Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 7
Advisory Committee on Complementary Medicines

Extracted ratified minutes
Seventh meeting

2nd September 2011

TGA Health Safety Regulation

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADRs	Adverse Drug Reactions
ANAO	Australian National Audit Office
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
ANZTPA	Australia New Zealand Therapeutic Products Agency
BSE	Bovine spongiform encephalopathy
CWD	Chronic wasting disease
DoHA	Department of Health and Ageing
EDQM	European Directorate for the Quality of Medicines
IJEACCM	TGA/Medsafe Interim Joint Expert Advisory Committee on Complementary Medicines
OCM	Office of Complementary Medicines
OIE	World Organisation for Animal Health
TGA	Therapeutic Goods Administration
the Act	*Therapeutic Goods Act 1989*
the Regulations	Therapeutic Goods Regulations 1990
TSE	Transmissible spongiform encephalopathies

The Advisory Committee on Complementary Medicines (ACCM) held its seventh meeting at the Stamford Hotel, Sydney Airport from 9:30 am to 4:00 pm on 2nd September 2011.

TGA note: This document is the extracted minutes from the 7th meeting of the ACCM. The type of information that may have been removed from the full meeting minutes includes: discussion in relation to member's declarations of interests; information considered commercial in confidence or sensitive; action items; and matters still under consideration by the committee for which an outcome has yet to be determined.

Members of ACCM present

Professor Alan Bensoussan (Chair)
Dr Lesley Braun
Ms Patricia Greenway
Ms Karen Martin
Professor Stephen Myers
Dr Richard Oppenheim
Dr Marie Pirotta
Dr Xianqin Qu
Dr Simon Spedding

Present from the Therapeutic Goods Administration

Ms Jenny Burnett (Secretary)
Dr Linda Lenton
Mr Ian Stehlik (OCM Head)
Ms Diane Wilkinson

Present for part of the meeting

Dr Dharam Sharma (TGA)

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9:40am, welcoming ACCM members and TGA staff.

1.2 Apologies

Professor Bill Webster
Professor Peter Williams
Dr Hans Wohlmuth
Dr Megan Keaney

1.3 Conflict of interest

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

The Chair and TGA officers advised members of the 'TGA Advisory Committee Chairs Forum' recently held at the TGA. The purpose of the forum was to: provide an opportunity for committee chairs to discuss how each committee might manage conflicts of interest; note the outcome of the recent reviews undertaken at the TGA relevant to advisory committees; and discuss changes to the *Freedom of Information Act* and Information Publication Scheme relevant to committee information and members' privacy.

Members noted that the '*TGA advisory committee guidelines: Declarations of interests, managing conflicts of interest and confidentiality obligations*' is now available on the TGA website.

Outcome

Members noted the outcome of a TGA Advisory Committee Chairs Forum where, among other issues, matters relating to conflicts of interest were discussed.

2. Confirmation of draft minutes of ACCM 6 (3 June 2011)

Members agreed that the minutes of ACCM 6 were thorough and provided a good representation of the items discussed at that meeting.

Members asked if committee meeting minutes, in general, could be ratified out of session, rather than waiting until the next meeting. While it was noted that it would be beneficial for members to receive the minutes as soon as possible after the meeting, as discussions would be easier to recollect, it would be difficult for the committee to ratify minutes out of session. It was agreed that, where agenda items are considered time critical e.g. the TGA is required to make a regulatory decision, early input from the committee on the accuracy of the minutes would be beneficial and in these instances out-of-session ratification may be appropriate.

Members sought clarification of the meeting dates for 2012 and were advised that these dates had been posted on the website and are as follows:

9 March 2012

1 June 2012

7 September 2012

7 December 2012

Recommendation 7.1

ACCM confirms that the draft minutes of its previous meeting ACCM 6 (3 June 2011), as amended, are a true and accurate record of that meeting.

3. Action arising from previous meetings

3.1 OCM decision making strategies

Background

A TGA officer introduced this item reminding members that at ACCM 6, members discussed the range of regulatory options available to the TGA to address potential safety concerns associated with complementary medicines and also the role of the committee in the regulatory decision-making process.

Members noted that with the change to the name of the committee (from the Complementary Medicines Evaluation Committee to the Advisory Committee on Complementary Medicines), it could be perceived that the committee's role had also changed. Particularly for the benefit of new members, it was suggested that the committee be provided with clarification on how the expert advice received from ACCM assists the TGA in making regulatory decisions.

