Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CMEC 70 COMPLEMENTARY MEDICINES EVALUATION COMMITTEE

EXTRACTED RATIFIED MINUTES SEVENTIETH MEETING 12 DECEMBER 2008

ABBREVIATIONS

ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
ADRs	Adverse Drug Reactions
ADRU	Adverse Drug Reaction Unit
AHS	Australian Approved Herbal Name
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self-Medication Industry Organisation
BP	*British Pharmacopoeia*
BWI	Bovine Whey Immunoglobulins
CAM	Complementary and Alternative Medicines
CATAG	Council of Australian Therapeutics Advisory Group
CHC	Complementary Healthcare Council
CMEC	Complementary Medicines Evaluation Committee
EAA	Excitatory Amino Acid
EAG	Expert Advisory Group
EFSA	European Food Safety Authority
EP	*European Pharmacopoeia*
EU	European Union
FSANZ	Food Standards Australia New Zealand
IP	Intraperitoneal

IU	International Units
IV	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LFT	Liver Function Test
LOEL	Lowest Observed Effect Level
MEC	Medicine Evaluation Committee
NDPSC	National Drugs and Poisons Schedule Committee
NH&MRC	National Health and Medical Research Council
NOEL	No Observed Effect Level
NPNZ	Natural Products New Zealand
OCM	Office of Complementary Medicines
OICG	Office of Complementary Medicines/ Industry Consultation Group
OMSM	Office of Medicines Safety Monitoring
PPRC	*Pharmacopoeia of the People's Republic of China*
RDI	Recommended Daily Intake
SATCM	State Drug Administration of the Republic of China
SDS-PAGE	Sodium dodecyl sulphate – polyacrylamide gel
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
UWS	University of Western Sydney

The Complementary Medicines Evaluation Committee (CMEC) held its seventieth meeting in the Hilton Hotel, Melbourne Airport, from 9.30 a.m. to 4 p.m. on Friday 12th December 2008.

Members of CMEC present

Emeritus Professor Tony Smith (Chair)
Professor Alan Bensoussan
Dr Richard Oppenheim
Dr Vicki Kotsirilos
Ms Karen Martin
Professor Stephen Myers
Mr Kevin Ryan
Dr Hans Wohlmuth
Dr Lesley Braun
Dr Gary Deed
Professor Bill Webster

Present from the Therapeutic Goods Administration (TGA)

Professor David Briggs
Ms Michelle McLaughlin
Ms Diane Wilkinson
Ms Nicola Powell

1 PROCEDURAL MATTERS

1.1 Opening of Meeting

The Chair opened the meeting at 9:30 am, welcoming CMEC Members and TGA staff.

Members noted with regret the resignation of Professor David Briggs from his position as the Head of the Office of Complementary Medicines (OCM) and the Secretary of the Complementary Medicines Evaluation Committee (CMEC). The Chair and Members acknowledged Prof Briggs' very valuable contributions to the work of the Committee, and wished him well in his future endeavours.

1.2 Apologies

Dr Ruth Lopert (TGA Principal Medical Advisor).

1.3 Conflict of Interest

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

2. CONFIRMATION OF DRAFT MINUTES OF CMEC 69 (10 OCTOBER 2008)

Members accepted the Minutes of the sixty-ninth meeting of CMEC as an accurate record of proceedings, subject to minor amendment.

Members made the following recommendation:

Recommendation 70.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 69, 10 October 2008), as amended, are a true and accurate record of that meeting.

3. GUIDELINES ON LEVELS AND KINDS OF EVIDENCE TO SUPPORT CLAIMS

CMEC did not consider any matters under this agenda item.

4. ACTION ARISING FROM PREVIOUS MEETINGS

4.1 Vitamin E update

A TGA Officer informed CMEC of the outcome of meetings between the TGA and representatives from industry and other regulatory authorities, in relation to potential safety concerns with vitamin E. The Committee noted that they would be informed of any progress of this matter.

OUTCOME

CMEC noted the developments in relation to this issue.

4.2 *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* update

Background

A TGA Officer introduced this item, reminding Members that a safety review of *Glycyrrhiza glabra* and *Glycyrrhiza uralensis* was considered by the Committee at CMEC 68. At this time Members recommended that medicines containing these ingredients should include a label advisory statement, with wording to the effect: *"Contains liquorice. Not suitable for people with a history of high blood pressure, or who are pregnant, or have kidney disease"*.

At CMEC 69, Members raised two additional issues. Firstly, Members questioned whether the label advisory statement should include a reference to breastfeeding; and secondly, Members questioned whether a cut-off dose could be established, below which the advisory statement would not apply.

Members were informed that the TGA library had expanded and updated the previous literature search on these herbs, specifically targeting the use of liquorice during breastfeeding. However, no scientific evidence to support the contraindication of liquorice during breastfeeding was found. That given, Members noted it was feasible that glycyrrhetinic acid (the metabolite of toxicological concern) is transferred into breast milk. However, how susceptible infants are to the effects of glycyrrhetinic acid is not known.

