Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 2
ADVISORY
COMMITTEE ON
COMPLEMENTARY MEDICINES
EXTRACTED RATIFIED MINUTES
SECOND MEETING
4 JUNE 2010

Abbreviations

AACMA	Australian Acupuncture and Chinese Medicines Association
ACCM	Advisory Committee on Complementary Medicines
ADI	Acceptable Daily Intake
ADRs	Adverse Drug Reactions
ARTG	Australian Register of Therapeutic Goods
CMEC	Complementary Medicines Evaluation Committee
CMIC	Chinese Medicine Industry Council of Australia Ltd
GMP	Good Manufacturing Practice
FSANZ	Food Standards Australia New Zealand
IRCH	International Cooperation of Herbal Medicines
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NDPSC	National Drugs and Poisons Schedule Committee
NOEL	No Observed Effect Level
OCM	Office of Complementary Medicines
OHP	Office of Health Protection
OTC	Over-the-Counter
RASML	Required Advisory Statements for Medicine Labels
SG	steviol glycosides
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
the Act	*Therapeutic Goods Act 1989*
the Regs	*Therapeutic Goods Regulations 1990*

The Advisory Committee on Complementary Medicines (ACCM) held its second meeting at the Melbourne Airport Hilton Hotel from 9:30 am to 4:00 pm on 4 June 2010.

Members of ACCM present

Professor Alan Bensoussan (Chair)
Dr Lesley Braun
Dr Gary Deed
Ms Patricia Greenway
Dr Vicki Kotsirilos
Ms Karen Martin
Professor Stephen Myers
Dr Richard Oppenheim
Mr Kevin Ryan
Dr Hans Wohlmuth

Present from the Therapeutic Goods Administration (TGA)

Mr Michael Smith (Secretary)
Ms Jenny Burnett
Ms Diane Wilkinson

1 Procedural Matters

1.1 Opening of Meeting

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

1.2 Apologies

Dr Ruth Lopert (TGA Principal Medical Advisor)
Professor Bill Webster

1.3 Conflict of Interest

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

2. Confirmation of Draft Minutes of ACCM 1 (5 March 2010)

Members accepted the Minutes of the first meeting of the ACCM as an accurate record of proceedings, subject to minor amendments as identified by Members.

In relation to Item 1.3 (‘Conflict of Interest’) Members questioned the appropriate method for disposal of ACCM documents (in either hard copy or electronic form) and whether Members were under any legal obligation to certify that these documents had been destroyed. A TGA Officer undertook to clarify this and report back to the Committee.

In relation to Item 3.2 (‘Amended Regulations and Criteria for ACCM Consideration’) Members reiterated the Committee’s opinion that documents presented to ACCM, such as herb safety

evaluations, should be accessible in the public domain. A TGA Officer undertook to explore possible mechanisms for this to occur.

As an aside, Members commented on the value of utilising another regulatory agency's monograph system, such as Health Canada's, as a means of avoiding replication of work. A TGA Officer advised that at a recent working group of the International Regulatory Cooperation for Herbal Medicines (IRCH), the issue of internationally accepted pre-cleared information was discussed. Members requested that any future developments from IRCH be communicated to the Committee.

Members made the following recommendation:

Recommendation 2.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 1 (5 March 2010), as amended, are a true and accurate record of that meeting.

3. Action Arising from Previous Meetings

Item 3.1 *Carthamus tinctorius*

Background

A TGA Officer introduced this item, reminding Members that briefing papers relating to the safety of *Carthamus tinctorius* were presented to Members of the ACCM's predecessor – the Complementary Medicines Evaluation Committee (CMEC) at its 62nd and 63rd meetings. In these discussions, after considerable deliberation, Members recommended that preparations of the flower of *C. tinctorius* are not suitable for use as an ingredient in Listed medicines due to potential teratogenic activity.

