Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 55 Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Fifty-fifth Meeting
17 February 2006

Abbreviations:

ADRAC	Adverse Drug Reactions Advisory Committee
ALT	alanine aminotransferase
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
AST	aspartate aminotransferase
BP	British Pharmacopoeia
CMEC	Complementary Medicines Evaluation Committee
CMIRG	Complementary Medicines Implementation Reference Group
ECCMHS	Expert Committee on Complementary Medicines in the Health System
ELF	Electronic Listing Facility
HD	High dose
IV	intravenous or intravenously
JIEACS	Joint Interim Expert Advisory Committee on Standards
MD	Middle dose
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
NOAEL	No observable adverse effect level
OCM	Office of Complementary Medicines
OICG	Office of Complementary Medicines/Industry Consultation Group
PSS	Pharmacopoeial Standards Subcommittee
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGAL	Therapeutic Goods Administration Laboratories
UK	United Kingdom
USP	United States Pharmacopoeia

The Complementary Medicines Evaluation Committee (CMEC) held its fifty-fifth meeting in the Botany Room, Stamford Hotel Sydney Airport, Sydney, from 9.35 a.m. to 4.15 p.m. on Friday 17th February 2006.

Members of CMEC present were:

Professor Tony Smith (Chair)

Professor Alan Bensoussan
Dr Vicki Kotsirilos
Associate Professor Douglas Moore
Professor Stephen Myers
Dr John Ryan
Mr Kevin Ryan
Professor Gillian Shenfield
Professor Bill Webster
Associate Professor Heather Yeatman

Present from the Therapeutic Goods Administration (TGA) were:

Dr David Briggs
Dr Fiona Cumming
Dr Rohan Hammett (afternoon session)
Dr John Hall
Ms Michelle McLaughlin

1. Procedural Matters

1.1 Opening of Meeting

The Chair opened the meeting at 9.35 am and welcomed CMEC Members and TGA staff

1.2 Apologies

There were no apologies for this meeting.

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 54 (9 December 2005)

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

CMEC Recommendation:
Members made the following recommendation:

Recommendation 55.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 54, 9 December 2005), as amended, are a true and accurate record of that 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. Joint Australian / New Zealand Therapeutic Products Agency Matters

4.1 Revision of TGO56 (the 'Labelling Order') – Draft for Consultation

A TGA Officer introduced this item and reminded Members that Therapeutic Goods Order No. 69 (TGO69): *General requirements for labels for medicines,* is being reviewed as part of the establishment of the *Australia New Zealand Therapeutic Products Authority* (ANZTPA).

The TGA Officer advised Members that items relating to the labelling of complementary medicines, in particular those relating to herbal, homoeopathic and anthroposophic medicines, have been reviewed in line with recommendations made by both the CMEC and the OCM Industry Consultation Group (OICG). A Draft Managing Director Order (MDO): *General requirements for the labelling of medicines: Australia New Zealand Therapeutic Products Authority* (Draft Labelling MDO) was provided as an attachment for the consideration of Members.

Members were advised that the direction was significantly different in three instances. The amendments proposed in the Draft Labelling MDO, for the most part, reflect the position recommended by the CMEC.

Members considered a number of matters where there were differences in the directions it, and the OICG, had conveyed earlier to the TGA and provided a series of final comments on these matters.

4.2 Progress report on harmonisation of advertising arrangements

A TGA Officer provided the Committee with a presentation on the model being developed for the trans Tasman regulation of the advertising of therapeutic products via the Interim Advertising Committee (IAC).

Members were reminded of the IAC recommendations, advised of the three Ministerial amendments to the initial recommendations, and advised of the potential future involvement of the Committee.

A Member discussed the altered timeline for the establishment of the Australia New Zealand Therapeutic Products Authority, and the impact this might have on the implementation of the revised advertising system.

5. Action Arising from Previous Meetings

CMEC did not consider any matters under this agenda item.

6. Evaluation of New Substances

6.1 *Trametes versicolor* proteoglycan concentrate

Background
A TGA Officer introduced this item and advised Members that the sponsor of the previously approved "*Trametes versicolor* hyphae aqueous extract – powder' had contacted the TGA, indicating that, as they proposed to source this active ingredient made by a revised manufacturing process, the original approved compositional guideline no longer adequately described the substance they wish to supply.