At CMEC 69, Members noted the common use of liquorice in medicines as a flavouring agent or sweetener in non-therapeutic doses, and considered that the proposed advisory statement had the potential to have a significant impact on over 70% of traditional Chinese medicines.

The Officer advised that a review of medicines included in the ARTG containing liquorice as an ingredient had revealed that in the vast majority of products, the liquorice ingredient is declared as an active ingredient, even in those with relatively low amounts of the ingredient.

There are only a relatively small number of products that contain liquorice as an excipient ingredient. In these products the levels of liquorice vary widely, with some products containing liquorice in relatively high levels per unit dose. As there is no limit to the quantity of liquorice permitted when declared as an excipient, the Officer advised that it does not appear to be appropriate to exempt products from the advisory statement on the basis of their declared use as an excipient.

Members also noted that a large proportion of TCM liquorice products contain quite low levels of *G. uralensis* per unit dose. Ostensibly, the liquorice levels are sufficiently low in many of these products that an adverse reaction should not be invoked in any of the groups of concern, even taking into account the possibility of high glycyrrhizin content. However, it is likely that the typical recommended daily dose for this type of product comprises many unit doses, so in practice, they may not be low daily dose products at all.

Members noted the evaluator comment that a maximum daily dose cut-off level of 10 mg equivalent herb would, at the most, provide only a few mg of glycyrrhizin. At such a low dose, groups at risk of adverse reactions are unlikely to be affected, particularly given that glycyrrhizin consumed in the diet is likely to be far greater than that provided in such a low-dose therapeutic product.

At CMEC 69, Members noted that the glycyrrhizin content is not required to be entered for products included in the ARTG. Therefore, it was recognised that it may not be practical to propose a cut-off level based on glycyrrhizin content, as this would entail a significant impost on industry to demonstrate, analytically, that the glycyrrhizin content was below the cut-off dose in each Listed product.

The Officer concluded that, due to lack of scientific evidence for determination of a cut-off dose level, and considering that glycyrrhizin levels are not available for most Listed products, and that a parallel dietary intake is also likely, any cut-off dose level for the inclusion of the label advisory statement is likely to be speculative.

In addition to providing advice on whether the proposed advisory statement should be expanded to include a contraindication when breastfeeding, and in relation to the feasibility of adopting a maximum daily dose cut-off level for *G. glabra* and *G. uralensis* (or glycyrrhizin) below which the label advisory statement would not apply, the CMEC was also asked to consider if the proposed advisory statement should be amended to specify oral products only.

Discussion

Lack of information

Members noted that there was insufficient information on which to base a decision about an advisory statement in relation to liquorice. In particular, there was limited information in relation to doses.

Breast milk

Members agreed that while there was no concrete evidence that glycyrrhizin was transferred into breast milk, it was highly likely that this occurs. However, the significance of this to an infant is unclear.

Members noted a Japanese paper by Shimada *et al.* (1984) [Simultaneous determination of ephedrine and glycyrrhizin in human breast milk by high performance liquid chromatography *Yakugaku Zasshi* 104: 347-50] and requested that the OCM acquire an English translation of this paper and provide it to Members for their consideration.

Pregnancy

A Member noted that the CMEC 68 recommendation included an advisory statement against the use of liquorice in pregnancy and questioned the basis of this recommendation. The Member considered that this was a deviation from previous CMEC considerations, where the Committee had advised that if an ingredient should be avoided in pregnancy, it was subsequently not suitable for inclusion in Listed medicines.

Other Members concurred, noting a study by Strandberg *et al.* (2002) [Preterm birth and liquorice consumption during pregnancy *American Journal of Clinical Epidemiology* 156: 803-805) in which glycyrrhizin was administered to pregnant women and, at doses greater than 500 mg, an increase in preterm infants was demonstrated. Members noted that this is the only literature source indicating a contraindication in pregnancy.

Members considered that low dose liquorice in pregnancy was not likely to be a safety concern, but pregnant women who consume high dosages of liquorice may be at risk of adverse events. However, while it was well established that high doses of liquorice can cause adverse effects, it has not been demonstrated that a pregnant woman would be at any higher risk than that of the general population.

Traditional and scientific evidence

Members discussed traditional warnings which contraindicate the use of liquorice in pregnancy, acknowledging that a number of references contain this contraindication. Members debated the issue of traditional *versus* scientific evidence. Some Members, while acknowledging the importance of traditional advice, considered that traditional contraindications could not stand alone if there is differing scientific evidence. These Members maintained that while there are traditional contraindications against the use of liquorice in pregnancy, the scientific evidence, at present, indicates that there is little risk from small amounts of glycyrrhizin.

However, other Members disagreed, stating that the traditional contraindication for liquorice in pregnancy is supported by the herb's known pharmacological activity. Liquorice is known to decrease renin and aldosterone, resulting in an antidiuretic action. It was considered feasible that traditional contraindications may have resulted from erring on the side of caution, given that the effect of liquorice in pregnancy is unknown.