At CMEC 71 (March 2009), CMEC was asked to advise if this safety concern was also applicable to topical use of *C. tinctorius* flower. Members requested data on dermal absorption of preparations of the flower, but were informed at CMEC 73 (September 2009) that no dermal absorption data could be obtained. Based on the limited evidence on hand, Members restated their previous recommendation that preparations of the flower did not appear suitable for use in Listed medicines.

In September 2009, representatives of the Australian Acupuncture and Chinese Medicines Association (AACMA) and members of the traditional Chinese medicine sector raised their concern regarding the CMEC Recommendation, on the basis that this herb is a major TCM herb and has a safe history of use in this paradigm. To ensure that CMEC had any additional available information from which to make a recommendation, the OCM agreed to allow time for an additional Chinese scientific literature search to be conducted by the AACMA and the industry representative to obtain any relevant data concerning the safety of *C. tinctorius* flower in pregnancy.

Subsequently, the OCM received Chinese data, with English summaries, from the newly formed Chinese Medicine Industry Council of Australia (CMIC). However, the data supplied did not provide conclusive evidence establishing the safe use, or otherwise, of *C. tinctorius* flower during pregnancy. The CMIC submission concluded that further investigation was necessary.

At ACCM 1, Members restated their previous concerns regarding the use of *C. tinctorius* flower in Listed medicines. However, Members indicated that, given concerns over the lack of quality data, they would be prepared to consider other possible options to mitigate potential risk to the Australian population, other than complete removal of the ingredient for use in Listed medicines.

To this end, at ACCM 2, the OCM identified that, as a provisional measure, *C. tinctorius* flower remain permitted for use in Listed medicines with risks mitigated through appropriate and specific labelling, consistent with other overseas regulatory agencies. It was proposed that the requirement of a label advisory statement, such as *'Do not use if pregnant or likely to become pregnant*' (a standard label advisory statement in the Required Advisory Statements for Medicine Labels [RASML]), would alert all women of child-bearing age to exercise caution in using a product including a preparation of *C. tinctorius* flower.

ACCM was asked to provide advice on the regulatory options for mitigating risk associated with the use of *C. tinctorius* flower in Listed medicines.

Discussion

The suitability of a substance contraindicated in pregnancy for use in Listed medicines

Members discussed that to date, ACCM recommendations took into consideration that if a substance was not suitable for use in pregnancy, it was not suitable as a 'low risk' medicine. This was based on the fact that women could consume a product while unaware that they are pregnant. Further, the presence of an advisory statement may cause anxiety in these women if they become aware that they are pregnant and had consumed a contraindicated product.

That given, Members commented that a number of herbs are traditionally contraindicated in pregnancy, with no available scientific or adverse reaction data supporting this safety concern. Mitigation of risk through labelling would provide a means of dealing with this 'grey zone'. Use of advisory statements would provide some degree of flexibility where a definitive decision on safety cannot be made based on the available evidence, and to a certain extent, allow flexibility in determining the risk *versus* benefit for the general community. Members recognised that it is not possible for a regulatory agency to eliminate all risks for therapeutic products.

A Member added that the provision of a 'middle ground' of regulatory control was consistent with the approach to assess the safety of pharmaceutical medicines in pregnancy.

Differentiation between preparations of seed and flower.

A Member questioned whether the seed was included in the flower of *C. tinctorius.* Another Member responded that the seed develops in the flower and by the time there is a seed, there is fruit. Members recalled that *C. tinctorius* seed was the source of safflower oil and that no safety concerns had been identified for this plant part and preparation.

Wording of label advisory statement

A Member proposed an alternative advisory statement such '*the safety of this medicine has not been established in pregnancy'*. However, a TGA Officer responded that this was not a current advisory statement in RASML, and in the interests of consistency, standard advisory statements were preferred.

Consumer awareness and industry consultation

Members discussed the importance of consumers being provided information to enable informed choice. A Member added that an additional benefit of a pregnancy advisory label statement might be increased consumer awareness and subsequent increased reporting of any adverse events.

