COMPLEMENTARY MEDICINES EVALUATION COMMITTEE

Extracted Ratified Minutes
Sixty-second Meeting
8 June 2007

Abbreviations:
ADR Adverse Drug Reaction
ADRAC Adverse Drug Reactions Advisory Committee
ADRU Adverse Drug Reactions Unit
ADEC Australian Drug Evaluation Committee
ANZTPA Australia New Zealand Therapeutic Products Authority
ARTG Australian Register of Therapeutic Goods
CMEC Complementary Medicines Evaluation Committee
CPI Customs Prohibited Import
EA Expert Advisor
ECCMHS Expert Committee on Complementary Medicines in the Health System
EDS Experimental Drugs Section
ELF Electronic Lodgement Facility
FDA Food and Drug Administration
FSANZ Food Standards Australia New Zealand
GMP Good Manufacturing Practice
IJJEACCM Interim Joint Expert Advisory Committee on Complementary Medicines
LD₅₀ Lethal Dose, 50%
NCCTG National Coordinating Committee on Therapeutic Goods
NDPSC National Drugs and Poisons Schedule Committee
NOEL No-Observed-Effect-Level
NTP National Toxicology Program
OCM Office of Complementary Medicines
OTC Over-the-Counter
RE Retinol Equivalents
The Complementary Medicines Evaluation Committee (CMEC) held its sixty-second meeting in the Botany Room, Stamford Hotel Sydney Airport, Sydney, from 9.35 a.m. to 3.00 p.m. on Friday 8th June 2007.

Members of CMEC present were:
Professor Tony Smith (Chair)
Professor Alan Bensoussan (afternoon session)
Dr Vicki Kotsirilos
Associate Professor Douglas Moore
Professor Stephen Myers
Mr Kevin Ryan
Professor Gillian Shenfield
Professor Bill Webster (morning session)

Present from the Therapeutic Goods Administration (TGA) were:
Dr David Briggs
Dr Rohan Hammett (afternoon session)
Dr Andrea Hinschen
Ms Michelle McLaethlin

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**
Associate Professor Heather Yeatman

1.3 **Conflict of Interest**
Members submitted, to the Chair, conflict of interest declarations specific to agenda items for this meeting.
CONFIRMATION OF MINUTES OF CMEC 61 (13 APRIL 2007)

Members accepted the minutes of the sixty-first meeting of CMEC as an accurate record of proceedings, subject to minor amendments.

Members made the following recommendation:

Recommendation 62.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 61, 13 April 2007), as amended, are a true and accurate record of that meeting.

GUIDELINES ON LEVELS AND KINDS OF EVIDENCE TO SUPPORT CLAIMS FOR THERAPEUTIC GOODS (GUIDELINES)

CMEC did not consider any matters under this agenda item.

JOINT AUSTRALIAN / NEW ZEALAND THERAPEUTIC PRODUCTS AGENCY MATTERS

Draft Therapeutic Products Order: Homoeopathic & Anthroposophic Medicines

Background

A TGA Officer introduced this item, reminding Members that following consultation with stakeholders, homoeopathic and anthroposophic medicines will be regulated under the proposed Australia New Zealand joint regulatory scheme. The Officer tabled a draft Therapeutic Products Order (TPO), indicating that this is one of a number of legislative and guidance documents currently being developed to support the proposed regulatory scheme. Members noted that the draft TPO includes relevant definitions for this group of remedies, outlines the relevant accepted pharmacopoeia, and lists the ingredients which may be used as starting materials in the preparation of various groups of homoeopathic and anthroposophic medicine. Restrictions are specified where necessary.

Members were advised that medicines schedules in the draft TPO will be populated with lists of mother substances from which homoeopathic and anthroposophic preparations may be derived.

Following TGA/Medsafe approval, and subsequent interim Ministerial Council approval as required, the draft TPO will be released for stakeholder consultation.

Discussion

CMEC endorsed in principle the draft Therapeutic Products Order for Homoeopathic and Anthroposophic medicines, prior to its release for stakeholder consultation in Australia and New Zealand.