As neither the existing legislation, nor the compositional guideline, cover the substance produced by the revised process, the TGA determined that a safety evaluation was required to ensure that the revised manufacturing process still results in a safe substance, suitable for use in Listed medicines.

The new substance is '*Trametes versicolor* proteoglycan concentrate'. This is a concentrated and dried hot-water extract of the hyphae of the edible fungus, *Trametes versicolor*. It is different from the original process of manufacture by the addition of an ethanol precipitation step, aimed to expedite the isolation procedure.

Members noted that the data package submitted for the previously approved herbal substance was re-supplied in the current application, although the extent of detail appeared to differ in some cases. For this reason, most of the toxicity data was reassessed. However the TGA Officer explained that the conclusions drawn were essentially the same.

Little new data was provided in support of this application. New studies were generally confined to acute toxicity studies and additional clinical efficacy studies for a related extract, Polysaccharide-K (PSK).

The safety of this new *T. versicolor* substance is based on chemical equivalence with the approved herbal substance. This assumption was seen as critical to this application, due to the absence of safety data for the new substance.

Members were informed that assessment of this chemical equivalence was an iterative process with the sponsor, and involved several rounds of discussion with the TGA. By the conclusion of these communications, the TGA formed the view that an argument for the chemical equivalence of the newly proposed and existing approved herbal substance had been adequately made – and this indicated that the safety of this new substance could reasonably be inferred from the evaluated safety of the existing approved herbal substance.

As with the original approved herbal substance, various sources of safety data for other, related *T. versicolor* extracts were also considered as supportive of safety for the proposed substance.

Overall both animal and human safety data, as supplied in the both original application for the approved herbal substance and the current application for the new herbal substance, was limited. Nonetheless, *T. versicolor* extracts appear to have low toxicity in animals. Similarly, limited clinical efficacy trials for *T. versicolor* extracts (predominantly involving PSK) were without any serious side effects.

As noted by Members for the original substance application, hot water decoctions of *Trametes versicolor* have had extensive traditional use in both Japan and China and, more recently, wide consumption of non-traditional *T. versicolor* extracts (PSK and Polysaccharide Protein P (PSP)) for over 20 years has been associated with only a few reported side-effects.

The TGA Officer explained that TGA is unaware of any cases of adverse reactions to the approved or proposed herbal substances. However, the global usage of these particular extracts is unknown. According to the WHO, there have been only eight cases of adverse reactions reported worldwide for the related *T. versicolor* extract, PSK, while none have been reported for Polysaccharide-protein (PSP).

In summary, Members were informed that safety data was not provided for the proposed new substance. However evaluated animal toxicology and clinical efficacy studies, low reported numbers of adverse drug reactions, and extensive traditional and non-traditional use of *T. versicolor* substances suggest this new substance is unlikely to provide a significant safety risk to consumers.

The CMEC were also asked to recall that in consideration of at least two previous applications, arguments for new substances being chemically or phytochemically equivalent to approved or traditionally used substances were accepted when approvals were made for use in Listed medicines – (*Santalum spicatum* (Australian sandal wood oil) and *Asparagus racemosus*). The TGA Officer suggested that the present application could be seen similarly.

Sponsor response
The sponsor's response to the OCM Evaluation Report was tabled. This included:

- pointing out a minor correction in the description of the extraction method for the approved substance;
- an argument that, because of the TGA Chemistry evaluators' comment that there are probably chemical components present in the previously approved extract that are NOT present in the proteoglycan concentrate, this implies that it might be even **safer** than the approved substance – an unsupportable assertion in the TGA's view; and
- clarification that it manufactures only one of the two *Trametes versicolor*-containing products on the ARTG.

CMEC was requested to decide, on the basis of the information presented, if *Trametes versicolor* proteoglycan concentrate meets the requirements for use in Listed medicines.

Current discussion
A CMEC Member declared a conflict of interest for this matter and Members agreed that it was appropriate that this Member be excluded from discussion and decisions for this Item.

However, given the Member's expertise, in terms of familiarity with the analytical procedures critical to establishing the identity and purity of the proteoglycan material, the Committee sought clarification with regard to the methodology used to establish chemical equivalence.

The Member, in response to questions from the broader Committee, advised that there were three determinations undertaken in principle for this substance, two of which are relatively non-specific (the determinations of the saccharide and the protein contents of the substance). The Member gave an overview of the benefits and limitations of the capillary electrophoresis methodology which has particular application in terms of this proteoglycan compound, as it is a series of high molecular weight (HMW) molecules extracted from the cell wall of the *Trametes versicolor* mycelia.