One Member reminded the Committee that, at CMEC 68, the Committee considered that the traditional and pharmacological activity of liquorice supported avoiding the use of this herb in pregnancy.

A Member brought to the Committee's attention a paper by Bernardi *et al.* (1994) [Effects of prolonged ingestion of graded doses of liquorice by healthy volunteers *Life Sci*. 1994; 55 (11):863-872]. This study showed that high levels of glycyrrhizin resulted in hypertension, hypokalemia and peripheral oedema. The levels reported to cause adverse events were 4.97 g/day of herb. Members also noted another case report in which chewing gum containing liquorice had a significant effect on one individual, at a dose of 50 mg of glycyrrhizin/day (equivalent to 4g of herb). This case was considered a demonstration of the fact that different people have different sensitivities to glycyrrhizin and that a cut-off would be difficult to establish. Members requested that the OCM provide copies of these papers to the Committee.

Consumption versus incidence of adverse events

A member commented that it was important to consider the degree of exposure to liquorice in the general population compared to the incidence of adverse events for liquorice. They added that, with the amount of liquorice consumed in the general population, more cases of adverse events would be expected to have been reported if there really was a safety concern.

In addition, the consumption of liquorice as a food was raised, with Members considering it feasible that more liquorice is consumed in the diet than would be consumed in therapeutic goods. Therefore, it would be inconsistent to require a label advisory statement for therapeutic goods, but not for food containing liquorice.

Cut off dose

Members agreed it seemed unreasonable to impose label requirements on medicines containing liquorice in small amounts, as this amount would be low risk. A number of Members were in favour of a 2.9 g/day cut-off dose (the dose at which no effect is observed). Members noted that in this instance, manufacturers may be required to assay the liquorice in their product(s) to make sure the level is below the cut-off dose.

Wording Label Advisory Statement

Members acknowledged that it was important to consider the needs of the consumer and how any advisory statement could be interpreted; that is, the advisory statement should adequately explain the risk, and not cause unnecessary concerns.

Function of liquorice

Members discussed the fact that liquorice can be used in medicines as a flavour, sweetener or an active, and discussed whether the labelling would only apply to medicines containing liquorice as an active ingredient. However, Members noted that as there is currently no limit to the amount of liquorice that can be used as an excipient, a restriction based on function was therefore not appropriate, as it is the level of liquorice that is the important factor.

Conclusion

Members agreed that there was insufficient evidence to indicate that liquorice would cause adverse events during pregnancy, or adverse events in a breastfed infant. Members requested that they be provided with articles (as identified in the text) which could be considered before a final recommendation is made.

OUTCOME

CMEC deferred a decision on this matter, pending consideration of further information to be provided by the OCM.

4.3

CMEC discussed one item under this agenda item.

4.4 *Quisqualis indica* update

Background

A TGA Officer introduced this item, reminding Members that at CMEC 69, Members recommended, conditionally, that preparations of the fruit and seed of *Quisqualis indica* could remain suitable for Listing, subject to the implementation of a maximum recommended daily dose of the dried fruit and seed. However, before formalising this recommendation, Members had requested clarification of the contraindication which has been reported in some traditional texts that the herb should not be consumed with hot (or strong) tea, as this may increase adverse events to the herb, namely belching and diarrhoea.

At CMEC 70 Members were advised that it has not been possible to establish a scientific explanation for the reported contraindication in the course of this review. However, possible theories include:

- It is likely that the process of making strong tea could potentially concentrate minor constituents present in the tea plant (*Camellia sinensis*). Therefore, consideration of not only the main constituents, but also the minor constituents in tea, and their interaction with *Q. indica*, should be considered. Tea contains 1-5% caffeine, 10-24% of tannin and also small quantities of theobromine, theophylline and volatile oil. The action of xanthines such as caffeine, theophylline and theobromine on the CNS has been well established.

- It is possible that constituents of *Q.indica* and *C. sinensis* may compete for the same excitatory amino acid (EAA) receptor sub-types of the CNS and that this may result in the observed increase in adverse events.
- In addition to the above considerations, it may also be noteworthy that the main adverse reactions reported when *Q. indica* and strong tea are consumed together, are gastrointestinal complaints, such as nausea, vomiting, belching and diarrhoea. This may indicate that an interaction occurs locally in the gut.

At CMEC 69, Members had also requested that the OCM contact a representative of the State Drug Administration of the Republic of China (SATCM), in an effort to obtain further details in relation to the contraindication included in the PPRC monograph for the herb. Members were advised that the OCM had not received a response to date.

CMEC was requested to advise whether a label warning statement, contraindicating the consumption of *Q. indica* with strong tea, is justified.

Discussion

Members discussed potential toxicity of *Q. indica*, given that the herb is used to kill parasites. It was agreed that there may be as yet unidentified safety concerns, particularly considering that the adverse events of belching and diarrhoea which could be indicative of significant pro-kinetic biochemical reactions.