Members remarked on the amount of work undertaken on this project, and the interesting matters raised in the draft TPO.
5 ACTION ARISING FROM PREVIOUS MEETINGS

5.1
CMEC considered one matter under this agenda item.

6 EVALUATION OF NEW SUBSTANCES
CMEC did not consider any matters under this agenda item.

7 SAFETY OR EFFICACY REVIEWS

7.1
CMEC considered one matter under this agenda item.

7.2.1
CMEC considered one matter under this agenda item.

7.2.2 Review of Curculigo orchioides

Background
A TGA Officer introduced this item, advising Members that a potential safety concern had been identified with respect to Curculigo orchioides. Members noted that high oral doses of the herb have been associated with specific adverse effects, including sweating, numbness of the limbs, swollen tongue, agitation and loss of consciousness.

Members were informed that the root of the herb C. orchioides has a tradition of use in both Traditional Chinese Medicine (TCM) and in Ayurvedic Medicine. The traditional dose for C. orchioides root in TCM is 3-10 g/day, and in Ayurvedic medicine the doses are reported to be 3-11 g/day.

Caution with respect to the use of large doses of the herb have been reported in various Chinese Medicine Herbal texts. However this caution has not been quantified in terms of dosage. Members were advised that the same caution does not appear in Ayurvedic texts, nor did the safety review identify any published papers that support or explain the traditional warning associated with the herb’s use in TCM.

The TGA Officer explained that a CMEC Expert Advisor on Ayurvedic medicine has advised the OCM that the herb is widely used in Ayurveda, with no restriction placed on its use.

According to TCM philosophy, C. orchioides has acrid, hot properties, and is associated with the kidney, liver and spleen meridians. It is used to strengthen yang and should not be used in conditions of yin deficiency. In TCM philosophy, as C. orchioides is a warming, yang strengthening herb, overdose, or use of the herb for long periods can be associated with symptoms of “excess heat”, ranging from dry mouth to unconsciousness.
Members noted that *C. orchioides* root or rhizome is currently included in 22 medicines (including 1 export-only product) Listed in the ARTG, with the equivalent amount of herb ranging from 16.2 mg to 406.84 mg per dosage unit.

Pre-clinical data for the herb are very limited and not suggestive of toxicity. No safe dose level of the herb has been established in the clinical setting.

There have been no reported adverse events for *C. orchioides* in Australia, nor in the World Health Organisation (WHO) database.

Members were asked to consider the acceptability of placing a restriction on the amount of a herbal ingredient based on accepted TCM use, even though scientific validation for this restriction could not currently be established. Further to this, CMEC’s advice was sought as to whether a change to the regulatory status of this herb was warranted.

**Discussion**

A Member commented that there is very little known about the serious adverse effects purported for this herb, except that they seem to be associated with ‘high’ doses. Although unclear as to what constituted a ‘high’ dose, it was presumed that this was at least 9-10 g/day. A TGA Officer responded that the TCM Expert Advisor had indicated that this was around 12 g/day.

A Member advised the Committee that unlike western herbal medicine, where herbs can be used in isolation, TCM tends to utilise patent formulas where herbs are generally always used in a fixed combination. The Member suggested that the Chinese, being often much more methodical than many other herbal traditions, were acutely aware of the toxicity of herbs. As a consequence of experience and experimentation, toxicity is reduced by combining herbs in such a way as to enhance the therapeutic effect and dampen the toxic effect. It follows that such herbs should only be able to be used in low risk medicines in traditional formulations.

With respect to the few toxicity studies reported, Members noted that a single oral dose toxicity in mice showed no deaths at [presumably] 15 g/kg [paper stated 150 g/kg, but appears in err]. Members considered this sub-chronic study conducted in rats given alcoholic extracts of particular herbs at high doses for 2 weeks to be a reasonable study, and acknowledged that a substance would have to be quite safe if it did not kill anything at the high doses given (5 and 10 g/kg/day). A Member stated that while there was no evidence of any real toxicity, there was no information about concentration in these doses.

However, this study is countered by another sub-chronic study mouse study reporting an LD$_{50}$ (Lethal Dose, 50%) at 15 g/kg, but no effect reported at 10 g/kg/day. The differences between these studies, made it difficult to make any firm conclusions. Nonetheless, Members considered that there was no obvious toxicity exhibited.

Members discussed the implications of requiring a restriction for a herb based on TCM usage, when there is no apparent concern in relation to its use in Ayurvedic medicine. Members concluded that Chinese herbal medicine prescriptions are generally in the form of patent or fixed combinations, and this may reflect a high degree of traditional understanding of the limitations of the herb.

