement of enzymatic activity involved monitoring the rate at which an enzyme catalyses a specific reaction; and
- in-principle, there should be some chromatographic profiles of each of these enzymes to determine if there were any residual components carried through from the production process. However, given that they have an extensive history of safe use and wide exposure, it is probably not necessary to pursue this matter.

Another Member questioned whether there were any monographs to describe the enzymes produced by each of the fungal fermentation processes described. A TGA Officer stated that there was a generic Food Chemical Codex monograph available for each of the enzymes. However, TGA would develop compositional guidelines for each of these enzymes based on the production process involved. The Officer explained that TGA would also have to consult with industry to establish limits for enzyme activity rates in the compositional guidelines for each of the enzymes to ensure that each had adequate activity as a starting material.

The Chair invited comment from Members about the safety of amylase, tilactase, protease derived from *A. oryzae*; cellulase derived from *T. longibrachiatum*; and lipase derived from *R. oryzae*. One Member commented that although the enzymes appeared to be relatively safe, there

are toxicity concerns if consumed in large amounts. For example, lipase has been associated with fibrosing colonopathy in young children when given for cystic fibrosis. However, the Member also noted that this was an extreme scenario in which patients received high doses of enzymes for prolonged periods of time. The Member remarked that the data suggested that these enzymes appeared to be relatively safe for human consumption in the amounts proposed for use in Listed medicines.

Several Members queried whether there was a potential risk to consumers of experiencing hypersensitivity reactions following the inhalation of powdered forms of these enzymes. A TGA Officer explained that protease was probably the only enzyme of any real concern to possible hypersensitivity following inhalation. Unfortunately, data was not furnished in this report to address this concern. A Member suggested that TGA could maintain a watching brief on this potential concern by continued monitoring of adverse drug reaction reports.

CMEC Recommendation:

Members made the following recommendation:

Recommendation 47.5

CMEC recommends to the TGA that the following enzymes:

- **amylase, tilactase, protease derived from *Aspergillus oryzae*;**
- **cellulase derived from *Trichoderma longibrachiatum*;**
- **and lipase derived from *Rhizopus oryzae***

are suitable for use as active ingredients in Listed medicines.

7. Safety or Efficacy Reviews

CMEC did not consider any matters under this agenda item.

8. Registration Applications

CMEC did not consider any matters under this agenda item.

9. Variation to a Registered Product

CMEC did not consider any matters under this agenda item.

10. Matters referred from within the TGA

10.1 ADRAC Matters

10.1.1 Adverse Drug Reaction Advisory Committee report (ADRAC) Meeting 276

Members noted the adverse drug reaction reports from 276th meeting of ADRAC which were associated with complementary medicines.

10.1.2 Adverse Drug Reaction Advisory Committee report (ADRAC) Meeting 277

Members noted the adverse drug reaction reports from 277th meeting of ADRAC which were associated with complementary medicines.

10.1.3 Glucosamine label warning statement

Background

At meeting 9 of CMEC (item 4.1, October 1998), the Committee made the following recommendation to TGA:

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.

At the time of preparing this item the ARTG currently contained 273 Listed, 7 Export-only and 1 Registered entries for medicines containing glucosamine salts and complexes. Sponsors making applications for Listed medicines, through the Electronic Lodgement Facility that contain glucosamine derived from seafood as an ingredient, must make the following label declaration on the label of the product: “*Derived from seafood.*”

Previous adverse drug reaction concerns

In April 2004 (meeting 45), CMEC considered a Safety Review of glucosamine adverse drug reaction reports to medicines containing glucosamine. The literature review was the result of previous concerns raised by ADRAC about reports on the effect that glucosamine might have on blood clotting parameters alone or in combination with other medicines such as warfarin. After considering the literature review, CMEC made the following recommendation to TGA:

CMEC notes a review of Australian adverse drug reaction data for glucosamine conducted by the TGA and recommends to TGA that glucosamine continues to be suitable for use as an ingredient in Listed medicines.

