Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 8th Advisory Committee on Complementary Medicines

Extracted ratified minutes

Eighth meeting

9 December 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
ASMI	Australian Self-Medication Industry
CHC	Complementary Healthcare Council
CMEC	Complementary Medicines Evaluation Committee
GRAS	Generally Recognised as Safe
HDL	High Density Lipoprotein
IJEACCM	TGA/Medsafe Interim Joint Expert Advisory Committee on Complementary Medicines
LDL	Low Density Lipoprotein
OCM	Office of Complementary Medicines
OICG	Office of Complementary Medicines/ Industry Consultation Group
OTC	Over the Counter
TGA	Therapeutic Goods Administration

The Advisory Committee on Complementary Medicines (ACCM) held its eighth meeting at the Stamford Hotel, Sydney Airport from 10am to 4:30 pm on 9th of December 2011.

TGA note: This document is the extracted minutes from the 8th 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 (ACCM Chair)
Dr Lesley Braun
Ms Patricia Greenway
Professor Stephen Myers
Dr Hans Wohlmuth
Dr Richard Oppenheim
Dr Xianqin Qu
Dr Simon Spedding
Professor Bill Webster
Professor Peter Williams

Present from the Therapeutic Goods Administration

Ms Jenny Burnett (ACCM Secretary)
Mr Ian Stehlik (Head, Office of Complementary Medicines)
Ms Diane Wilkinson
Dr David Tattersall

Present for part of the meeting

Dr Jane Cook (Head, Office of Product Review)

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

Ms Karen Martin, ACCM member.
Dr Marie Pirotta, ACCM member.
Dr Megan Keaney, TGA Principal Medical Advisor.

1.3 Conflict of interest

1.3.1 Meeting declaration

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

1.3.2 Discussion on conflict of interest matters

The Chair introduced this item, reminding members that the TGA published guidelines and forms relating to declaration of interests in 2010. A forum of the statutory committee chairs was held in August 2011 which provided an opportunity for the chairs to discuss the types of issues that commonly arise for each committee and consider a consistent approach to address potential or perceived conflicts of interest across committees. At this forum the chairs agreed that each committee should be given an opportunity to consider principles used to determine when declared interests could present as a potential conflict and also discuss conflict of interest scenarios specific to that committee.

In considering specific scenarios, a member raised the situation where a member may be personally consuming a complementary medicine that is associated with an agenda item and questioned whether this would be considered a conflict. It was agreed that the member should declare that they are using the medicine for personal medication, but the committee should use commonsense to consider if this is a conflict. As with all declarations of interest, the committee needs to consider all the facts relating to a declared interest and consider each situation on a case by case basis. In this scenario, the member's personal experience of the medicine may, in fact, contribute to the breadth of committee discussion and may not preclude the member from deliberations, particularly if the use of the medicine is common in the community. However, conversely, if a member would be adversely or positively affected by a committee decision on the matter e.g. the availability of the medicine may be affected, then this could be perceived as a potential conflict of interest.

A member raised the situation where a company provided minor sponsorship e.g. hospitality, at a patient education session and questioned if this was a conflict of interest. Members considered the proportionality and level of association with the company needed to be considered. If the member was speaking independently at such a gathering and received no direct pecuniary benefit from the company, this was unlikely to represent a conflict. However, if the member received a speaker's fee from the company, or was required to use company material for their presentation, this was likely to be perceived as a conflict.

It was noted that if a member worked in the commercial environment it is likely they would have associations with companies that have a wide range of products. The member may have not been associated with the current product before the committee, but may have worked on other products within the company's range. It was agreed that the proportionality and timing of this association would need to be considered by the committee. That is, if the member had received, or will be likely to receive significant pecuniary benefit from the company and the association is current or recent, this may be perceived as a conflict. However, if this was not the case, it may be perceived as less of a potential conflict. When the committee has considered the proportionality and timing of the association, the committee may then determine the degree of participation that the member should have in the committee's discussions e.g. the member can provide advice of a technical nature, but not participate in the forming of a recommendation.

