CMEC 51
Complementary Medicines Evaluation Committee

Extracted Ratified Minutes
Fifty-first Meeting
10 June 2005

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 fifty-first meeting of the Complementary Medicines Evaluation Committee (CMEC) was held in the Botany Room, Stamford Hotel, Sydney from 9.30 a.m. to 4.30 p.m. on Friday 10 June 2005.

Members of CMEC present were:

- Associate Professor Heather Yeatman (Acting Chair)
- Dr Vicki Kotsirilos
- Associate Professor Douglas Moore
- Professor Stephen Myers
- Dr John Ryan
- Mr Kevin Ryan
- Professor Bill Webster

Present from the Therapeutic Goods Administration (TGA) were:

- Dr David Briggs
- Dr Fiona Cumming
- Dr John Hall
- Dr Leonie Hunt
- Ms Michelle McLaughlin
- Mr Karl Skewes

Other attendees:

- Mr Robert Medhurst – CMEC Expert Advisor

1. **Procedural Matters**

1.1 **Opening of Meeting**

1.2 **Apologies**

Professor Gillian Shenfield and Dr Iggy Soosay.

1.3 **Conflict of Interest**

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

2. **Ratified (out of session) Minutes of CMEC 50 (11 February 2005)**

Members noted the minutes of the fiftieth meeting of CMEC held on 11 February 2005. The Committee had previously ratified these minutes out of session.
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 Progress report on consultation papers – summary reports

TGA Officers presented the following agenda item as a PowerPoint presentation to the Committee.

Background
Following consideration by CMEC at meeting 49 (December 2004), the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) and TGA released the following Consultation Papers to Australia and New Zealand stakeholders in January 2005:

- Proposed Regulatory Definitions for Complementary Medicines and Homoeopathic and Related Medicines in a Joint Australia New Zealand Therapeutic Products Agency;
- Regulation of Herbal Medicines in a Joint Australia New Zealand Therapeutic Products Agency; and
- Regulation of Homoeopathic and Related Medicines in a Joint Australia New Zealand Therapeutic Products Agency.

The Consultation Papers proposed new regulatory definitions for complementary medicines and homoeopathic medicines, and identified issues relating to the regulation of herbal substances, and the regulation of homoeopathic and related medicines, under the joint Agency. In addition, the papers focused on the development of an appropriate regulatory system for these medicines, to meet the needs of consumers, industry, health professionals and regulators, while protecting and enhancing public health and safety in Australia and New Zealand.

Medsafe and TGA requested that stakeholders provide comment to help inform the development of a risk-based regulatory framework for complementary medicines (including herbal, homoeopathic and related medicines). Both regulatory agencies also invited stakeholders to provide any other comment to assist the development of appropriate regulatory arrangements for these types of medicines.

To clarify matters directly related to the content of the Consultation Papers, Medsafe and TGA held information sessions for stakeholders in Auckland, Christchurch, Sydney, Melbourne and Brisbane. Over 260 stakeholders attended the information sessions.

The consultation period closed on 11 March 2005. There were fifty-three submissions received from a wide range of stakeholders (thirty from Australia, twenty-one from New Zealand, one from Canada and one from Switzerland) with the following number of responses to each paper:
Regulatory Definitions for Complementary and Homoeopathic Medicines = 33 responses
Regulation of Herbal Substances = 30 responses
Regulation of Homoeopathic and Related Medicines = 29 responses

The submissions have also been used to inform the development of the draft Rules\(^1\) relating to complementary medicines under the joint Agency, as well as the development of other legislative instruments (such as Managing Director’s Orders\(^2\)) for regulating complementary medicines.

After finalisation of the Rules and Managing Director’s Orders for the joint regulatory scheme, there will be a compilation of regulatory guidance documents for the joint scheme. The current Australian Regulatory Guidelines for Complementary Medicines (ARGCM) will form the basis of the new regulatory guidance documents following consultation with stakeholders.