Another Member queried whether it is possible to use this method both qualitatively and quantitatively. In response, the Member confirmed that, similarly to HPLC, this could be done. However, standards are needed, and it difficult to get appropriate standards to use for quantitative purposes.

A Member queried whether, given that standards are important, is it reasonable to assume that there were no major substances in either concentrate that were unable to be identified. The Member explained that the two materials have the same protein analysis and the same saccharide analysis, and essentially the same fingerprints, with very minor variations in baseline components and that, therefore, it was not unreasonable to come to the conclusion that the two concentrates are not very different.

Members queried why the application had been made if the concentrates are essentially the same, and about the significance of the precipitation step do, if they are essentially the same substance. The Member explained that the precipitation speeds up the process of extraction and ensures that the substance is less exposed to the degradation that may occur whilst the lengthy process of evaporation takes place.

The Member with the conflict of interest left the room, and discussion continued.

One Member commented that it was likely that the substance was essentially safe, but expressed concern that this may be because it is not actually absorbed into the body.

Another Member indicated a concern that chemical equivalence might not have been established, and expressed particular concern that the process could produce structural isomers that are pharmacologically different. (It was subsequently confirmed that structural isomers would not be identified using this system, but also that energetic changes (initiated by water, temperature, light etc) may also result in isomerization.) This Member stated that they would prefer to see data showing the two substances produced the same pharmacological effects, as this is the ultimate way of establishing equivalence in a biological system.

One Member commented that there are essentially two ways of determining whether or not the extracts are the same. The first method is to do profiling, as has been done in this case. The main question that arises with respect to this method relates to the quantification of the molecules. The other question centres on the use of ethanol to precipitate the extract, and whether any compounds of toxicological or clinical significance are drawn out that weren't present in the original extract. The second method of establishing equivalence is that of biological testing, which is in itself very difficult, and would raise a number of issues also.

In summary, Members agreed that apart from minor concerns relating to potential isomerization and the presence or absence of unidentified component, the advice of the TGA laboratories suggesting that chemical equivalence has been established should be concurred with.

A Member expressed concern regarding the ultimate usage of the substance given the presence of advertisements on the internet for indications such as a cure for cancer. The Member questioned when such advertising of a substance might increase the potential risk associated with the substance. Subsequent discussion, during item 4.2, confirmed that while Australian-based advertisements of this kind would be in breach of the Therapeutic Goods Advertising Code, advertisements sourced from overseas could not be readily followed up although there were regular international efforts to minimise such practices.

Recommendation 55.2

CMEC recommends to the TGA that *Trametes versicolor* proteoglycan concentrate is suitable for use as an active ingredient in oral Listed medicines.

7. Safety or Efficacy Reviews

CMEC did not consider any matters under this agenda item.

8. Registration Applications

The Committee considered one matter under this agenda item.

9. Variation to a Registered Product

Nil items for consideration

10. Matters Referred from within TGA

10.1 Adverse Drug Reactions Advisory Committee (ADRAC)

A Member introduced this item to the Committee.

Members noted the adverse drug reaction reports involving complementary medicines from 289th meeting of ADRAC and requested follow up of several matters.

The Committee acknowledged with thanks the receipt of the recent ADRAC Bulletin.

A TGA Officer raised the issue of lack of knowledge around common interactions with complementary medicines, and asked the Committee to give thought to publicising this matter. This matter is also being pursued through ADRAC.

The Committee considered three further matters under this agenda item.

11. For Information

The Committee considered two matters under this agenda item.

12. Sponsor representations to CMEC

CMEC did not consider any matters under this agenda item.

13. Other Business

CMEC did not consider any matters under this agenda item.

14. Recommendation Record

Item 2 Confirmation of Draft Minutes of CMEC 54 (9 December 2005)

Recommendation 55.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 54, 9 December 2005), as amended, are a true and accurate record of that meeting.

Item 6.1 *Trametes versicolor* proteoglycan concentrate

Recommendation 55.2

CMEC recommends to the TGA that *Trametes versicolor* proteoglycan concentrate is suitable for use as an active ingredient in oral Listed medicines.

The Chair closed the meeting at 4.15 p.m.