Potential conflicts that may arise in the research arena were discussed, such as the situation where a researcher may be undertaking a clinical trial for a competitor or an alternative product, or had been the unsuccessful applicant for a competing research grant application. It was agreed that these interests should be declared as they arise and the perceived or actual conflicts of interest determined on the facts of each case. Again, it is important to declare these interests so that the integrity of the committee's discussions is beyond reproach.

Members questioned the time frame for declaring interests. A TGA Officer responded that upon application to a committee, an applicant must declare any interests arising within the past 5 years. Once appointed to the committee, a member is required to declare interests arising in the past 3 years. However, that given, significant interests should always be declared, irrespective of the time lapsed e.g. if a member had ever been Chief Executive Officer or a member of an advisory board for a therapeutic goods company.

A member commented that, due to the nature of their work, they have been associated with a large number of companies and, as such, would frequently need to declare their interests and absent themselves from the room. Other members reiterated that the purpose of declaring interests was to ensure the integrity of the committee's processes. The onus was on the member to declare their interests and "if in doubt, the member should step out". It is then up to the rest of the committee to determine if a potential actual or perceived conflict exists and if so, to determine the level of harm this could present, such as the committee reaching a 'bad' conclusion, or damage caused to the committee or organisation. The committee has a number of management options available to them to manage potential actual or perceived conflicts of interests appropriately.

The role of the Chair in discussions of conflicts of interests was raised. While it is the whole committee's role to determine the significance of a member's declared interest, the Chair has a role in monitoring the consistency of the member's declarations and committee determinations. To assist the Chair, a TGA officer stated that the Chair would receive a summary of all members' annual declarations of interests, a summary of interests declared at meetings and the outcome of the

committee's previous considerations of declared interests prior to each meeting. In addition, the secretariat would provide an initial draft agenda to members three weeks before a meeting that will provide sufficient details (e.g. sponsors, active ingredients, products) for the members to anticipate if a potential conflict is likely to arise.

A member questioned how they could declare additional interests, which may not necessarily be specific to the current meeting, but arise through the course of the year. A TGA Officer stated that there is a provision on the 'meeting declaration form' for members to declare additional interests that have arisen since the member last completed an annual declaration form.

Members agreed that the discussion had been useful and they supported the draft principles for determining the significance of member's declared interests.

Outcome

Members discussed matters relating to conflicts of interest and endorsed the draft principles for 'consideration of conflicts of interest'.

2. Confirmation of draft minutes of ACCM 7 (2nd September 2011)

Discussion

A member noted a discussion under Item 8.1, in relation to the substances 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 member had sought details of the TGA's intentions for the substances that had been approved as 'low risk' substances by IJEACCM, to which a TGA officer had responded that new formal applications (for these substances to be approved for use in listed medicines) will be required, however, these submissions could be based on the IJEACCM dossier. The member questioned if industry groups such as the Complementary Healthcare Council (CHC) and the Australian Self Medication Industry (AMI) were aware of this situation. A TGA Officer responded that these groups were aware of this, *via* their membership of the OCM/Industry Consultation Group (OICG) which comprised representatives from the TGA, CHC and ASMI.

A member also noted the statement under Item 8.2 'Progress report on TGA Regulatory Reform Projects' which stated that a number of guidance documents had been identified as a priority for TGA review. The member questioned the timeframe for the completion of the revised documents. A TGA Officer responded that this would be discussed later in the meeting as 'other business' (*TGA note: due to time limitations, this matter was not discussed in 'other business' at ACCM 8th and was carried over to ACCM 9th).*

Recommendation 8.1

ACCM confirms that the draft minutes of its previous meeting ACCM 7 (2nd September 2011), as amended, are a true and accurate record of that meeting.

3. Action arising from previous meetings

3.1 Substances on a 'watching brief'

Background

A TGA officer introduced this item reminding members that, at ACCM 7, members had requested a list of the substances placed on 'watching briefs' by the ACCM and the Complementary Medicine Evaluation Committee (CMEC).

At ACCM 8 members were provided with a list of herbal species and other substances currently considered to be on a watching brief and noted the internal TGA procedures in place to monitor these substances including:

- Regular monitoring of adverse drug reaction reports received by the TGA.

- TGA library alerts of recent literature.
- Monitoring of international alerts e.g. International Regulatory Cooperation for Herbal Medicines, Health Canada and FDA MedWatch.