Notwithstanding this, a Member further remarked that even in isolation, this preparation appeared to be of very low toxicity.

A Member then queried whether all 22 products on the ARTG were multi-ingredient preparations, noting the large range of *C. orchioides* dry weight equivalence, from 16.2 to 406.84 mg. A TGA Officer responded that this was not known, but it was possible that some
of these figures may have been based on theoretical equivalent doses, given that many traditional formulations are co-prepared (i.e., multiple herbs are extracted/prepared together).

Several Members considered that if the Committee was to maintain a consistent approach, similar credence should be given to a traditional history of a safety concern, particularly where applied within a particular therapeutic paradigm, as to traditional history of safe use supporting safety. A Member pointed out that a dose limit on this herb would not be inconsistent with its traditional (TCM) use, and that all products currently on the ARTG are well under this limit, so would not be affected. Moreover, they considered this dose limit should be controlled.

A TGA Officer commented that if traditional Ayurvedic doses were below the proposed maximum daily dose limit, as appeared to be the case, then there would not really be an issue in this respect either. Members also recognised that alcoholic preparations are often used in TCM, in contrast to the preparations used in Ayurveda, and this may also influence the relative safety profiles.

A Member remarked that even if there were many traditions using this particular herb, and for some reason only two or three traditions identified some risks associated with its use, it would be negligent not to recognise the perceived concerns, as differences between traditions might relate to issues such as genetic makeup of the indigenous group, etc. Such differences are recognised for pharmaceuticals.

Nonetheless, the Member considered that from a regulatory point of view, it was a matter of being prudent in recognising these concerns, which have been documented historically in China. Given that a dosage restriction would not impact on current products, and practitioners could still access higher doses if required, this would appear a responsible and pragmatic approach.

Members also noted that with respect to imposing a possible maximum daily dose limit, labels should remain unchanged, with the only difference being a flagged dosage limit in ELF.

In summary, Members supported restriction of *C. orchioides* use via a maximum daily dose limit of 10g, based on a history of TCM concerns. Given there was no traditional evidence of use for any other plant part of *C. orchioides* other than the root (or rhizome) in both TCM and Ayurvedic paradigms, only this plant part was considered suitable for use in Listed medicines.

**Members made the following recommendations:**

<table>
<thead>
<tr>
<th>Recommendation 62.3.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>That the root or rhizome of <em>Curculigo orchioides</em> is suitable for use as an ingredient in Listed medicines, with a restriction on the maximum daily dose equivalent to not more than 10 g/day.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation 62.3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>That only the root or rhizome of <em>Curculigo orchioides</em> is currently suitable for use as an ingredient in Listed medicines.</td>
</tr>
</tbody>
</table>
7.2.3
CMEC considered one matter under this agenda item.

7.2.4    Review of *Citrullus colocynthis*

*Background*
A TGA Officer introduced this item, advising Members that the NDPSC has asked the OCM to consider the safety and regulation of ‘Colocynth’, as they move towards harmonising the scheduling arrangements between Australia and New Zealand.

‘Colocynth’ is currently scheduled as ‘Pharmacy only’ in New Zealand, and the use of colocynthis was banned in the USA in 1991 by the FDA. However, the use of *C. colocynthis* is currently not restricted in Australia.

Various parts of the plant have been used traditionally, notably in Ayurvedic and Arabic medicine. The root of *C. colocynthis* has been used for jaundice, ascites, urinary disease and rheumatism. The seed of *C. colocynthis* has been used topically for hair growth, sterility, snake bites and neuralgia. The fruit is an irritant cathartic and a drastic purgative. It is used for constipation, painful menstruation, jaundice, intestinal cramps, neuralgia, and as an abortifacient.

Members noted that internal use of the herb has been reported to cause severe irritation of gastric mucosa, bloody diarrhoea, kidney damage, haemorrhagic cystitis, diuresis leaning to anuria, and acute toxic colitis. Caution with respect to the use of the herb is reported in various herbal texts and also in scientific papers. The alkaloid colocynthin has been reported to be the ‘cathartic bitter principle’.