Traditional contraindication with tea

Given that the contraindication for consumption of *Q.indica* with tea was reported in association with the use of the herb in traditional Chinese medicine, Members agreed that this matter should be considered in context of what constitutes 'tea' in China. Members acknowledged that the concept of 'tea' in China is very different to that in Australia, in that traditional Chinese tea is green tea that has been stewed for a considerable time, while in Australia, 'tea' is usually black tea, comparatively lightly stewed.

Members discussed the fact that some TCM texts contraindicate the use of *Q.indica* with hot tea, whilst others contraindicate use of the herb with strong tea. This difference was identified as potentially significant. A Member stated that as tea is high in polyphenolic compounds, the stronger the tea, the more the bioavailability of other substance should be decreased, not increased. If the interaction is with *hot* tea, it might be possible that the increased temperature causes increased absorption.

Absorption

Members acknowledged that the herb is used to kill worms, but considered that the low bioavailability of the herb may reduce the level of concern relating to absorption.

A TGA Officer referred Members to the original evaluation paper for this herb, which referenced a paper by Dharmananda (2008). This paper stated that quisqualic acid, in quantity, is considered toxic, with possible neurological effects. However, quisqualic acid is poorly absorbed orally, remaining in the digestive tract where it causes impairment of the nervous system of intestinal worms, allowing them to be eliminated.

Further, the original evaluation paper also referred to Wu (1926), in which toxicity studies of 'Shijunzi' in laboratory animals did not show reactions until very high oral dosages were administered (e.g. 26 grams/kg in dogs caused non-lethal adverse effects). However, there were obvious reactions to injection of the extract (quantity not provided). Wu (1926) concluded that this difference in response probably indicates low intestinal absorption of the quisqualic acid.

Use of *Q. indica*

Members questioned whether the herb was commonly used in TCM, noting that the herb is freely available, is commonly extemporaneously prepared by practitioners, and is considered an effective vermifuge.

Members noted that while the herb is contained in small quantities in medicines Listed in the ARTG, the ARTG did not include information in relation to the recommended unit dose which, in TCM, can often involve multiple tablets. Members also noted that TCM formulation usually involves numerous ingredients which are considered to work synergistically.

Conclusion

Members considered that restricting the maximum recommended daily dose of *Quisqualis indica* in Listed medicines to an equivalent of 12 g of the dried fruit, or 9 g of the dried seed (as outlined in the PPRC), would ensure that the herb remains suitable for use in Listed medicines. In relation to the proposed implementation of a label advisory statement contraindicating the use of the herb with hot or strong tea, Members considered that there was insufficient information to make a recommendation.

Members made the following recommendation:

Recommendation 70.2

CMEC recommends to the TGA that unprocessed preparations of the fruit or seed, and processed preparations of the seed (as described in the current edition of the Pharmacopoeia of the People's Republic of China) of *Quisqualis indica,* remain suitable as ingredients in Listed medicines, subject to a maximum recommended daily dose equivalent to 12g of the dried fruit, or 9g of the dried seed.

4.5

CMEC discussed one matter under this agenda item.

4.6 Bovine Whey Immunoglobulins

Background

A TGA Officer introduced this item, reminding Members that the suitability of Bovine Whey Immunoglobulins (BWI) for use in Listed medicines was initially considered at CMEC 67. At this meeting, the Committee requested additional data demonstrating adequate characterisation of the substance and additional information to address safety issues, including supportive toxicological studies and/or clinical use data.

Members were reminded that, for the initial evaluation, the assessment of the safety of the substance was inferred from data for related substances containing bovine immunoglobulins.

Members were informed that, in response to the CMEC requests, the applicant had provided new data comprising a comparative analysis of BWI and other currently Listable substances by SDS-PAGE (sodium dodecyl sulphate – polyacrylamide gel) electrophoresis, and preliminary clinical data from a study in humans using a product that contains BWI as one of the ingredients, and other supporting information.

Members noted that the electrophoresis results show that the protein profile of BWI, at least with respect to the major proteins, is similar to another currently Listable substance. Therefore, the Committee accepted that BWI is not substantially different from another Listable substance used in the comparative analysis, at least with respect to the major proteins, and considered it may be appropriate to conclude that the two substances are substantially equivalent with respect to safety.

Members also noted that the clinical trial data provided are limited to preliminary results from a pilot study. From a safety perspective, no clinically relevant adverse effects were documented. Intestinal upsets were reported only for some subjects in the top dose group, so this may have been treatment-related. However, the symptoms were minor in nature, and transient. Because a combination product was used, it is not possible to determine if BWI contributes to these reactions.

The Officer concluded that the new data provided by the applicant primarily addresses the CMEC's request for additional information to better characterise the substance, and establish its safety for the proposed use. The clinical evidence provided, although not directly relevant, raises no safety concerns. As the characterisation data indicate that BWI has a similar constituent profile to a currently Listable substance, it is reasonable to accept that this suggests that BWI is essentially equivalent in terms of safety.