The main areas where the TGA relies on the advice of ACCM include: the approval of new substances; the consideration of new registered complementary medicines; changes in policy *e.g.* evidence guidelines; and other areas such as additional conditions of listing being place on a group or class of medicines.

At ACCM 7, flow charts were provided outlining the OCM decision strategies for: approval/rejection to list a new complementary medicine substance; approval/rejection of a new registered complementary medicine; cancellation of a listed medicine; suspension of a listed medicine; and additional conditions of listing or registration.

Discussion

Members agreed that the flow charts are informative and provide a helpful depiction of how the advice received from ACCM is incorporated into the TGA regulatory decision making process.

It was noted that the rejection of a new complementary medicine substance is not considered a regulatory decision, as there is currently no provision under the *Therapeutic Goods Act 1989* (the Act) to either accept or reject such an application. The mechanism used to make new ingredients available relies on a particular power provided to the Minister *via* the Act and separate provisions in the Therapeutic Goods Regulations 1990 (the Regulations). Requests for the evaluation of new ingredients are received under Regulation 16GA of the Regulations. Section 9A (5) of the Act provides that the Minister may, by notice published in the Gazette, require that specified therapeutic goods be included in the part of the Register for listed goods; and may specify the conditions subject to which such goods may be included in that part of the Register. It is this part of the Act that is used to create a legislative instrument stating that goods containing a particular ingredient be included in the part of the Register for listed goods (*via* a change to Schedule 4 to the Regulations or a listing notice), after the evaluation of a substance concludes that it is suitable for such use.

It was questioned if the flow charts could be expanded to indicate where, what and how information on decision making processes is communicated to consumers and industry. With respect to communicating with industry stakeholders, the TGA officer advised that these documents are the basis for the flowcharts are already included in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM). The TGA noted the potential for publishing the flowcharts with contextually appropriate information for all stakeholders on the TGA website.

A Member suggested that the flowcharts should include a timeframe for the evaluation of new complementary substances/medicines, similar to that provided for the evaluation of prescription medicines. A TGA officer responded that it is difficult to predict how long an evaluation will take, given that the nature of complementary medicines is quite different to prescription medicines. The evaluation of a new prescription medicine consists of the evaluation of a particular chemical entity that is well characterised and the subject of a comprehensive data package. In comparison, complementary medicines are complex substances and the quantity and quality of the data included in applications varies considerably. Where a data package is of poor quality, lengthy communication between the applicant and the TGA is often necessary, which results in considerable delays in the evaluation process. The better the quality of the data package, the more assurance can be given that the application can be processed in a timely manner. A member stated that the ARGCM was developed to assist applicants with their applications for a new substance evaluation, with the intent that if not all 'the boxes were ticked' then the application should not be accepted.

Outcome

ACCM noted the decision making strategies in relation to the regulatory activity undertaken by the OCM.

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

Nil items

5. Evaluation of New Substances

5.1 *Lepidium meyenii*

Background

A TGA officer introduced this item, informing members that the OCM had received an application for evaluation of a new substance for use as an active ingredient in listed medicines, 'pregelatinised *Lepidium meyenii* root powder'. ACCM noted that the application was initially submitted to the TGA in 2008, but was rejected for evaluation at this time due to insufficient information being provided. In 2009 a supplemented data package was accepted for evaluation. This current application has

been the subject of numerous requests for additional information and the applicant's last response was received in June 2011.

L. meyenii (maca) is a perennial plant from the *Brassicaceae* family and exists as a number of differently coloured phenotypes. Like other cruciferous vegetables, maca is reported to contain glucosinolates (which are hydrolysed to glucose and isothiocyanates upon disruption of the plant tissue). Maca is a staple in the diets of people indigenous to the Andes and used in folk medicine for increasing energy and enhancing fertility. Maca is currently sold as a food in Australia and is available as a dietary supplement in a number of other countries.

It was noted that, in 2006 (in the context of the proposal to establish a trans-Tasman joint regulatory agency for therapeutic goods), the TGA/Medsafe Interim Joint Expert Advisory Committee on Complementary Medicines (IJEACCM) considered a *Lepidium meyenii* preparation consisting of the dried, powdered, uncooked tuberous root. IJEACCM recommended that this preparation of *Lepidium meyenii* (dried tuber) was suitable for use in 'Class 1 (low risk)' medicines, without restriction. However, a compositional guideline was not able to be developed at that time because of a lack of quality related data available to the committee.