Priorities
The Joint Agency Establishment Group (JAEG), which includes officials from TGA and Medsafe, has responsibility for overseeing the drafting of the trans-Tasman legislation to include agreed proposals for the design and establishment of the new Joint Agency. This includes the regulatory and legislative frameworks, and governance and funding arrangements. Shortly, JAEG will be coordinating the stakeholder consultation process on the draft Rules. Therefore, the development of definitions and regulatory matters for inclusion in the draft Rules is a matter of priority. This includes definitions for complementary medicines and herbal substances. JAEG will also consider other regulatory matters raised from the complementary medicines consultation papers in the near future.

Discussion
Members discussed the draft definitions and other regulatory matters for inclusion into the draft Rules.

5. Action Arising from Previous Meetings

5.1 The Committee considered one confidential matter under this item and made one recommendation to the TGA.

5.2 Iron and prevalence of poisoning in children

Discussion
Members agreed that, based on the current evidence of the prevalence of iron poisoning from medicines in Australia, the current regulatory arrangements for medicines containing iron as an

\(^1\) The Ministerial Council will make a single set of Rules (analogous to Regulations in the current Australian and New Zealand regulatory systems). These Rules will contain much of the detail of the regulatory requirements and some institutional matters. The regulatory requirements for medicines and those for medical devices will be set out in separate parts of the Rules. There will also be a part of the Rules that deals with other therapeutic products that do not fit elsewhere in the regulatory scheme.

\(^2\) The Managing Director of the joint Agency will make Managing Director’s Orders in relation to technical matters such as standards, manufacturing principles and packaging and labelling requirements.
ingredient, in terms of packaging and labelling requirements were suitable and did not require any changes.

*CMEC Recommendation*
Members made the following recommendation:

**Recommendation 51.2**
CMEC recommends to TGA that the current regulatory arrangement requiring products with more than 5 mg iron in each solid dosage form or more than 250 mg in liquid preparations, to have child-resistant containers is adequate.

5.3 The Committee noted one confidential matter under this item.

6. **Evaluation of New Substances**
6.1 The Committee considered one confidential matter under this item and deferred making a recommendation until the sponsor provided further supporting data to the TGA.

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 TGA**
10.1 **Adverse Drug Reactions Advisory Committee (ADRAC)**
10.1.1 ADRAC - Extract of Minutes from Meeting 282

A Member introduced this item to the Committee.

Members noted the adverse drug reaction reports from 282\(^{nd}\) meeting of ADRAC.
10.1.2 ADRAC - Extract of Minutes from Meeting 283

A Member introduced this item to the Committee.

Members noted the adverse drug reaction reports from 283rd meeting of ADRAC.

10.2 Caffeine cut-off doses for labelling herbal medicines

*Background*

When originally considered by CMEC (meetings 34 & 36 in May 2002 & July 2002 respectively), the Committee considered that, as opposed to some beverages and foods, consumers might not expect complementary medicines to contain caffeine. Based on safety concerns, the Committee recommended that such medicines should have an appropriate advisory statement on the label to alert consumers to the presence of caffeine in their product.

TGA endorsed the CMEC approach and recommended that only products containing 1mg or more per dose unit required a label advisory statement together with a declaration of the actual caffeine content. TGA suggested the 1 mg per unit dose of caffeine because it appeared to be a ‘safe’ unit dose cut-off for caffeine and did not have significant pharmacological effect, even if taken as multiple doses over a day. In addition, a survey of products on the ARTG at that time indicated that there was a reasonably natural grouping of products either side of the 1mg cut-off making it slightly easy to identify those products affected by this requirement.

In June 2004, TGA consulted with industry on the issue and out of 135 sponsors sent letters, 18 responded, including one industry association. A number of sponsors suggested, with limited scientific justification that the cut-off dose, which triggered the labelling requirement, should be between 10 to 50 mg of caffeine per daily dose instead of the proposed 1 mg per unit dose. Following this consultation process, TGA sought further advice from CMEC.