Discussion

Members agreed that there did not appear to be anything suggestive of a safety concern for this substance. As the establishment of safety is the primary concern of the Committee, there did not appear to be a reason not to allow the ingredient to be included in Listed medicines. In addition, Members noted that a precedent had been established when other similar ingredients were permitted as ingredients in Listed medicines. Members did however, express reservations in relation to the claims that could be made for medicines including the ingredient, but noted that such aspects are currently considered in the post market environment.

Members made the following recommendation:

Recommendation 70.3

CMEC recommends to the TGA that Bovine Whey Immunoglobulins (BWI) is suitable for use as an active ingredient in Listed medicines, where supported by appropriate evidence for any indications and claims made for the product.

4.7 Magnesium sulfate in Listed medicines

Background

A TGA Officer introduced this item, informing Members that the OCM had identified potential safety concerns with respect to Listed medicines containing the ingredient magnesium sulfate, in relation to potential inappropriate indications, dosage form, and dosage instructions. Specifically, concern was raised in relation to the presentation of these medicines in capsule form.

Members were informed that the ADRAC had also considered this matter and requested a nephrologist's report that was discussed at the 309th ADRAC meeting in July 2008. The nephrologist's report concluded that a particular medicine (containing magnesium sulfate)

should only be taken after advice from a health professional who was aware of the risks of overuse in chronic kidney disease sufferers (known or unknown), the primary concern being that the medicine could cause volume depletion, resulting in worsening renal failure.

The pertinent safety concerns considered by ADRAC were:

- a potential resurgence in the incidence of hypermagnesemia; and
- that inappropriate use may place the following population groups at risk: those with known, or undiagnosed, renal impairment; individuals suffering with dehydration; children; the elderly; and for individuals taking other medicine(s) that may interact with magnesium sulfate.

ADRAC recommended that the matter should be referred to the National Drugs and Poisons Schedule Committee (NDPSC) and suggested that the NDPSC could consider including magnesium sulfate in Schedule 3 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), which would result in the medicine only being available following advice from a pharmacist.

Members noted that, while there is currently no legislative basis for the TGA to cancel the medicines of concern from the ARTG, should the NDPSC include magnesium sulfate in Schedule 3 with no qualification, medicines containing this ingredient would not be eligible for Listing, except where any relevant conditions are met.

Members were informed that, where identified as necessary, the Secretary could impose additional conditions of Listing (under Section 28 of the Act) on all Listed medicines that are hyperosmotic saline laxatives.

CMEC was asked to advise whether the use of magnesium sulfate (and other hyperosmotic saline laxatives), in capsule form, should be subject to further regulatory control.

Discussion

Members noted that there were two issues to be considered by the Committee. Firstly, a decision in relation to the presentation of medicines containing magnesium sulfate and secondly, a decision regarding potential safety concerns in relation to other hyperosmotic laxatives in capsule form.

A Member questioned why this matter had been tabled at CMEC, as opposed to the Medicines Evaluation Committee (MEC). A TGA Officer responded that magnesium sulphate meets the definition of a complementary medicine and hence, CMEC was the appropriate Committee for consideration of this matter.

<u>Scheduling</u>

A TGA Officer clarified that inclusion of an ingredient in a schedule of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) restricts access to the substance. Members agreed that the ingredient, magnesium sulfate, should be referred to the NDPSC for possible inclusion in a schedule of the SUSDP, possibly Schedule 3 (Pharmacist only). However, Members considered that particular consideration would need to be given to the dosage form, and the determination of a single unit dose bolus at which point it was appropriate that the ingredient should be scheduled.

<u>Consideration of additional conditions of Listing</u>

Prior to the NPDSC consideration of the matter, and in order to prevent products of concern being Listed in the ARTG, Members agreed that the TGA should impose additional relevant

conditions of Listing on Listed medicines containing magnesium sulphate in capsule form, and at a particular dosage consistent with that in the current product of concern.

Consideration of other hyperosmotic saline laxatives

A Member informed the Committee that in their deliberations of the matter, ADRAC had only considered the ingredient magnesium sulfate, and other hyperosmotic saline laxatives were not considered.

Members agreed that other hyperosmotic saline laxatives, depending on presentation, might present the same safety concerns to at-risk individuals. However, the Committee agreed that potential safety concerns relating to other hyperosmotic saline laxatives is a separate issue and was beyond the scope of the present discussion. Members agreed, at this time, to consider the ingredient magnesium sulfate, and requested that the TGA bring the broader issue of other hyperosmotic saline laxatives to a future meeting.

Conclusion

Members agreed that, in the first instance, additional conditions of listing should be imposed on all Listed Medicines, presented in capsule form, containing more than 14 g of magnesium sulfate in a single dose. As a future precautionary measure, the matter should be referred to NDPSC for their consideration.

Members made the following recommendations:

Recommendation 70.4

CMEC recommends to the TGA that the use of magnesium sulfate in medicines be referred to the National Drugs and Poisons Schedule Committee (NDPSC) to consider if there should be restrictions on access to certain doses of magnesium sulfate, when used for human therapeutic purposes, with particular emphasis on appropriate warnings, dosage form and the amount of the ingredient appropriate for use as a single bolus dose.