'Pregelatinised *L. meyenii* root powder', the subject of the present application, consists of the powdered dried root ('hypocotyl') of the plant which has been subjected to a proprietary manufacturing process.

A study of the biological activity of pregelatinised *L. meyenii* root powder in ovariectomised and intact female rats reported changes in serum levels of a number of reproductive and thyroid hormones, as well as antidepressive and sedative effects. The significance of these findings in relation to humans is unclear. Other rodent studies using different maca preparations reported changes in circulating hormone levels, changes in mating and other behaviour, effects on the reproductive system and bone sparing effects. However, overall results are difficult to interpret due to inconsistent effects across studies which may have been influenced by variation in dose levels, duration of treatment and test material preparation. Interestingly, some results appeared to be specific to *L. meyenii* phenotypes of particular colours.

Toxicology studies on pregelatinised *L. meyenii* root powder were limited to acute studies (mice and rats) and 4-week and 3-month studies in rats, mostly performed as part of the one study. The substance had low acute oral toxicity in mice and rats. Repeat dose studies of 4 weeks and 3 months duration did not raise any toxicological concerns, but these studies were not methodologically sound. Results from repeat dose toxicology studies with other maca preparations, including reproduction and developmental studies, also did not raise any safety concerns, though again, guideline-compliant studies of good quality were not available. Genotoxicity and carcinogenicity studies were lacking.

Four published papers (from the same group) described crossover trials in which early postmenopausal or perimenopausal women took 2 g/day of pregelatinised *L. meyenii* root powder for 2-8 months. While adverse reactions were not reported, group sizes were generally small. Reported changes in hormone levels appeared to be related to the order in which the placebo and active treatments were administered, so were not consistent across groups. In contrast, a recent small study with uncooked maca did not detect any serum sex hormone changes in postmenopausal women, but according to the authors, the study was underpowered for detection of changes of less than 30%.

The TGA noted that after four rounds of evaluation of the chemistry, manufacturing and quality control data, a number of critical issues remain unresolved. The officer stated that the TGA proposes that the application for evaluation of 'pregelatinised *Lepidium meyenii* root powder' be rejected as the applicant has been given ample opportunity to address outstanding issues, but this has not been achieved.

ACCM was asked to advise if the data submitted in the application for pregelatinised *Lepidium meyenii* root powder was adequate to support the safety and quality of a new complementary medicine substance for use in listed medicines.

Discussion

Members commented that processed maca was widely used as a food in Australia and, while there was a wide range of phenotypes and a wide range of specifications, there did not appear to be any

safety concerns associated with this use. That given, an application may need to simply establish appropriate quality for the substance *via* adequate identification of the plant material, including chemical identification of specific phenotypes. Unfortunately, members considered that the data package provided in the current application was inadequate to support the use of the substance in listed medicines.

Characterisation of substance

Members considered there were significant deficiencies associated with the characterisation of the substance in the current application. The Australian Regulatory Guidelines for Complementary Medicines (ARGCM) provide clear guidance for starting material specifications including the requirement for macroscopic identification. There was concern that the *L. meyenii* species had not been adequately identified and distinction between other similar plant materials not provided. Further, no analytical marker was nominated.

Manufacture of substance

Members noted that the reporting of the details of the method of manufacture had changed through the course of the application.

Possible contaminants

Members concurred with the TGA concern that the material could contain potentially toxic isothiocyanates (benzylisothiocyanate and m-methoxybenzylisothiocyanate), particularly as the applicant had not proposed to test for these compounds in batches of the processed material. Further, it is not clear what effect the manufacturing process has on the presence of isothiocyanates. A member reported that it has been shown that treating other species of the Brassica family with high pressure at moderate temperatures promotes the conversion of glucosinolates into isothiocyanates and can increase the quantity of these compounds up to 6-fold. Therefore, the manufacturing process could, in fact, be increasing the quantity of isothiocyanates.

It was also noted that darker coloured maca roots (red, purple, black) may contain significant amounts of natural iodine, with half of the Recommended Daily Intake (RDI) of iodine potentially obtained in one dose of maca. Members considered it an additional deficiency in the application that the level of iodine in the material had not been examined, particularly as rodent studies using pregelatinised *L. meyenii* root powder indicated thyroid changes had occurred.