The OCM provided the ADRAC Secretariat with a copy of the review together with the ratified minutes from this meeting. CMEC also asked OCM to contact the ADRAC Secretariat about whether there had ever been a bulletin issued about the potential association of glucosamine and

warfarin with increased international normalised ratio (INR). The ADRAc Secretariat advised OCM that there has never been a bulletin issued to this effect.

Current concern

At meeting 277 of ADRAc, the Committee considered the literature review provided by the OCM. ADRAc noted that the commonest adverse reactions to glucosamine seen in Australia were allergic reactions, namely skin reactions and oedema. The Committee sought clarification on whether there was a need to review the labelling of supplements containing glucosamine to better inform consumers about the possibility of allergic reactions to the shellfish-derived ingredient.

Present discussion

A TGA Officer advised the Committee that at the last meeting of ADRAc in July 2004, the Committee had requested that TGA prepare a short ADRAc Bulletin item regarding the possibility of glucosamine and warfarin interactions, and allergic reactions to glucosamine. The Officer commented that ADRAc considered that “*derived from seafood*” might not be implicit enough to warn consumers about the potential of allergic reactions. A Member considered that given the relatively low number of adverse drug reaction reports compared to the large amount of consumption by the community that the warning was probably adequate. The Member suggested that an additional warning (e.g. “*Could cause allergic reaction*”) might be of little added value to the consumer. Another Member also noted that the food industry identifies the source of an allergy on the labelling of products to warn those who are potentially affected.

A Member commented that sponsors with synthetically derived glucosamine might make positive claims about “*non-seafood derived*” for those individuals who are sensitive to seafood products. However, the Chair warned that it was not the role of the Committee to provide this sort of marketing advice, particularly since ADRAc did not appear to specifically identify the sources of glucosamine in the reports. Another Member remarked that there was a potential for contaminants appearing in the synthesis of glucosamine that could also produce clinical events. However, there was no data at present to suggest that synthetic glucosamine could cause allergic reactions. Members suggested that future reporting from ADRAc could identify the origin of the glucosamine in the medicines reported.

Members unanimously agreed that it was not necessary to change the current label warning statement for medicines that contain shellfish-derived glucosamine as an ingredient.

CMEC Recommendation:

Members made the following recommendation:

Recommendation 47.6

CMEC recommends that the current label warning statement “derived from seafood” be retained on medicines that contain shellfish-derived glucosamine as an ingredient.

10.1.4 The Committee considered one matter under this agenda item.

10.2 & 10.3 The Committee considered two matters and made a recommendation on one of these agenda items.

10.4 Draft Australian Regulatory Guidelines for Complementary Medicines - Parts IV and V

Background

TGA, in consultation with the complementary medicines industry peak bodies, has been developing the *Australian Regulatory Guidelines for Complementary Medicines* (ARGCM). The intended purpose of ARGCM is to:

- provide information to help sponsors of complementary medicines to meet their obligations under therapeutic goods legislation;
- help ensure that applications to the TGA relating to complementary medicines uniformly meet all essential regulatory requirements so that applications may be processed successfully within minimum timeframes;
- enhance clarity and transparency of processes leading to the Registration and Listing of complementary medicines in the Australian Register of Therapeutic Goods; and
- strengthen the basis for regulatory decisions made by the TGA.

These guidelines will also provide a basis for the development of new guidelines for complementary medicines under a Trans-Tasman Joint Regulatory Agency.

Introduction

As part of the development process, TGA and the complementary medicines industry peak bodies – the Australian Self-Medication Industry (ASMI) and the Complementary Healthcare Council of Australia (CHC) - proposed that ARGCM contain the following five distinct parts:

- Part I - guidance on the Registration of complementary medicines;
- Part II – guidance on the Listing of complementary medicines;
- Part III - guidance on the evaluation of complementary medicine substances for use in Listed medicines (that is, for inclusion in Schedule 4 of the *Therapeutic Goods Regulations 1990*) including new substances, ‘switch’ substances and excipients used in complementary medicines;
- Part IV - details the requirements that are particular to specific complementary medicine modalities such as homoeopathy, traditional Chinese medicine and aromatherapy. This part will also provide information on exempt medicines, combination complementary / pharmaceutical medicines and the food / medicine interface.
- Part V - details of TGA policy guidelines relevant to complementary medicines (for example, TSE minimisation), references and a glossary of terms.