TGA conducted a new literature search in an effort to identify a level for caffeine at which measurable physiological effects did not occur. Literature supported the existence of a threshold for the central nervous system (CNS) stimulatory affects of oral caffeine in adults, at somewhere around 20 mg. TGA has considered that it is the CNS effects, which would be of interest to consumers wishing to avoid them, particularly where ingestion of caffeine by children might be of concern. Inhibition of central adenosine receptors is regarded as the likely mechanism of caffeine’s CNS effects and as has been reported to CMEC previously during its consideration of guarana labelling for caffeine in June 1999 (meeting 13), the 20 mg oral dose approximates that which produces measurable adenosine receptor blockade.

TGA sought advice from CMEC about the following two caffeine content cut-off proposals:

- The trigger for the labelling requirement would be for medicines that contained 1 mg or below of caffeine per recommended unit dose. The rationale for this proposal was that
this dose was unlikely to have any biological activity and it was a somewhat natural
divide between products on the ARTG; or

- The trigger for the labelling requirement would be for medicines that contained 10 mg or
below of caffeine per recommended daily dose. The rationale for this proposal was that
the literature supported an absence of measurable biological effects of caffeine below
about 20mg and by applying the appropriate ‘safety factors’, established a limit of 10mg
per recommended daily dose for caffeine (compared with a single unit dose).

Discussion
Several Members supported the premise that consumers probably wanted to know if there was
any caffeine present in their complementary medicine. Members considered that this was
especially important for individuals who could potentially obtain caffeine from a number of
medicinal and dietary sources and were hypersensitive to it. One Member remarked that
although the evidence for hypersensitivity was mostly anecdotal, there was a need for sponsors
to declare the amounts of caffeine above 1 mg per unit dose. TGA Officers explained that it was
difficult for TGA to justify making such a regulatory decision based on the current scientific,
safety evidence for caffeine. One Officer suggested that the Committee consider setting a
‘trigger’ for the requirement for declaring the amount of caffeine in a medicine, by establishing a
maximum daily dose of caffeine. Another Member mentioned that TGA should also note, “That
consumer choice is a safety factor” for this matter. Yet another Member proposed that there be a
division for declarable amounts above a certain level of caffeine whereas below this level a
sponsor would only require the inclusion of a label advisory statement similar to “contains small
amounts of caffeine”. A TGA Officer confirmed that this was a possible way of addressing the
concerns of the Committee. The Officer asked the Committee whether they would consider the
following proposals in their recommendations to TGA:

- medicines that had a maximum recommended daily dose of greater than 10 mg of
caffeine would have to declare the content of caffeine on the product label (in milligrams
caffeine per unit dose); and
- medicines that contained 1mg or more of caffeine per dosage unit but for which a
maximum daily dose of 10 mg or less of caffeine was recommended, should carry a label
advisory statement: “contains small amounts of caffeine” (or words to that effect).

Members also considered the situation where it might be difficult to calculate the maximum
recommended dose of a medicine, which included a caffeine-containing herb, e.g. “Take 2
tablets as required”. Members agreed that, for the purposes of compliance with these new
caffeine-labelling requirements, the dose calculation would be by assuming the recommended
dose to be the maximum recommended dose. In the example above, “Take 2 tablets as
required”, the caffeine provided by two tablets would determine, if any, the labelling required.

Members agreed that these proposals adequately addressed the safety concerns for consumers of
medicines containing caffeine.

CMEC Recommendations:
Members made the following recommendations:
**Recommendation 51.3**

CMEC recommends to TGA that complementary medicines that have a maximum recommended daily dose of greater than 10 mg of caffeine must declare the content of caffeine on the product label (milligrams caffeine per unit dose).