5. EVALUATION OF NEW SUBSTANCES

CMEC did not consider any matters under this agenda item.

6. SAFETY OR EFFICACY REVIEWS

6.1 Fish Oil Safety Review

Background

A TGA Officer introduced this item, reminding Members that at CMEC 69, the Committee was asked to consider the safety of fish oil ingredients, specifically with regard to potential anticoagulant properties of these ingredients.

CMEC were reminded that they have previously considered the safety of the ingredients ‘natural fish oil’, ‘fish oil rich in omega 3 fatty acids’ and ‘concentrated omega 3 marine triglycerides’. These ingredients are approved for use in Listed medicines without restriction and do not currently attract any advisory statements for labelling purposes.

At CMEC 69, Members requested that the OCM undertake a safety review of fish oil with specific regard to pre-surgical consumption and bleeding events.

CMEC were advised that a review of the literature indicates that while *in vitro* and *in vivo* data demonstrate an increased bleeding tendency is possible based on well-described mechanisms, these theoretical results are not reflected, functionally, in human clinical trials.

CMEC noted, however, that despite inconclusive results in clinical trials, omega 3 fatty acids are identified as a significant risk for haemorrhagic events in literature targeted at health care professionals. These concerns appear to originate from well documented cases of three elderly patients on multiple medications (including anticoagulant therapy), coupled with the theoretical possibility of clinically significant bleeding.

At CMEC 69, a Member informed the Committee that fish oil supplementation has been demonstrated to be beneficial as a premedication in cardiac surgery patients at the Alfred Hospital, Melbourne, as an anti-clotting agent, without any evidence of adverse bleeding effects.

The Officer concluded that, with regard to the potential anticoagulant properties of fish oil, it appears that the theoretical safety concerns are not reflected in the available data derived from clinical trials and, in general, experts agree that the benefits of omega 3 fatty acids, for reduction of cardiovascular risk, out-weigh the risk of increased bleeding.

Discussion

In general, Members commented on the concise summary of available information in the review of the literature and agreed that the available evidence appears to indicate that fish oil consumption, in usual daily doses, is not associated with an increase risk of bleeding.

However, Members also noted the apparent dose dependant effect, as some studies demonstrate an increase in bleeding in doses over 9g/day. Conversely, Members noted a review by Harris (2007) [Expert Opinion: Omega-3 fatty acids and Bleeding – Cause for Concern? *American Journal of Cardiology*, 99(6A):44C-46C], which states that doses up to 20g have been used with no adverse effect. Hence, Members agreed it was not possible to tell at what dose adverse effects might eventuate.

In conclusion, Members agreed that based on currently available evidence, there does not appear to be a safety concern linking fish oil consumption with an increased risk of bleeding. Members suggested that the Office of Medicine and Chemical Safety Monitoring (OMSM) be requested to consider including a statement in the ADRAC Bulletin, to advise health care professionals that there is currently inadequate evidence to support increased risk of bleeding in association with the use of fish oils, particularly peri- and post- operatively. In addition, Members supported the OCM's proposal to include a public advisory statement on the TGA website in relation to this matter, including relevant references to permit the public and practitioners to access and assess the relevant information.

Members made the following recommendation:

Recommendation 70.6

CMEC recommends to the TGA that the use of fish oil containing omega-3 fatty acids in oral Listed medicines does not require any additional regulatory controls at this point in time.

7. HERBAL SAFETY REVIEW/PLANT PART PROJECT

7.1 Update on the Herbal Safety Review Project

Background

A TGA Officer introduced this item, reminding Members that in June 2006, the OCM began a project to review a list of herbal materials to ensure that the regulatory controls, currently in place, are appropriate.

At CMEC 58 (August 2006), Members provided the OCM advice in relation to prioritising the herbs for review. In April 2007, the CMEC discussed the first round of herbal materials and noted that, while considerable progress has been made on the Herbal Safety review project, there remain a number of herbs to be reviewed.

The CMEC was asked to note the progress of the Herb Safety Review Project.

Discussion

Members noted the progress of the project to date and requested that the Committee be provided an update of the project biannually.

OUTCOME:

CMEC noted the progress, to date, on the Herb Safety Review Project.

8. REGISTRATION APPLICATIONS

8.1

CMEC discussed 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) Meetings 310 and 311

Adverse Drug Reactions Advisory Committee (ADRAC) Meeting 310

CMEC discussed adverse drug reaction reports involving complementary medicines, and related issues of interest, from the 310th and 311th meetings of ADRAC, held 5th September 2008 and 24th October 2008.

10.2 Medicinal interchangeability of BP/EP Monograph herbs

Background

A TGA Officer introduced this item, reminding Members that at CMEC 58 (August 2006) Members noted that the *British Pharmacopoeia* (BP) is currently the default standard for therapeutic goods supplied in Australia. It references a number of herbal monographs that are included in the *European Pharmacopoeia* (*EP*), which is the official standard for therapeutic products supplied in the European Union (*EU*).