Comment was sought from ACCM on a proposed approach to ensure effective monitoring of those substances placed on a 'watching brief'.

Discussion

Members appreciated being provided the list of substances considered to be on a 'watching brief' and expressed surprise at the relatively small number of substances included in the list. A member questioned how information for the substances was monitored, noting that as there are a relatively small number of substances, a literature update through a search engine would not be labour intensive.

Members questioned the length of time a substance should remain on the list. That is, could a substance be removed from the list if there have been no adverse events or literature reports for five years. Members agreed that substances should not remain on the list indefinitely and a TGA officer undertook to review the list to determine if any substances could be removed.

Outcome

Members noted substances allocated to a watching brief by CMEC/ACCM.

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

Nil items

5. Evaluation of New Substances

5.1 Betaine-anhydrous and monohydrate

Background

A TGA officer introduced this item, informing members of an application for betaine and betaine monohydrate as active ingredients to be approved for use in oral listed medicines.

Betaine (also commonly known as trimethylglycine or glycine betaine) is a derivative of choline and is obtained from sugar beet. Betaine is an endogenous metabolite of choline in the human body, as well as being absorbed directly from dietary sources such as fish, beets, legumes, and wheat flour. Intake of betaine in the diet has been estimated as 0.5 g/day on average, with up to 2.5 g/day consumed in a high seafood diet. Betaine has Generally Recognised as Safe (GRAS) status in the USA.

Members noted that in Australia, betaine is approved for use as an active ingredient in registered oral medicines. The related substance, betaine hydrochloride, is approved for use, as an excipient ingredient only, in listed medicines without quantity restriction.

In 2006 the Interim Joint Expert Advisory Committee on Complementary Medicines (IJEACCM) (in the context of the proposed Australia New Zealand joint therapeutic products regulatory scheme) recommended that betaine and its hydrochloride salt were suitable for use in Class 1 medicines (equivalent to listed medicines). ACCM noted that new information, that raises questions about the safety of betaine supplementation, has become available since the IJEACCM recommendation.

The officer informed members that two sets of 28-day and 90-day dietary studies with betaine had been conducted in rats (reviewed in Hayes *et al*., 2003). In the first set of studies, changes to the liver at all doses tested, as well as changes to clinical chemistry and haematology parameters, were observed in treated rats. These changes were not observed in a second set of studies designed to determine a no observed effect level, though there were shortcomings with the design of the latter studies.

The lowest dose at which effects were seen in rats was approximately equivalent to 800 mg/kg bw/day, which converts to a dose of 5.8 g/day for a 60 kg individual on a body surface area basis. From the information available for individuals with homocystinuria being treated with betaine, doses of the order of 20 g/day appear to be well tolerated.

The officer stated that the relevance of these findings in animal studies to humans taking betaine orally is unclear. The findings appear to be at odds with the fact that betaine is an endogenous metabolite in humans; that the dietary intake of betaine may be quite high; and the apparent absence of reported adverse reactions to doses that may exceed dietary intake, both in the scientific literature and for oral medicines containing betaine or betaine HCl that are already on the ARTG.

Members noted that in several clinical studies, it has been claimed that betaine supplementation increased plasma/serum levels of total cholesterol, Low Density Lipoprotein (LDL) and triglycerides to a statistically significant extent, with High Density Lipoprotein (HDL) unaffected. However, the officer stated that there is some controversy in the literature about whether the effect of betaine on blood lipids is clinically significant, or an artefact resulting from different baseline levels in the placebo and active groups.

A recent study by Schwab et al., 2011 reported no significant changes in serum lipids in 32 healthy subjects given a betaine dose of 4 g/day for 6 months. Also, in a 2-week crossover study in which 8 healthy males received either a high betaine diet (~800 mg/day) or a betaine supplement (1 g/day), Atkinson *et al.* (2009) observed no change from baseline in serum lipids at the end of the treatment period, but a statistically significant reduction in serum total cholesterol and LDL after a high betaine diet, relative to baseline levels. However, the authors suggested that reduction in lipid levels with the high betaine diet more likely reflected the poor diet choices of the subjects prior to treatment.