Members questioned what consultation would occur with respect to the proposed label advisory statement. A TGA Officer responded that a general consultation occurs as part of the periodic revision process for RASML and that any proposed new label advisory statements are part of this consultation process. Members requested that they be informed of any outcomes of this consultation process (specific to the proposed *C. tinctorius* label advisory statement).

As an aside, Members commented it would be useful to review label warning statements relevant for complementary medicines with respect to consistency and process improvement.

Provisional Recommendation

Members agreed that the requirement of a label advisory statement, with specific caveats, was a pragmatic outcome. Members reiterated that this was a provisional measure, subject to OCM liaising with stakeholders and ACCM reviewing the matter in 18 months, or as any new data comes to hand.

As an aside, Members commented that this liaison process may result in increased government / stakeholder collaboration and communication.

Recommendation 2.2

ACCM recommends that the TGA mandate the inclusion of RASML advisory statement no.14: '*Do not use if pregnant or likely to become pregnant*' on the labels of all Listed medicines containing preparations of *Carthamus tinctorius* flower.

The following caveats apply to the above Recommendation:

- Recommendation 2.2 to be reviewed in 18 months.
- OCM to liaise through established channels with relevant Chinese Government bodies, in particular the State Administration of Traditional Chinese Medicine, to encourage further investigation into potential safety concerns for *Carthamus tinctorius* flower.

Item 3.2 CMEC Expert Advisory panel update

Background

A TGA Officer introduced this item reminding Members that, historically, the CMEC had an attached Expert Advisory Panel to call on for specific advice on subjects that required input from outside the CMEC.

Under the previous Committee (CMEC) provisions in the *Therapeutic Goods Regulations 1990* (the Regs) enabled the Minister to nominate up to 8 people to give expert advice to assist the Committee in the performance of its functions. However, Members were informed that, under recent legislative amendments to Committee provisions (detailed in item 3.2, ACCM 1), there is no ability for the Minister to nominate expert advisers outside ACCM. Furthermore, the terms of the previous Expert Advisory Panel have either expired or been dissolved with the commencement of the Regulation amendments.

Discussion

Members noted the contribution of the CMEC Expert Advisory Panel to the Committee's work and requested that their gratitude be conveyed to the outgoing members of the panel.

Outcome

ACCM noted the new committee provisions in the Regs for obtaining expert advice from outside the Committee: establishment of a subcommittee or contracting experts on an 'ad-hoc' basis.

Item 3.3

One matter was discussed under this agenda item.

Item 3.4 Resource guide for ACCM Members

Background

A TGA Officer introduced this Item, reminding Members that at previous meetings they had requested a 'resource tool' that would provide relevant legislative documents and other resources useful in aiding Members with decision making processes. To this end, the OCM has drafted up a list providing internet links to relevant legislation, guidelines, etc. to be posted on the ACCM discussion database. Members were asked if there were any additional resources that should be added to the list.

Discussion

In addition to the list of resources provided, Members suggested that links to the TGA's electronic Business System portal, Good Manufacturing Practice documents and the list of ingredients permitted in Listed medicines (when available) would provide useful sources of information for Members.

Outcome

ACCM noted the 'List of TGA regulatory documents' to be used as a resource tool by Committee Members.

4. Guidelines on Levels and Kinds of Evidence to Support Claims

Nil items.

5. Evaluation of New Substances

Item 5.1 Steviol glycosides

A TGA Officer introduced this item, advising Members that a new complementary substance application had been received for steviol glycosides (SG) as an excipient ingredient in Listed and Registered medicines, for use as a sweetener.