Wherever possible, the guidelines will reflect consistency with, and draw from, the Australian Regulatory Guidelines for OTC Medicines (ARGOM).

The TGA / Industry Consultation Group identified draft *Part IV (General Guidance)* and *Part V (Policy)* as the last instalments in the development of the ARGCM. CMEC has already commented on Parts I, II and III at meetings 45 (April 2004), 39 (April 2003) and 46 (11 June 2004) respectively.

Present discussion

The Chair commented that links to the documents were available from the TGA website and that they were relatively simple to read. The CMEC Secretariat then took on notice a number of comments from Members on Parts IV and V of the draft ARGCM.

10.5 Safe Access to Chinese Medicines

The CMEC examined a discussion paper jointly prepared by the Chinese Medicine Registration Board of Victoria (CMRBV) and the Victorian Department of Human Services, which provided an overview of how the legislative scheme, to regulate prescribing and dispensing of otherwise restricted Chinese herbs, is intended to work.

10.6 Curcumin

Background

Curcumin is widely used around the world in numerous food applications. It is approved for use as a food additive (colouring) in Australia, New Zealand, the European Union, the United States (as tumeric oleoresin) and Canada. As a food colour, curcumin is commonly known by the synonyms: 'tumeric yellow' and 'CI natural yellow 3.' Curcumin is also currently permitted in Australia for use as an excipient in complementary, OTC and prescription medicines for oral use.

Curcumin is a component of tumeric (*Curcuma longa*), a member of the ginger family. The dried rhizomes typically contain 3-5 % of curcuminoids – a mixture of dicinnamoylmethane derivatives such as curcumin (diferuloylmethane). Curcumin may be obtained from extraction of tumeric.

TGA currently permits the use of tumeric and tumeric extracts as active ingredients in Listed medicines. An Australian manufacturer of raw herbal materials for use in complementary medicines noted in its review of the tumeric (*Curcuma longa*) extract, that the manufacturing process did not follow the specifications required by TGA for herbal extracts. The ethyl acetate extraction and subsequent crystallisation process results in the substance curcumin which is in fact only permitted for use as an active ingredient in export medicines only. Currently, the ARTG contains 172 products containing *Curcuma longa* as an ingredient

It is not known how many medicines marketed in Australia contain the ingredient supplied by the 'extract' manufacturer, but the number is likely to be substantial. It is also likely that others

(i.e. overseas suppliers of the same ingredient) are using the same or a similar extraction process, followed by crystallisation. Therefore, at this stage it is likely that many of the products listing tumeric (*Curcuma longa*) extract as an ingredient are in breach of *Therapeutic Goods Act* (the “Act,” 1989).

The Australian supplier of tumeric (*Curcuma longa*) extract (ethyl acetate) which is not in compliance with current legislation, has notified all manufacturers of finished products containing the ingredient, advising them to hold any finished product that is in process.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has previously reviewed the safety and specifications for curcumin on several occasions and most recently at its 61st meeting held in June 2003. Based on the JECFA review, the OCM has proposed to extend the current permission for curcumin as an excipient to an active ingredient in Listed medicines and this item sought the CMEC’s view on this proposal.

Toxicological Evaluation

JECFA has reviewed the data on curcumin at a number of its meetings, and most recently, at its 61st meeting held in June 2003. In the past, JECFA has focused its toxicological evaluation of curcumin, including the establishment of the temporary ADI, on the tumeric oleoresin (79-85% curcuminoids), the substance that did not comply with the current specification. However, during the most recent meeting, the Committee obtained data from a new multigeneration study in rats, which were fed curcumin for periods up to 24 weeks, and the material tested met the current specification. Based on results of that study, i.e. a no observed effect level (NOEL) of 250–320 mg/kg/day, and using a safety factor of 100, an acceptable daily intake (ADI) of 0-3 mg/kg was allocated for curcumin, resulting in a removal of a temporary ADI of 0-1 mg/kg, which was established at JECFA's 57th meeting.