At CMEC 56 (April 2006), Members considered a number of naming categories that apply to herbal-derived ingredients. One of these categories is the (Australian) Approved Herbal Substance (or AHS) category, which is the only type of herbal name that is considered to be a complete name, as it is linked to a pharmacopoeial monograph which outlines the part and preparation for the herb species(s) to which it applies.

The TGA Officer explained that most monographs in the BP name a single herbal species and plant part from which the substance is to be prepared. However, in some cases, two or more herb species and/or two or more plant parts are included in the description of the herbal preparation. Where the species referred to are eligible for inclusion in Listed medicines, there is currently no real issue in terms of safety or quality. However, there are some instances where there are multiple species referenced, some of which are not currently eligible for inclusion in lower risk medicines.

The Officer advised that, according to industry representatives, one of the reasons 'multiple species' are included in a compendial monograph is because some species are not easy to differentiate, or can easily hybridise (eg. *Crataegus spp.*). In some reported cases, it is impossible to source batches which only contain, or are derived from, the Listable species referenced in multiple species monographs, as the compendial material is generally the material of commerce. Industry members have also argued that 'multiple species' are only included in a compendial monograph when it is acknowledged they are medicinally interchangeable.

Members noted that inclusion of a herbal species in a compendial monograph does not establish the herbal material as safe for use in Listed medicines. However, industry argues that inclusion in a compendial monograph is acknowledgement that different species are phytochemically equivalent, and therefore, if at least one of the species included in the compendial monograph is currently permitted in Listed medicines, then the other species referenced in the monograph should also be permitted.

Members noted that the PPRC often recognises more than one species as the source of a preparation, and that the substance detailed in the PPRC pharmacopoeial monograph is likely to be what is available commercially.

Members noted that this issue has also been considered by the Office of Complementary Medicines/ Industry Consultation Group (OICG). At OICG 14, industry groups (ASMI, CHC & NPNZ) agreed to write to sponsors explaining the problems that arise from the use of compendial monographs that reference multiple species (some of which may not be listable), and to ask for input in terms of documented similarities in chemical profile. At OICG18 (Nov 2007), Members agreed that compendial monographs containing non Listable species should be prioritised based on risk, and that a 'case by case approach' should be undertaken for the review of safety, and as applies, medicinal interchangeability of the herbal species.

CMEC was asked to consider:

- how best to approach the issue of non-listable species in BP/EP or other compendial monographs that reference multiple species, and
- in which cases it might be appropriate to acknowledge medicinal interchangeability for species in multiple species monographs.

Discussion

Members noted that OICG have debated this issue many times, but that expert consideration of the matter appears to have reached an *impassé*. Industry members have stated that the multiple species raw material is often the only raw material available commercially. Some manufacturers may be aware of this, whereas others may be purchasing in ignorance.

Members considered whether the logical choice was not to accept the interchangeable species' listed in the BP, as they have not been specifically evaluated for safety, and whether an application to evaluate these substances is required, whether from the peak bodies or from sponsors.

Members noted that attempts to authenticate certain species of herbs e.g. *Salix alba*, have proven to be extremely difficult, with a Member adding that some species which seem to be morphologically identical, are not genetically identical.

Members also discussed the fact that while multiple species might be deemed 'safe', they may not, in fact, be medicinally interchangeable.

OUTCOME

CMEC noted the issues with respect to multi-herb monographs and medicinal interchangeability and requested that this matter be reconsidered at a future meeting, allowing sufficient time to fully debate the issues that arise.

11. FOR INFORMATION

11.1 CATAG Guiding Principles for the Use of Complementary and Alternative Medicines in hospitals

Background

A TGA Officer introduced this item, informing Members that the Chairman of the Council of Australian Therapeutics Advisory Groups (CATAG) had provided the TGA with a copy of the group's publication '*CATAG Guiding Principles for the Use of Complementary and Alternative Medicines in hospitals'* .

Members noted that the CATAG represents state-wide and hospital-based drugs and therapeutic committees, medication safety groups, policy makers and others with expertise in medicines' management. The group was formed to develop a policy for handling requests from patients to use complementary medicines in hospitals.

Members were asked to note the document: *'CATAG Guiding Principles for the Use of Complementary and Alternative Medicines in hospitals.'*

Discussion

Members considered the numerous issues associated with the document, and requested that comments be provided to the CATAG.

11.2 Adverse event linked to *Polygonum multiflorum*

Background

A TGA Officer introduced this item, informing Members of an article recently published in the *Journal of Clinical Gastroenterology*, Volume 42, number 7, August 2008, entitled: 'Acute hepatitis associated with the use of an herbal supplement (*Polygonum multiflorum*) mimicking iron-overload syndrome'.

The paper reports the case of a 35 year old man who presented with a 1 week history of tea coloured urine and nausea, and who was subsequently diagnosed with acute hepatitis with a presentation suggestive of iron-overload syndrome. The only implicated medication was a herbal supplement (taken for hair growth), containing the herbal ingredient *P. multiflorum.* The patient recovered after stopping the herbal medication, and liver function tests were normal 4 months after hospitalisation.