Members were reminded that SG was approved by Food Standards Australia New Zealand (FSANZ) for use as a novel food ingredient in 2008, with restrictions imposed on its concentration in a range of foods. The FSANZ safety assessment formed the basis of the current application. Members also noted that the substance has been the subject of recent reviews by the

Joint FAO/WHO Expert Committee on Food Additives (JECFA). Both JECFA and FSANZ established an Acceptable Daily Intake (ADI) of 4 mg/kg bw/day (expressed as steviol). A literature search indicated that no new safety data have become available since the FSANZ assessment.

SG is a natural substance containing a range of glycosides found in the plant *Stevia rebaudiana* Bertoni. All SG contain one molecule of steviol (i.e. the aglycone) as a common central component. Hence, steviol content is commonly used as a means to quantify steviol glycosides. Also, it is the aglycone which is systemically absorbed, and, therefore, the toxicologically relevant molecule. The main glycosides are stevioside and rebaudioside A.

Members noted that, from a chemistry, manufacturing and quality control perspective, SG has been adequately characterised. The substance has a substantial history of use as the main non-sucrose sweetener in Japan; it is permitted for use as a sweetener in a number of other countries; and there is a long history of use of water extracts of *S. rebaudiana* as a sweetener in South America.

Pharmacological effects of SG have been observed in normal and diabetic animals and in humans. Stevioside is completely metabolised to steviol by the micro flora of the gastrointestinal tract, and is excreted via the faeces in animals or via the urine in humans. It has been demonstrated that rebaudioside A is metabolised to steviol in a similar manner, albeit more slowly.

The database for stevioside covers an adequate range of endpoints, demonstrating that it has low acute toxicity, and there is no evidence of carcinogenicity, developmental, reproductive or genotoxic effects. The highest doses in the key toxicology studies were essentially limit doses, at which, according to FSANZ, there were no toxicologically significant findings. It is therefore likely that the true No Observed Effect Level (NOEL) is greater than the maximum dose tested.

The key studies comprise 2-year and 3-month dietary studies in rats, for which the test substances were stevioside and rebaudioside A, respectively. Expressed as steviol equivalents, the respective maximum doses in these studies were ~800 mg/kg bw/day and ~680 mg/kg bw/day. In contrast to the FSANZ opinion, JECFA considered effects seen at the top dose in the 2-year rat study to be toxicologically significant, and chose the lower dose of ~400 mg/kg bw/day as the NOEL, incorporating a 100-fold uncertainty factor to arrive at an ADI of 4 mg/kg bw/day (as steviol). FSANZ has adopted the JECFA ADI.

A number of studies have been conducted in humans to examine the effects of SG on blood pressure and blood glucose levels. JECFA and FSANZ concluded that SG are unlikely to produce hypertensive or hypoglycaemic effects, or affect other physiological parameters in the general population, at doses up to 11 mg/kg bw/day. However, deficiencies in these studies led FSANZ to conclude that they were not a suitable basis for the ADI.

No adverse reactions for products containing the substance were retrieved from the Australian or Canadian adverse reactions databases.

According to the OCM estimates of intake of SG from future therapeutic products, it is unlikely that approval of this substance for use as an excipient ingredient in Listed medicines will result in any safety concerns. That given, Members were asked to advise if it was appropriate to conclude that the level of exposure of children to SG is unlikely to be a safety concern.

Discussion

In general, Members agreed that the FSANZ report and the data provided were of high quality and indicated that the substance was relatively safe. Members noted that the clinical data indicated that substantially high doses were required for adverse events to occur. Members noted that SG was 250 to 300 times sweeter than sucrose, was a very acrid substance and required blending with another substance in order to be used. Members therefore considered that it was unlikely that large amounts of the substance would be included in medicines. Further, the amount used in foods was much higher than would be included in medicines.

Members concluded that the substance steviol glycosides was low risk and eligible for inclusion as an excipient ingredient in medicines included in the ARTG

Recommendation 2.5

ACCM recommends to the TGA that the level of exposure of children to steviol glycosides in future therapeutic products is unlikely to be a safety concern.

6. Safety or Efficacy Reviews

Nil items.