Recommendation 7.2

ACCM advises the TGA that data submitted for evaluation in the current application for pregelatinised *Lepidium meyenii* root powder are inadequate to support the safety and quality of the substance as a new complementary medicine substance for use in listed medicines. In particular, there is inadequate identification of the starting material, inadequate assurance of the quality of the final product and concern regarding the level of certain components (e.g. isothiocyanates and possible contaminants).

5.2 Deer velvet antler

Background

A TGA officer introduced this item, advising ACCM that the TGA was currently evaluating deer velvet antler slice and deer velvet antler powder as new substances for use as ingredients in listed complementary medicines. The quality data evaluated for this application relate specifically to deer velvet antler slice and deer velvet antler powder derived from the antlers (including the velvet) of red deer (*Cervus elaphus*) and elk/wapiti (*Cervus canadensis*) or a crossbreed of these species, which are exclusively of stock bred and raised on farms in New Zealand according to the requirements for human consumption provided in the *Animal Products Act 1999* (New Zealand) and the regulations made under that Act.

ACCM noted that in 2006 (in the context of the proposal to establish a trans-Tasman joint regulatory agency for therapeutic goods) the TGA/Medsafe Interim Joint Expert Advisory Committee on Complementary Medicines (IJEACCM) considered deer velvet antler for use in Class 1 ('low risk') medicines. The evaluation report identified three potential safety concerns:

- native constituents with hormonal, steroidal or growth promoting activities

- residual levels of veterinary medicines and the need to control for the potential safety issues of TSE (transmissible spongiform encephalopathies), namely chronic wasting disease (CWD); and
- the need to restrict the harvesting of deer velvet antler to farmed deer.

The IJEACCM considered that the issues identified during evaluation could be satisfactorily addressed via appropriate compositional guidelines and relevant national TSE policies or, in the case of hormonal and/or steroidal component levels, were not of toxicological concern. IJEACCM recommended that deer velvet antler was suitable for use in 'low risk medicines', without any restriction. The evaluation of the current application is in agreement with the previous IJEACCM evaluation in identifying potential safety issues related to deer velvet antler ingredients. To ensure the safety and quality of listed therapeutic goods that would contain these active ingredients, it is proposed to restrict approval to only those substances produced under the following conditions:

- the preparations are for oral use only
- the antlers (including the velvet) are sourced only from red deer (*Cervus elaphus*) and elk/wapiti (*Cervus canadensis*) or a crossbreed of these species
- the deer are sourced only from farmed stock bred and raised in New Zealand
- the deer are sourced only from herds farmed for food in accordance with the *Animal Products Act 1999* (New Zealand) and the regulations made under that Act; and
- the antlers are removed from the deer only according to the *Animal Welfare Act 1999* (New Zealand) and the regulations made under that Act.

These conditions will be included in the Listing Notice and in the proposed compositional guidelines published on the TGA website and communicated to sponsors by a validation message generated when deer velvet antler ingredients are included in an application for a new listed medicine lodged using the Electronic Listing Facility (ELF). However, the OCM recognises that implementation of these conditions relies on the certification provided by the sponsor at time of listing of a new medicine via the ELF. Enforcement of these requirements relies on post-market listing compliance reviews and with respect to potential TSE risk, it could be considered that these post-market measures are not sufficient to ensure the safe use of deer velvet antler ingredients.

Current TGA policy to reduce the risk of exposure to TSE through medicines and devices classifies animal material as 'high risk' (category A), 'low/moderate risk' (category B) and 'no detectable activity' (category C). Animal materials such as brain, dura mater, spinal cord, cerebrospinal fluid, eye, ileum and lymph nodes as 'higher risk animal material' (Categories A and B). Category A and B materials must be sourced from countries free of bovine spongiform encephalopathy (BSE) and are subject to full TGA viral and prion safety evaluation. As a general principle, the TGA considers it desirable to avoid the use of all bovine materials from high BSE risk countries (currently identified by the TGA as UK, Portugal and Ireland).

Other materials, such as animal antler, horn and velvet, are recognised as Category C where there is little evidence in the literature to suggest transmission of TSE. However, there is also little available scientific data to support an absence of risk from these materials. The TGA approach requires sponsors to self-assess the TSE safety of Category C materials and to hold supporting data on their source. If these substances are obtained from countries considered by the TGA to be free or provisionally free of BSE, sponsors are required to retain appropriate documentation for possible TGA audit. For those obtained from countries with low or moderate risk, assessment by the TGA is required prior to their inclusion in any medicine on the Register.