However, in its most recent considerations, the JECFA was unable to estimate a daily intake of curcumin in food. Nevertheless, a recently published safety review of curcumin suggested that the average dietary intake of tumeric in India is approx. 2-2.5 g in a 60 kg person, corresponding to approx. 60-100 mg/day of curcumin. Assuming an average concentration of curcuminoids in tumeric is 3%, the upper estimated dietary intake based on the above figure of 2.5 g/day should be 75 mg/day rather than 100 mg/day.

Characterisation of Curcumin

According to the recently (June 2003) updated JECFA specification monograph, manufacturers produce curcumin by solvent extraction of the ground rhizomes of *Curcuma longa* L. In order to obtain a concentrated curcumin powder, the extract is purified by crystallisation, resulting in a product consisting essentially of curcumins, i.e. the colouring principle (1,7-bis-(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione) and its desmethoxy- and bis-desmethoxy-derivatives in varying proportions. The total content of curcuminoids in curcumin should be not less than 90%, with the rest being minor amounts of oils and resins naturally occurring in tumeric.

Also, the updated JECFA specification monograph for curcumin permits the use of two alternative extraction solvents, ethyl acetate and carbon dioxide, with the residual limit for the former (50 mg/kg) specified in the monograph.

Compendial Specifications

In the absence of a British Pharmacopoeia (*BP*) monograph, colours permitted in medicines in Australia should conform to either the specifications in the Food and Agriculture Organization/World Health Organization Compendium of Food Additive Specifications, as published on the JECFA website. Alternatively there are specifications defined in the European Commission Directive 95/45/EC (*Specific purity criteria concerning colours for use in foodstuffs*). JECFA is currently publishing the most recent monograph (June 2003) for tumeric extract. The changes to the previous monograph have been outlined in the Final Draft Report of 61st JECFA meeting, which includes extraction of tumeric with ethyl acetate.

TGA has proposed the adoption of the JECFA monograph in Australia for sponsors to use curcumin as an active ingredient in Listed medicines.

Present discussion

A TGA Officer informed Members that although manufacturers used a ‘crystallisation’ step to obtain curcumin, the same product could be obtained using a series of selective solvent steps; so in many respects curcumin qualified as a herbal substance.

Members agreed that there did not appear to be any safety concerns with curcumin and noted that it appeared to be suitable for use as an active ingredient in Listed medicines.

CMEC Recommendation:

Members made the following recommendation:

Recommendation 47.8

CMEC notes the proposal by the OCM to permit the use of curcumin as an active ingredient in Listed medicines.

10.7 – 10.10 TGA deferred one agenda item and the Committee considered three other agenda items.

11. For Information

11.1 American Ginseng (*Panax quinquefolius*) reduces Warfarin’s effect in healthy patients

Members noted a recent journal article relating to the effect of *Panax quinquefolius* on warfarin in healthy patients.

12. Sponsor representations to CMEC

CMEC did not consider any matters under this agenda item.

13. Other business

There was no other business for consideration by CMEC.

14. Recommendation record

Item 2 Minutes of CMEC's 46th Meeting

Recommendation 47.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 46, 11 June 2004), as amended, are a true and accurate record of that previous meeting.

Item 6.1 Application for the Evaluation of a New Substance - Digestive enzymes: amylase, tilactase, protease derived from *Aspergillus oryzae*; cellulase derived from *Trichoderma longibrachiatum*; and lipase derived from *Rhizopus oryzae*

Recommendation 47.5

CMEC recommends to the TGA that the following enzymes:

- amylase, tilactase, protease derived from *Aspergillus oryzae*;
- cellulase derived from *Trichoderma longibrachiatum*;
- and lipase derived from *Rhizopus oryzae*

are suitable for use as active ingredients in Listed medicines.

Item 10.6 Matters Referred from within TGA: Curcumin

Recommendation 47.8

CMEC notes the proposal by the Office of Complementary Medicines to permit the use of curcumin as an active ingredient in Listed medicines.

The Chair closed the meeting at 3.45 p.m.