7. Herbal Safety Review/Plant part project

Item 7.1 Oxalic acid in herbal species used in Listed medicines

Background

A TGA Officer introduced this item, reminding Members that since 2006, the ACCM (previously the CMEC) had reviewed a significant number of herbal ingredients in terms of their safety for use in Listed medicines in Australia. In the course of this project, herbs identified as containing oxalic acid were flagged for further investigation.

Members noted that oxalic acid is a ubiquitous substance in mammalian tissues and plants. It is endogenously produced in humans and excreted at amounts of about 25 mg daily, via urine. Plant derived foods constitute the major source of dietary oxalic acid and its uptake in the European diet can be roughly estimated to be in the range of 5 to 500 mg (but exceeding 1000 mg in individuals who are vegetarians).

Members were informed that the OCM has been unable to locate any studies in laboratory animals or observations in humans which would allow conclusions to be drawn regarding a NOEL, in particular for the relevant histological and functional alterations of the kidney induced by oxalic acid. Extrapolation of a safe dietary intake in humans on the basis of studies in laboratory animals is also hampered by the fact that rodents appear to be much less sensitive to oral toxic effects of oxalic acid than human subjects. Huge variations in genetic/physiological dispositions and vulnerabilities (e.g. individuals with a tendency to rheumatism, arthritis, gout, kidney stones and hyperacidity) of human populations are added barriers to drawing satisfactory conclusions.

The TGA Officer concluded that the OCM review of herbs containing oxalic acid had not identified any evidence to support restriction of these herbal species in Listed medicines.

Discussion

Members noted that oxalic acid was a naturally occurring component of numerous plants widely available, consumed and encouraged in the average human diet e.g. spinach. Members agreed that the level of oxalic acid present in medicines is likely to be significantly less than that provided in an average diet.

Members noted that there are a number of herbs containing oxalic acid that are currently permitted for inclusion in Listed medicines.

Members also noted that the subset of the population (e.g. individuals with a tendency to rheumatism, arthritis, gout, kidney stones and hyperacidity) should be aware of the foods that they should not consume in high quantities. It was really a matter for these patients and their practitioners to be educated and aware of foods to be avoided.

Members agreed that the quantity of oxalic acid in a therapeutic product was likely to be less that that available in the diet. Furthermore, it was problematic to associate an action or risk arising from a chemical component with a risk posed by a product. Regulation would have to be based on the content of the component within the product and testing of products for oxalic acid content was considered impractical.

Recommendation 2.6

ACCM recommends to the TGA that herbal species identified to contain oxalic acid remain eligible for inclusion in Listed medicines with no regulatory restrictions.

8. Nil agenda items

9. Registration Applications

Nil items.

10. Regulatory Reforms

10.1 Scheduling reforms

Background

A TGA Officer introduced this item advising Members of changes to the scheduling of drugs and poisons in Australia.

Currently, State and Territory governments are responsible for controls on the supply of and access to medicines and chemicals (e.g. agricultural, veterinary, industrial and domestic chemicals). The Australian Government, through the National Drugs and Poisons Schedule Committee (NDPSC) (a statutory committee established under therapeutic goods legislation), provides a forum to achieve consistency and uniformity of these controls at the national level. Medicines and chemicals are grouped into ‘schedules’ according to the appropriate level of control required over access to protect public health and safety. The schedules recommended by the Committee are currently published in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). The supply and access controls at the State and Territory level flow from the

schedule in which the substance has been included, but do not come into operation until the NDPSC recommendation is adopted into the relevant State and Territory legislation.