There are currently 20 medicines Listed in the ARTG containing *C. colocynthis*. Of these, 15 medicines contain homoeopathic preparations of the fruit, and 5 medicines contain the ‘herb’ of *C. colocynthis* (although these are unlikely to be in supply).

Pre-clinical data suggest that the fruit of *C. colocynthis* has a well-defined toxicological profile relating to gastrointestinal toxicity. Similarly, a number of cases of severe gastrointestinal adverse reactions following intake of traditional preparations of the fruit have been reported in the medical literature.

The Adverse Drug Reactions Unit (ADRU) has only one adverse report recorded in 2004 relating to a female who suffered nausea from a multi-ingredient ‘detox-kit’ containing ‘Citrullus’ (no AUST L provided). However, this may be reflective of the lack of use of the herb in products.

In considering the regulatory options for this herb, CMEC was asked to recognise its valid use as a homoeopathic, and the current scheduling of the herb in New Zealand.

*Discussion*
A Member pointed out that this herb is widely used by homoeopaths, in a variety of indications (particularly those involving painful varieties of diarrhoea, such as colic), in a wide range of potencies (possibly up to 30 centesimal (30C)).

Members discussed whether the potency limit of ‘not less than 4X’ for homoeopathic remedies was appropriate (as proposed in one of the options set out for CMEC), and the potential impact on homoeopathic products already on the ARTG. Members noted that *C. colocynthis* is used in
a wide range of potencies from around 6X up to possibly 30C in some over-the-counter (OTC) products, and that the potency of the substance in these products is generally based on what is known to work well in a wide group of people.

A Member expressed concern that there is potential for inaccuracies with potenisation, doses or usage of *C. colocynthis*, and it is therefore not suitable for use in Listed medicines. Another Member acknowledged this concern, but pointed out that homoeopathic preparations are clearly labelled as homoeopathic.

Given its wide-spread use, Members were in favour, with one exception, of retaining *C. colocynthis* as an ingredient in Listed medicines. However, this was on the basis that products would be limited to homoeopathic remedies with a potency of not less than 4X, given its potential for severe clinical toxicity, recognising that ‘typical’ homoeopathic use is at potencies ranging from 6X to 30C.

A Member commented that this decision was also consistent with that taken by the United States FDA, with the exception of homoeopathics. However, a TGA Officer remarked that they may actually regulate homoeopathics separately.

In summary, CMEC considered that *C. colocynthis* should continue to be available on the basis of its wide-spread use, but limited to homoeopathic remedies with a potency of not less than 4X on the basis of its potential for severe clinical toxicity.

**Members made the following recommendation:**

CMEC, having considered a preliminary safety review of *Citrullus colocynthis* Schrad. L., makes the following recommendation to the TGA:

Recommendation 62.5

*That *Citrullus colocynthis* may only be included as an ingredient in Listed medicines as a homoeopathic preparation, at a potency of not less than 4X.*

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) Meeting 299

A CMEC Member introduced this item to the Committee.

CMEC noted the adverse drug reaction reports involving complementary medicines, considered at the 299th meeting of ADRAC.
Complementary medicine issues

Members discussed complementary medicine issues of interest from the 299th meeting of ADRAC.

Case reports

Members discussed case reports of interest from the meeting.

10.2 Changes to the scheduling of selenium

Background

A TGA Officer introduced this item, advising Members that in February 2007, the National Drugs and Poisons Committee (NDPSC) proposed amendments to the scheduling of selenium in the SUSDP as part of the harmonisation of substance regulation between Australia and New Zealand.

Currently, medicines Listed in Australia may only contain a maximum of 26 micrograms of organic selenium, or 52 micrograms of inorganic selenium (or a combination of these forms) per daily dose. However, if the SUSDP amendments come into effect, the proposed selenium scheduling will allow Listed medicines to contain up to 150 micrograms of selenium as an ingredient.

As proposed, the new scheduling for selenium does not specify differentiated restrictions for the organic or inorganic forms.

Members were advised that the OCM has discussed this issue with the NDPSC, and has been informed that it will be considered at the next NDPSC meeting scheduled for 26/28 June.

The SUSDP amendments, as they stand, are due to come in to effect on the 1st of September 2007, if there is no further change at the next NDPSC meeting.