In studies in healthy individuals, results for blood lipid measurements were not consistent for betaine doses of 6 g/day. The changes observed were slight and unlikely to be of clinical significance and the validity of the findings, which were based on combined study results, is questionable. In studies performed at lower doses of ≤4 g/day for up to 6 months, no significant changes were observed.

Members were informed that one adverse reaction to a multi-ingredient oral product containing betaine HCl was retrieved from the Australian database, for which the symptoms were consistent with an allergic reaction after taking a single dose. No other relevant reports of adverse reactions were located.

Members noted a proposal that, if betaine is approved for use in listed medicines, an upper dose limit may be appropriate. The evaluator suggested that the limit could be based on typical products on the market that contain choline, such as multivitamins where it is most commonly used at a level of 50 mg/unit dose. However the officer stated that, for a number of reasons, it does not appear possible to justify on scientific grounds an upper limit for betaine of 50 mg/day based on choline.

In conclusion, the officer stated that consideration of whether or not it is necessary to apply an upper daily dose limit should take into account the evidence that betaine in the diet and in dietary supplements is similarly absorbed. As the daily diet is expected to deliver 0.5 – 2.5 g of betaine, supplementation in this range would therefore be expected to be safe. Also, clinical trials in which healthy subjects have taken doses at up to 4 g/day for 6 months, thereby exceeding the dietary range, have raised no safety concerns, though potential effects on blood lipids at 6 g/day have been proposed. On this basis, it may be possible to justify a limit of 4 g/day. However, it should be noted that dose limits do not apply to the related substances choline bitartrate (active and excipient ingredient) and betaine hydrochloride (excipient ingredient) when used in listed medicines.

ACCM was asked to consider the suitability of betaine and betaine monohydrate as active ingredients in listed medicines. Specifically, the committee's comment was sought on:

1. The relevance of the findings in the repeat dose studies in rats to potential human exposure to betaine in oral listed medicines.
2. Whether increases in blood lipid levels associated with high doses of betaine are a safety concern.

3. Whether the data justify an upper daily dose limit, possibly exceeding levels of exposure expected in a normal diet.

Discussion

Balance of evidence

Members agreed the balance of evidence needs to be considered to determine if there are potential safety concerns associated with the use of betaine as an ingredient in oral listed medicines.

Members noted betaine's occurrence in nature; the regulatory status of the ingredient in Australia and overseas; and that few adverse events have been reported. However, it was commented that while betaine is currently included as an excipient in listed medicines, the ingredient is likely to be present in only very small quantities, so the safety of the ingredient cannot be assumed from this use. Further, in certain circumstances, rat studies have shown that betaine has adverse effects and alters lipid metabolism, which may have safety implications for use in humans. In addition, human studies indicate there may be an effect on lipoprotein levels at certain doses.

Members commented that as betaine is endogenous and ubiquitous, there could be an assumption that the substance is safe, but it was contended that not all ubiquitous substances are innocuous e.g. cholesterol.

Members noted that the evaluation undertaken in 2010 considered that there were safety concerns regarding the use of betaine as a nutritional supplement due to a potential for an increase in plasma LDL and triglyceride levels. The evaluation recommended that if the substance was approved for use in listed medicines, the maximum permitted dose should be less than 50 mg per day. A TGA officer stated that this report had been based on the information available in 2010 and since that time, additional reports have been published, which ACCM is now being asked to consider.

The significance of an increase in LDL at an individual level compared to an increase in LDL across a population was discussed by the committee. That is, a small increase in LDL for an individual is unlikely to increased cardiovascular risk for that individual, however, a small increase in LDL levels across a population may increase the cardiovascular risk for that population.

Members considered it unfortunate that the animal and clinical studies were not independent, but supported by the manufacturer identified as the supplier of the proposed new ingredient. A TGA officer stated that, in addition to the information provided by the applicant, the TGA undertook a literature search to ensure all available information is taken into consideration.

Animal studies

Members discussed the results of the studies in *Hayes et al*., 2003 which reviewed two sets of 28-day and 90-day rat dietary studies. In the initial set of studies, changes to the liver occurred at all dose levels. The second set of studies did not show the same changes, although there were shortcomings with the design of these studies, including failure to perform histological examination of the liver in the 90-day study. It was also noted that the rodent chow in these studies included twice the energy from fat and 40% more energy from protein per gram of diet compared to the diet used in the first set of studies.