CMEC was reminded that they have previously considered other adverse events for *P. multiflorum*, and in September 2006 the Adverse Drug Reactions Advisory Committee (ADRAC) considered there to be sound evidence linking the use of *P. multiforum* with the development of hepatic toxicity. ADRAC recommended that products containing *P. multiflorum* should be required to carry a label statement warning of potential liver toxicity.

At CMEC 61 (April 2007), Members considered a safety review of *P. multiflorum*, and made the recommendation that labels on products containing *P. multiflorum* should include a warning statement to the effect that it may harm the liver in some people. Members were advised that Listed medicines containing preparations of *P. multiflorum* are now required to display this advisory statement. The TGA is also maintaining a watching brief on the safety of this herb.

Members were requested to note the article published in the *Journal of Clinical Gastroenterology*, reporting an adverse liver event linked to use of the herb *P. multiflorum*.

Discussion

Members noted the article published in the *Journal of Clinical Gastroenterology*, Volume 42, Number 7, August 2008, entitled: 'Acute hepatitis associated with the use of an herbal supplement (*Polygonum multiflorum*) mimicking iron-overload syndrome'.

11.3 Adverse event linked to *Valeriana officinalis*

Background

A TGA Officer introduced this item, informing Members of an article recently published in the *Journal of Clinical Gastroenterology*, entitled *'A case of valerian-associated hepatotoxicity*'. This article described the case of a 27 year old woman, who presented with a 2 week history of epigastric pain and fatigue, and whose liver ultrasound revealed mild hepatomegaly. The only medication the patient had taken prior to the event was 'valerian 300mg' capsules, twice a day for 3 months. The patient's symptoms resolved after ceasing the valerian medication and commencing a proton pump inhibitor medication. As the patient's hepatic inflammation on examination, laboratory tests, and imaging, all returned to normal after discontinuation of valerian, the authors believed that this case represents a case of valerian-associated hepatotoxicity.

The Officer reminded Members that at CMEC 17 (December 1999), *V. officinalis* was selected for review as part of a program of reviewing the safety of commonly used herbal substances. At this time, Members noted that some of the reported adverse events for valerian have been of hepatotoxicity, but considered that there is little potential for hepatotoxicity from valerian and also that the rate of allergic reactions to valerian is very low.

Members were asked to note the article published in the *Journal of Clinical Gastroenterology* reporting a liver adverse event linked to *V. officinalis.*

Discussion

Members noted the article published in the *Journal of Clinical Gastroenterology*, entitled *'A case of valerian-associated hepatotoxicity*'.

12. SPONSOR REPRESENTATIONS TO CMEC

Nil items for consideration

13. OTHER BUSINESS

13.1 CMEC Members' travel and accommodation guidelines

Background

A TGA Officer introduced this item, reminding members of travel and accommodation guidelines. The guidelines detail TGA policy relating to booking arrangements; travel allowances; accommodation arrangements and accommodation allowances; ticketing; flight variations; frequent flyer points; vehicle allowance; parking fees and fines; and telephone, fax, photocopying and administrative expenses.

CMEC Members were asked to note the Members' Travel and Accommodation Guidelines.

Discussion

Members noted the Members' Travel and Accommodation Guidelines.

14. RECOMMENDATION RECORD

Item 2. Confirmation of Draft Minutes of CMEC 69 (10 October 2008)

Recommendation 70.1

CMEC confirms that the draft Minutes of its previous meeting (CMEC 69, 10 October 2008), as amended, are a true and accurate record of that meeting.

Item 4.4 *Quisqualis indica* update

Recommendation 70.2

CMEC recommends to the TGA that unprocessed preparations of the fruit or seed, and processed preparations of the seed (as described in the current edition of the *Pharmacopoeia of the People's Republic of China*) of *Quisqualis indica*, remain suitable as ingredients in Listed medicines, subject to a maximum recommended daily dose equivalent to 12g of the dried fruit, or 9g of the dried seed.

Item 4.6 Bovine Whey Immunoglobulins

Recommendation 70.3

CMEC recommends to the TGA that Bovine Whey Immunoglobulins (BWI) is suitable for use as an active ingredient in Listed medicines, where supported by appropriate evidence for any indications and claims made for the product.

Item 4.7 Magnesium sulfate in Listed medicines

Recommendation 70.4

CMEC recommends to the TGA that the use of magnesium sulfate in medicines be referred to the National Drugs and Poisons Schedule Committee (NDPSC) to consider if there should be restrictions on access to certain doses of magnesium sulfate, when used for human therapeutic purposes, with particular emphasis on appropriate warnings, dosage form and the amount of the ingredient appropriate for use as a single bolus dose.

Item 6.1 Fish Oil Safety Review

Recommendation 70.6

CMEC recommends to the TGA that the use of fish oil containing omega-3 fatty acids in oral Listed medicines does not require any additional regulatory controls at this point in time.

The Chair closed the meeting at 4:35 pm.