Since 2008 the TGA, the Office of Health Protection (OHP), the Australian Pesticides and Veterinary Medicines Authority and the National Industrial Chemicals Notification and Assessment Scheme have been working together to develop and implement revised arrangements for medicines and chemicals scheduling. Members noted that the new scheduling arrangements for medicines and chemicals take effect on 1 July 2010. The changes include:

- the Secretary of the Department of Health and Ageing will replace the NDPSC as the decision maker for the scheduling of medicines and chemicals;
- two new expert advisory committees, one for medicines scheduling and one chemicals scheduling, will be established to provide advice and make recommendations to the Secretary (or delegate) on scheduling decisions;
- a single secretariat, supporting both Advisory Committees, will ensure ongoing consistency and cohesiveness of processes and decisions;
- closer alignment of the revised scheduling arrangements with existing Commonwealth evaluation and product registration systems; and
- the SUSDP will be renamed the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

In order to make the scheduling process more efficient, scheduling decisions will be made by delegates of the Secretary located within TGA and the Office of Chemical Safety and Environmental Health (within the OHP). Under the new arrangements only applications for rescheduling, or contentious new applications, need be referred to the advisory committees.

The changes aim to improve the efficiency and timeliness of scheduling decisions, while maintaining the existing high level of scheduling uniformity across Australian states and territories. Government policy is that the costs associated with these new scheduling arrangements will be fully recovered from industry. A draft Cost Recovery Impact Statement was released for public consultation between mid-January and mid-March 2010, and further examination of cost recovery arrangements is now being undertaken in light of comments received.

Discussion

Members questioned whether the changes to the scheduling of drugs and poisons will be affected by an election, should it occur this year. A TGA Officer responded that an election would not have an effect on the reforms, as the new scheduling arrangements will take effect on 1 July 2010.

Outcome

ACCM noted the revised arrangements for scheduling of medicines and poisons, which will come into effect on 1 July 2010.

11. Matters Referred from within TGA

Item 11.1 ADRs associated with complementary medicines from 1 Dec 2009 to 30 Apr 2010

ACCM noted the adverse events reported for complementary medicines from 1 December 2009 to 30 April 2010.

Item 11.2

ACCM discussed one matter under this agenda item.

Item 11.3 Verbal report from TGA delegate on Canadian visit

Background

A TGA Officer provided a verbal report of their recent visit to Canada.

During this visit, the Officer attended an IRCH meeting on pharmacovigilance which was held in Ottawa. Of particular note at this meeting was discussion on individual countries regulatory action undertaken in response to the safety concerns for a number of plant species.

The Officer also attended a 4 day conference on the science of botanicals at the University of Mississippi, USA.

The trip concluded with a 5 day technical visit to Health Canada, concentrating on the Canadian approach to the regulation of homoeopathic medicines, sharing of pre-cleared information between regulatory agencies and the Canadian Natural Health Products Online Solution (equivalent to the TGA's Electronic Listing Facility).

Outcome

ACCM noted the report of a TGA delegate's visit to Canada and the USA.

12. For Information

Nil items.

13. Sponsor Representations to ACCM

Nil items.

Item 14 Other business

14.1 ACCM proposed meeting dates for 2011 and expiration of Member's terms.

Background

A TGA Officer provided Members with the proposed meeting dates for 2011.

Members were reminded that a number of ACCM member terms will expire in December 2010 and that the TGA would be seeking expression of interests for these positions in the near future.

Outcome

ACCM noted:

- that a number of ACCM member terms will expire in December 2010; and
- proposed meeting dates for 2011.

15. Recommendation Record

Recommendation 2.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 1 (5 March 2010), as amended, are a true and accurate record of that meeting.

Recommendation 2.2

ACCM recommends that the TGA mandate the inclusion of RASML advisory statement no.14: '*Do not use if pregnant or likely to become pregnant*' on the labels of all Listed medicines containing preparations of *Carthamus tinctorius* flower.

The following caveats apply to the above Recommendation:

- Recommendation 2.2 to be reviewed in 18 months.
- OCM to liaise with relevant Chinese Government bodies, in particular, the State Administration of Traditional Chinese Medicine, to encourage further investigation into potential safety concerns for *Carthamus tinctorius* flower.

The Chair closed the meeting at 4:00 pm.