While betaine is metabolised the same way in humans and rats, and therefore these studies are relevant to human consumption of betaine, members noted that the reasons for the observed adverse events in rats was not understood. It was also noted that these events occurred at 800 mg/kg bw/day in rats, and as this dose could not be extrapolated to humans, a safe level for human consumption could not be determined.

Human studies

Members agreed that the adverse liver findings in the rat studies may indicate a cause for concern but the human studies were of more relevance. Earlier human studies with betaine supplementation have shown elevated LDL levels as did the rat studies. Betaine supplementation at 6 g has shown an increase in serum LDL cholesterol concentration in healthy subjects (Olthof *et al*., 2005) and obese subjects (Schwab *et al*., 2002). Betaine supplementation at 4 g in patients with chronic renal failure (McGregor *et al*., 2002) has also shown an increase in serum LDL cholesterol concentration.

Members discussed the paper by Schwab et al., (2011), in which 63 volunteers (31 treatment group, 31 control group) participated in a placebo controlled, randomised, parallel double-blinded study. The subjects consumed 4 g betaine/day over a period of 6 months. The authors concluded that betaine had no effect on serum lipid profile in the long term in young healthy subjects. However, members noted that data included at Table 4 in this paper showed that, at 24 weeks, low-density lipoprotein (LDL) had increased in the treatment group (2.64±0.70 to 2.74±0.65) and decreased in the placebo group (2.63±0.72 to 2.61±0.74). While members agreed that these results were clinically not significant, they contended that they were not insignificant statistically. Members also noted with interest that in this study the HDL and the total-to-HDL cholesterol ratio did not change in either the treatment or control groups.

Members agreed that the results in these human studies could have been affected by confounding factors such as diet, which was not possible for the committee to ascertain without having access to the original data. While it was acknowledged that some human studies have shown betaine supplementation increases LDL, the studies were lacking detail, inconsistent and did not provide clear outcomes.

Therapeutic activity

Members discussed correspondence from the applicant which stated the intention to use betaine in listed medicines as a 'nutritional supplement' with therapeutic claims such as "maintenance of normal homocysteine metabolism", "maintenance of liver health" and "a recovery aid after training". A member questioned the real benefit of these claimed effects, but other members responded that reducing homocysteine levels may have a beneficial effect for the cardiovascular system. Members noted the claim that a reduction in homocysteine levels negates any adverse events from an increase in lipids, but this was unanimously discounted.

Members also considered the effect on hepatic lipids was contrary to the proposed claim of maintaining liver health. Members postulated that the claim relating to liver health may be based on the general naturopathic philosophy that improving digestion and detoxification reduces liver burden.

Possible cut-off

Members agreed that at a certain dose level betaine was a low risk ingredient, but there was enough evidence of a potential safety concern associated with certain dosages of betaine to justify a dose restriction. While inconsistent outcomes arose from the human studies, the studies performed on rats raised doubts on the safety of the substance. Noting that although adverse clinical outcomes for humans were not suggested by these studies, changes to lipid levels were observed and this resulted in the need for a limit on human consumption. The committee considered however, that there was limited information to determine the dose at which a safety concern would arise and in what population group.

Members questioned the level of betaine currently included as an excipient in listed medicines. A TGA officer stated that choline is currently permitted in listed medicines without restriction, but the majority of products contain 50 mg choline bitartrate per unit dose. However, as it is not known to what extent orally administered choline is metabolised to betaine, it is not appropriate to base the dose of betaine on the choline present in listed medicines.

Members questioned what doses had been reported in association with therapeutic benefits. A TGA officer responded that the European Food Safety Authority panel determined that consumption of 1.5 g of betaine/day was required to obtain the claimed effect "betaine contributes to normal homocysteine metabolism", assuming the target population was the general population. Members discussed the different dosage regimes that consumers may adopt, regardless of dosage instructions.