The Officer advised that the World Organisation for Animal Health (OIE) has recently provided updated TSE guidelines, which the TGA is yet to consider. It was noted that 'antler' and 'skin' have been moved from Category C to Category B and would be required to be sourced from a BSE free country or hold European Directorate for the Quality of medicines (EDQM) certificates.

ACCM was asked to comment on the adequacy of the risk mitigation strategies proposed by the TGA to address potential safety issues associated with deer velvet antler powder and deer velvet antler slice from New Zealand being included as active ingredients in listed medicines.

Discussion

It was noted that New Zealand is considered a BSE free country and therefore the risk of exposure to TSE from animal products sourced from this country is minimal. ACCM questioned if deer velvet antler material could be sourced from other countries. A TGA officer responded that the listing notice for 'Deer velvet antler slice and deer velvet antler powder' will stipulate that it is sourced from New Zealand only. In addition, Australian Quarantine and Inspection Service (AQIS) and Australian Customs and Border Protection Service have controls in place restricting imports from countries considered a high risk for TSE.

It was questioned if 'New Zealand' should be included in the name of the ingredient to ensure that this is the only source of the material. However, a TGA officer responded that it is more practical to include restrictions in the ingredient's rules in the ELF, as these were easier to change, rather than include them in the ingredient name.

A Member questioned if each sponsor is required to hold European Directorate for the Quality of Medicines (EDQM) certificates. It was stated that if clearance for a source country is obtained by a national agricultural department, or an equivalent of AQIS, then certificates are not required; however, sources within TSE risk countries would require EDQM certificates.

Members questioned why the OIE has reclassified skin from category C to category B and if this would have any effect on the availability of gelatine? A TGA Officer responded that skin was considered a higher risk due to the close association with nerve endings and noted that the reclassification would be considered at an upcoming TGA TSE working group meeting.

A member commented that deer velvet antler has a 2000 year history of use in Traditional Chinese Medicine with evidence of safety, clinical efficacy and no toxicity. The substance is used traditionally to treat conditions considered to be deficient in 'Yang', such as arthritis, to improve male reproductive function and libido. It is an expensive treatment used for specific indications, not as a supplement to improve general health. Members agreed that extensive traditional use is a significant factor in establishing an ingredient's safety.

Members noted that the deer velvet were sourced from a particular herd in accordance with the *Animal Products Act 1999* (New Zealand) and that the antlers were removed from the deer only according to the *NZ Animal Welfare Act 1999*; that New Zealand is classified as a BSE free country and the sponsor would be required to hold documentation to verify source.

Recommendation 7.3

ACCM advises that the TGA's proposed risk mitigation strategies are considered adequate to address any potential safety issues associated with the use of New Zealand deer velvet antler powder and deer velvet antler slice as active ingredients in listed medicines.

6. Safety or efficacy reviews

Nil items

7. Registration Applications

7.1 Registration application for a medicine containing bovine whey extracts as the therapeutically active ingredients

Background

A TGA officer introduced this item advising ACCM that, in October 2010, the Office of Complementary Medicines (OCM) received an application for the registration of a new oral complementary medicine containing bovine whey extracts as the therapeutically active ingredients. These ingredients are available for use in listed medicines and furthermore, a range of similar products is currently available as listed medicines on the Australian Register of Therapeutic Goods (ARTG).

The application for registration of the proposed new medicine was based on an indication for the prevention of colds. The 'prevention' of a condition is considered a high level therapeutic indication that can only be made in association with a registered medicine.

Guidance on the level of evidence required to support a high level indication/claim is provided in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM) which refers to the *Guidelines for Levels and Kinds of Evidence to Support Indications and Claims* as follows:

> "High level indications/claims require scientific evidence obtained from: a systematic review of all relevant randomised, controlled trials without significant variations in the directions and degrees of results; or at least one properly designed, randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. Advice should be sought from the TGA."

Originally, the efficacy dossier submitted in the application consisted of a single clinical trial. During the initial assessment of the dossier, the OCM identified a number of critical deficiencies in the clinical trial methodology and these were raised with the applicant as issues that may prevent a full evaluation. In response, the applicant sought time to address the issues with the assistance of the study investigators rather than withdraw the application.

A revised dossier was subsequently received by the OCM, consisting of a revised clinical trial report that was later supplemented with a review of the related literature. However, while the applicant had addressed some of the issues raised by the OCM in relation to the efficacy data, fundamental problems with the study methodology remained. Added to this, it appeared that the evidence contained in the literature review was not of sufficient strength and/or relevance to compensate for the need to conduct further clinical trials.