Members were asked to note that:

- the NDPSC has proposed amendments to the scheduling of selenium;
- the proposed amendments will affect current restrictions on selenium in Listed medicines;
- the NDPSC intends to review the initial proposal in order to address apparent differences in bioavailability between organic and inorganic forms of selenium; and
- the OCM will provide Members with an update on this issue at CMEC 63.

Discussion

A Member indicated that this move would be welcomed as some practitioners wish to use higher levels of selenium (up to approximately 100 µg), particularly in the treatment of fatty liver disease. A Member recalled that this limit had been initially recommended by the CMEC, and was based on the WHO limit of 400 micrograms, which is considered an acceptable safe limit (associated with no toxicity concerns).

A TGA Officer advised that a large number of intervention studies were conducted in selenium deficient areas, particularly in China, where relatively large doses have been tolerated over a 10 year period. In this context, concerns related not to the increase in selenium, but to whether
there is a need for distinguishing between the organic and inorganic forms on the basis of bioavailability.

A TGA Officer also highlighted that the change in the level of selenium permitted in Listed medicines would need to be reflected in the label advisory statements.

In summary, the Committee concluded that the proposed amendment to selenium scheduling did not raise concerns, and in fact this change might be welcomed. However, there were still unresolved issues surrounding the differentiation between the organic and inorganic forms. The Committee noted that this would be discussed at the next NDPSC meeting, and that CMEC would be informed of the outcome at CMEC63.

10.3 Changes to the scheduling of vitamin A

Background

A TGA Officer introduced this item, advising Members that in February 2007, the NDPSC proposed amendments to the scheduling of vitamin A in the SUSDP as part of the harmonisation of substance’s regulation between Australia and New Zealand.

Currently, Listed medicines may only contain 5000 IU or less of vitamin A. However, if the SUSDP amendments come in to effect, the proposed vitamin A scheduling will allow Listed medicines to contain up to 3000 µg Retinol Equivalents (RE) (10,000 IU) as an ingredient.

The OCM has been informed by the NDPSC that the scheduling of vitamin A will be considered again at the Committee’s next meeting (scheduled for 26/28 June), particularly with respect to whether a warning for pregnancy should apply.

The SUSDP amendments, as they stand, are due to come in to effect on the 1st of September 2007, if there is no further change at the next NDPSC meeting.

Members were asked to note that:

- the NDPSC has proposed amendments to the scheduling of vitamin A;
- the proposed amendments will affect current restrictions on vitamin A in Listed medicines;
- the OCM has sent a Minute to NDPSC requesting they consider the issue of whether different cut-offs should be given between adults and children; and
- the OCM will provide Members with an update on this issue at CMEC 63.

Discussion

Members noted that the NDPSC had already been advised of concerns relating to scheduling cut-offs for children. Members noted that the issue of whether a warning label for pregnancy should apply was to be discussed at the next meeting.

11 FOR INFORMATION

11.1

CMEC considered one matter under this agenda item.
11.2 Article in the Australian newspaper: Vitamins link to prostate deaths
CMEC noted the article in the Australian newspaper: Vitamins link to prostate deaths, and the article in the JNCI: Multivitamin Use and Risk of Prostate Cancer in the National Institutes of Health – AARP Diet and Health Study.

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 61 (13 April 2007)
Recommendation 62.1
CMEC confirms that the draft Minutes of its previous meeting (CMEC 61, 13 April 2007), as amended, are a true and accurate record of that meeting.

Item 7.2.2 Review of Curculigo orchioides
CMEC, having considered a preliminary safety review of Curculigo orchioides Gaertn., makes the following recommendations to the TGA:
Recommendation 62.3.1
That the root or rhizome of Curculigo orchioides is suitable for use as an ingredient in Listed medicines, with a restriction on the maximum daily dose equivalent to not more than 10 g/day.
Recommendation 62.3.2
That only the root or rhizome of C. orchioides is currently suitable for use as an ingredient in Listed medicines.

Item 7.2.4 Review of Citrullus colocynthis
CMEC, having considered a preliminary safety review of Citrullus colocynthis Schrad. L., makes the following recommendation to the TGA:
Recommendation 62.5
That Citrullus colocynthis may only be included as an ingredient in Listed medicines as a homoeopathic preparation, at a potency of not less than 4X.

The Chair closed the meeting at 3:00 pm.