**Recommendation 51.4**

CMEC recommends to TGA that complementary medicines that contain 1mg or more of caffeine per dosage unit and which provide a recommended maximum daily dose containing 10 mg or less of caffeine should carry the following label statement: “The recommended dose of this medicine provides a small amount of caffeine” (or words to that affect).

TGA is now considering these recommendations.

**10.3 Results of Arthrospira (Spirulina) consultation**

The Committee deferred this agenda item to the next scheduled meeting of CMEC.

**10.4 Proposed scheduling arrangements**

The Committee deferred this agenda item to the next scheduled meeting of CMEC.

**10.5** The Committee noted one confidential matter under this item.

**10.6 Required Advisory Statements for Medicine Labels (RASML)**

The Committee deferred this agenda item to the next scheduled meeting of CMEC.

**10.7 Approval of sodium monofluorophosphate for use in listed medicines**

The Committee deferred this agenda item to the next scheduled meeting of CMEC.

**10.8 Approval of citric acid monohydrate and anhydrous citric acid**

The Committee deferred this agenda item to the next scheduled meeting of CMEC.
10.9 The Committee deferred this agenda item to the next scheduled meeting of CMEC.

10.10 The Committee deferred this agenda item to the next scheduled meeting of CMEC.

10.10 Government response to Expert Committee on Complementary Medicines in the Health System (ECCMHS) recommendations

The Committee deferred this agenda item to the next scheduled meeting of CMEC.

11. For Information
11.1 Press and journal articles
11.1.1 Leafy greens: the acid test of evolution (Sydney Morning Herald)

Members noted a recent newspaper report that cited evidence from a Nature Reviews article that claimed that diets high in folic acid could be slowly affecting human evolution.

11.1.2 Folic acid – vitamin and panacea or genetic time bomb? (Nature Reviews)

Members noted a recent journal article that claimed that diets high in folic acid could be slowly affecting human evolution.

11.1.3 Effect of Coenzyme Q10 and Ginkgo biloba on warfarin dosage in stable, long-term warfarin treated outpatients. (Thromb. Haemost.)

Members noted a report that studied the effects of coenzyme Q10 and Ginkgo biloba on warfarin dosage in warfarin treated patients.

11.1.4 Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects (British Journ. of Clinical Pharm.)

Members noted a report that studied the effects of Ginkgo biloba and ginger on warfarin dosage in healthy subjects.

11.1.5 Effects of long-term vitamin E supplementation on cardiovascular events and cancer (JAMA)

Members noted a report that studied the effects of vitamin E supplementation on cardiovascular events and cancer.
11.1.6 Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John’s wort) (*BMJ*)

Members noted a report that studied the effects of hypericum extract WS 5570 in acute treatment of moderate to severe depression.

11.1.7 St. Johns Wort (*Choice magazine*)

Members noted a magazine article that investigated the evidence used by Australian sponsors in support of the use of St. Johns wort in treating mild depression.

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 5.2 Action Arising from Previous Meetings - Iron and prevalence of poisoning in children**

**Recommendation 51.2**

CMEC recommends to TGA that the current regulatory arrangement requiring products with more than 5 mg iron in each solid dosage form or more than 250 mg in liquid preparations, to have child-resistant containers is adequate.

**Item 10.2 Matters Referred from within TGA - Caffeine cut-off doses for herbal medicines**

**Recommendation 51.3**

CMEC recommends to TGA that complementary medicines that have a maximum recommended daily dose of greater than 10 mg of caffeine must declare the content of caffeine on the product label (milligrams caffeine per unit dose).
Recommendation 51.4

CMEC recommends to TGA that complementary medicines that contain 1mg or more of caffeine per dosage unit and which provide a recommended maximum daily dose containing 10 mg or less of caffeine should carry the following label statement: “The recommended dose of this medicine provides a small amount of caffeine” (or words to that effect).

The Acting Chair closed the meeting at 4.30 p.m.