For complementary medicine registration applications it is usual practice for the efficacy component to be evaluated by a clinician under contract to the TGA. The view of the OCM is that the clinical data are preliminary in nature and of an insufficient standard to support the efficacy of the product. As a result, proceeding to full evaluation of the application, which would include comprehensive assessment of all quality, safety and efficacy aspects, is not justified. To maintain oversight of the OCM processes in dealing with this application, comment was sought from the ACCM on the adequacy of the information provided to support the efficacy of the product.

Discussion

A TGA officer advised that after consideration of the revised dossier, concerns in relation to the adequacy of the efficacy data for which clarification had been sought from the applicant still remained. Provision of additional details of the clinical trial and changes to the proposed indications and target populations had not affected the critical deficiencies associated with the trial methodology.

Clinical trial

Members noted that the registration application rested on a single clinical trial, and although the trial was randomised, double-blinded and placebo-controlled, members expressed concerns regarding the robustness of the trial methodology and the quality of the evaluation of the primary outcome.

ACCM considered that a number of critical deficiencies were evident in the trial methodology. These included concerns with allocation concealment, selection of appropriate measurement instruments or primary outcome factors, determination of 'numbers needed to treat' and evaluation of endpoints.

A member queried the lack of information regarding the level of involvement of the identified commercial sponsor of the trial and noted that the study had not been published.

In relation to the inclusion measures for the clinical trial, ACCM considered it an omission that conditions such as asthma and hay fever were not included in the baseline measures of the subjects. It was also noted that the percentage of patients who were smokers was 5.7% in the treatment group and 13.7% in the placebo group. The lack of differentiation between medical conditions similar to colds, lack of control of other confounders and declared concomitant use of corticosteroid medication was felt to potentially have significant effect on the study outcome.

A TGA officer advised that the sponsor had provided the following definition of a cold "a cold was diagnosed when participants recorded two or more of the following symptoms: sore or scratchy throat, nasal congestion or discharge, headache, stinging eyes, muscle aches and fever". The officer drew member's attention to the fact the common cold symptoms such as coughing and sneezing were not included in this symptom list. Further, in response to questions raised in relation to the validity of the diagnostic process, the applicant stated the symptoms were standard symptoms used by physicians to diagnose respiratory illnesses. However, members considered a quality diagnostic marker was lacking, hence it was difficult to distinguish the symptoms of a cold from other upper respiratory illnesses and, as a result, the trial provided no clear primary outcome measure.

In general, members agreed that the inclusion criteria and the outcome measures used in the clinical trial were inadequate.

Ancillary literature

The relevance of the data provided in the applicant's literature review was discussed by members. Members were in agreement that there was little data that addressed the committee's concerns with the proposed medicine. It was noted that a randomised placebo controlled study by King *et al.,* 2007 in formula fed infants found that there were no differences seen in the frequency of upper respiratory tract infections between the treatment groups.

Conclusion

In conclusion, the Committee was unanimous that the clinical trial was not of sufficient quality to support the proposed indication. Furthermore, the ancillary literature provided by the applicant did not compensate for the inadequate quality of the primary evidence.

Recommendation 7.4

ACCM advises the TGA that efficacy data provided in the application for the registration of a medicine containing bovine whey extracts are insufficient to allow the dossier to be accepted for full clinical evaluation. Specifically, the clinical trial on which the efficacy of the substance is based is considered of inadequate quality. Further, the ancillary literature provided in the dossier does not provide sufficient human clinical data to compensate for the inadequacy of the primary clinical trial.

8. Regulatory reforms

8.1 Update on 26BB list

Background

A TGA Officer introduced this item advising ACCM that the TGA is developing a comprehensive list of all excipient and active ingredients (including their associated restrictions) permitted for use in listed medicines (the 26BB list). The list will be published as a new legislative instrument on the Federal Register of Legislative Instruments and is supported by the recent amendments to section 26BB of the Act. However, use of the new legislation requires amendments of Schedule 4 to the Regulations that need to be made concurrently with publication of the legislative instrument.

As an aside, a member sought details of the TGA's intentions for the ingredients that had been evaluated by the TGA/Medsafe Interim Joint Expert Advisory Committee on Complementary Medicines (IJEACCM) (in the context of the proposal to establish a trans-Tasman joint regulatory agency for therapeutic goods). A TGA officer responded that new formal applications for these ingredients will be required, however, the submission could be based on the IJEACCM dossier.

Outcome

ACCM noted the progress on the implementation of the 26BB legislative instrument for ingredients permitted for use in listed medicines.

8.2 Progress report on TGA regulatory reform projects

A TGA officer introduced this item, providing members an update of recent TGA regulatory reform projects, as follows:

ANZTPA

Members noted the announcement by the Australian and New Zealand Prime Ministers on 20 July 2011 advising of the re-establishment of Australian New Zealand Therapeutic Products Agency (ANZTPA), in accordance with the 2003 Australian and New Zealand treaty which undertakes to establish closer economic relations between the two countries.

Members recalled that the establishment of the joint agency had been initially proposed in 2003, but was postponed in 2007.

The re-establishment of ANZTPA involves a three staged approach over a period of up to 5 years. The countries will initially share resources and information, followed by the establishment of a single entry point for industry and a common trans-Tasman regulatory framework, after which the single regulator will be established.

During the first phase of the scheme the Australian Government acknowledges that the NZ Government is developing a stand-alone framework for domestic regulation of low risk complementary medicines. This NZ regulation scheme will be reviewed in 5 years, at which time consideration will be given as to whether or not a separate scheme for certain natural products in New Zealand should be maintained. Members noted that until a common framework is agreed, all complementary products in Australia will be required to meet Australian standards.

Australian National Audit Office report on Therapeutic Goods Regulation: Complementary Medicines

Members noted a report (No. 3 2011-12) released in August 2011 by the Australian National Audit Office (ANAO) on the Department of Health and Ageing (DoHA)'s regulation of complementary medicines. It was noted that the report did not recommend changing the 'light touch' regulatory approach to 'low risk' medicines, but recommended that this approach be balanced with a stronger post market activity. The report provides five specific recommendations, four of which relate to complementary medicines and one recommendation relates to advertising breaches. All recommendations have been accepted by the DoHA.

Recommendation 1 of the ANAO Report recommends the timely completion of key guidance material for complementary medicines (to help guide industry in the complexity of complementary medicine regulation) and regular progress reports on the development of these documents be provided on the TGA website. ACCM noted that this is regarded as a high priority within TGA, with the Australian Regulatory Guidelines on Complementary Medicines (ARGCM) and guidance documentation on the levels and kinds of evidence required for listed medicines identified as the first documents for review.

Recommendation 2 recommends the completion of the 'coded indications project', to limit the inappropriate claims and indications for listed medicines in the ARTG.

Recommendation 3 of the ANAO Report states that the TGA should provide timely information to the Australian public for each listed medicine in relation to if/when the medicine has been reviewed and the outcome of any review. ACCM noted that this recommendation was in alignment with recommendations of the TGA Transparency review for a more robust TGA communication strategy.

Recommendation 4 relates to the enhancement of post-market monitoring so as to more efficiently focus post-market resources towards problem areas.

Recommendation 5 states that the TGA should develop a standard operating procedure for investigations of advertising breaches which includes appropriate timeframes and regular reports to the TGA executive on progress of investigations and trends of non-compliance.

Advertising review

ACCM noted the recent review of arrangements for the regulation of therapeutic goods advertisements, which included a public consultation inviting comments on proposals for changes to the pre-approval process, complaints handling and the level and types of sanctions.

The review has identified a cluster of issues that have been provided to the Parliamentary Secretary for consideration.

TGA Transparency review

Members noted the report of the TGA transparency review was released in July 2011. This review was initially undertaken at the request of the Parliamentary Secretary with the purpose to improve public knowledge and understanding of how the TGA operates and the reasons for its key decisions.

The report includes 21 recommendations to improve the transparency of the TGA's regulatory decision processes. The recommendations have been provided to the Parliamentary Secretary for endorsement.

Working group on complementary medicine regulation

Members noted that a working group (comprising 12 participants providing representation from consumers, health professions, academic organisations, industry and ACCM members) attended two informal workshops to facilitate the review of the regulation of complementary medicines.

In general, members agreed that more information in relation to the evaluation of listed medicines should be available to consumers.

Outstanding issues and activity plan

A member noted a number of issues identified by industry, discussed at ACCM or the OCM/Industry Consultation Group. A TGA officer undertook to provide ACCM with a project plan of the significant reform activity to be undertaken in the next 12 to 18 months, including the status of outstanding issues and a plan for the progression of outstanding issues identified as high priority.

Outcome

ACCM noted the progress of a number of TGA regulatory reform projects, including: an ANAO performance audit; the TGA Transparency Review; the working group on the regulation of complementary medicines; and an advertising review.

9. Adverse drug reactions associated with complementary medicines

9.1 ADRs associated with complementary medicines from May to July

ACCM was asked to note details of selected adverse drug reactions (ADRs) associated with complementary medicines reported from 1 May 2011 to 31 July 2011.

In general, Members discussed the importance of increasing communication and engagement with practitioners with respect to reports of ADRs to complementary medicines, as this group is currently disenfranchised from the process. It was considered that there was a lack of understanding on the process of reporting adverse reactions and the misconception that reporting these events could result in increased regulatory control and subsequent reduced availability of certain substances. It was suggested that the TGA should engage with professional organisations such as the National Herbalists Association of Australia and the Chinese Medicine Registration Board of Victoria in order to increase practitioner education, engagement and cooperation on this issue.

Outcome

ACCM noted the ADRs associated with complementary medicines from May to July 2011.

10. Matters referred from within TGA

10.1 ASMI paper: Complementary medicines: the registration pathway.

A TGA officer introduced this item, advising members that the Australian Self-Medication Industry (ASMI) was an industry association that was actively involved in communications with the TGA, particularly via the OCM/Industry Consultation Group.

The current agenda item involved correspondence from ASMI which stated that there are a number of issues, barriers and disincentives for sponsors in relation to the registration process for complementary medicines, such as: the high costs of research and evaluation fees; the long

evaluation timelines; the unpredictability of the evaluation process; the lack of market exclusivity for complementary medicines; and the lack of advantage in the marketplace with respect to AUST R and AUST L products.

Members commented that a number of issues raised by ASMI had also been raised in a number of the regulatory reviews recently undertaken at the TGA and there was currently a raft of reform activity proposed for the TGA, particularly with respect to the regulation of complementary medicines, which may in some part address some of the issues raised by ASMI. ACCM asked the OCM to thank the ASMI for their correspondence and encouraged OCM to maintain an active dialogue with ASMI in relation to the progress of the regulatory reform activity within the TGA.

Outcome

ACCM noted suggested reforms to the registration pathway proposed by ASMI. ACCM noted that some issues raised in this paper had been identified during current TGA reform activities.

11. For information

11.1 Advisory Committee on Non-prescription Medicines March

ACCM noted the minutes of Advisory Committee on Non-prescription Medicines March 2011.

11.2 Medicines Safety Update No 3 bulletin 2011

ACCM noted the Medicine Safety Update No 3 bulletin 2011.

11.3 Medicines Safety Update No 4 bulletin 2011

ACCM noted the Medicine Safety Update No 4 bulletin 2011.

11.4 Advisory Committee on the Safety of Medicines May 2011 minutes

ACCM noted the minutes of Advisory Committee on the Safety of Medicines May 2011 meeting.

11.5 Therapeutic Goods Committee (TGC) 37th meeting minutes

ACCM noted the Therapeutic Goods Committee (TGC) 37th meeting minutes.

12. Sponsor representations to ACCM

Nil items

13. Other business

Nil items

14. Recommendation record

Recommendation 7.1

ACCM confirms that the draft minutes of its previous meeting ACCM 6 (3 June 2011), as amended, are a true and accurate record of that meeting

Recommendation 7.2

ACCM advises the TGA that data submitted for evaluation in the current application for pregelatinised *Lepidium meyenii* root powder are inadequate to support the safety and quality of the substance as a new complementary medicine substance for use in listed medicines. In particular there is inadequate identification of the starting material, inadequate assurance of the quality of the final product and concerns regarding the level of certain components (e.g. isothiocyanates and possible contaminants).

Recommendation 7.3

ACCM advises that the TGA's proposed risk mitigation strategies are considered adequate to address any potential safety issues associated with the use of New Zealand deer velvet antler powder and deer velvet antler slice as active ingredients in listed medicines.

Recommendation 7.4

ACCM advises the TGA that efficacy data provided in the application for the registration of a medicine containing bovine whey extracts are insufficient to allow the dossier to be accepted for full clinical evaluation. Specifically, the clinical trial on which the efficacy of the substance is based is considered of inadequate quality. Further, the ancillary literature provided in the dossier does not provide sufficient human clinical data to compensate for the inadequacy of the primary clinical trial.

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