Members noted that the clinical studies showed no statistically significant changes in LDL at 1.5 and 3 g/day, though effects were seen at 6 g/day (Olthoff *et al.,* 2005). Members discussed the difficulties of using these data to establish a maximum daily dose. A TGA officer stated that in a potential situation where the evidence of efficacy was for a dose of 1.5 g, yet the medicine was restricted to a lower dose, the sponsor would not be considered to hold evidence of efficacy for their medicine and would be in breach of the conditions of listing on the ARTG.

It was questioned if a daily dose restriction would also apply to the use of betaine as an excipient. A TGA officer confirmed that any restriction on an ingredient would apply to use of the ingredient in both active and excipient roles.

In conclusion, members agreed that betaine was a low risk ingredient suitable for inclusion in listed medicines if an appropriate daily dose restriction was applied. In general, the committee was comfortable with a daily dose of betaine at approximately 1 g per day, but agreed that the TGA should determine the cut-off figure, taking into consideration efficacy in addition to the identified safety concerns.

Recommendation 8.2

ACCM advises the TGA that, at an appropriate dosage level (as determined by the TGA), betaine and betaine monohydrate have demonstrated the appropriate level of safety for an ingredient considered suitable for use in listed medicines.

6. Safety or efficacy reviews

6.1 Potential safety issues relating to the use of *Nardostachys chinensis* and *Juniperus species* in listed medicines

This item was not considered due to time limitations.

7. Registration Applications

Nil items

8. Regulatory reforms

Nil items

9. Adverse drug reactions associated with complementary medicines.

9.1 Office of Product Review overview on reporting of ADRS associated with complementary medicines

Discussion

Members welcomed the Head of the TGA's Office of Product Review (OPR) who provided the committee with an overview of the work of the office.

The OPR came into effect in July 2010 as a result of a TGA internal restructure, with the purpose of separating and streamlining the pre and post market regulatory activities of the TGA. The OPR now consists of 50 multi skilled staff, including eight medical officers, numerous pharmacists and two naturopaths. The medical officers are employed based on their experience and receive internal and external training in such areas as pharmacokinetics, epidemiology and biostatistics.

Functions of the OPR

The OPR is responsible for a broad range of post market activity, including:

- Monitoring of adverse events to therapeutic products

  The OPR is responsible for reviewing all adverse events reported for all medicines and devices. On average, over 15000 ADRs are reported for medicines and 4,500 ADRs are reported for devices each year.

  The OPR has developed an ADR database which is used to generate safety signals, track safety related issues and allocate and prioritise the OPR's activities. The database has been in use for 6 months and currently there are over 300 safety issues related to medicines and devices included in the database. Members questioned how many of these issues related to

complementary medicines. This was estimated to be approximately 1-2% of the total.. ACCM expressed interest in receiving a summary of the current issues identified for complementary medicines.

The TGA officer advised that all serious ADRs are reviewed by a medical officer who endeavours to obtain as much information from the reporter as possible. Three attempts are made to follow-up with the reporter.

· Risk Management plans

The OPR develops risk management plans for pharmaceutical medicines with new chemical entities, major extensions of therapeutic indications and/or known or unknown safety concerns. Risk management plans are concerned with minimising potential risks associated with the use of a medicine e.g. if there is a potential for liver adverse events associated with the use of a medicine, the risk management plan may include the requirement for liver function tests pre and post treatment. For new medicines and/or new or extended indications, periodic safety reports are required for 3 years after the medicine is available in the marketplace. Risk management plans are provided to the Delegate to aid in the determination of whether a medicine should be approved or not approved for inclusion on the ARTG.

· Product Recalls

The OPR is also responsible for product recalls, whether these be at the wholesale, retail or consumer level. The recall process requires communication and co-ordination with other sections within the TGA such as Office of Manufacturing Quality, the Office of Laboratory and Scientific Services and the Advertising Unit. Where a recall is considered necessary, a consumer statement is posted on the TGA website.

Reporting ADRS

Adverse events are reported to the TGA from multiple sources: sponsors, practitioners, hospitals, pharmacies, members of the public, other regulators and international alerts.

It was noted that there is no mandatory requirement under the *Therapeutic Goods Act 1989* (the Act) for medical practitioners to report ADRs. However, there are Australian State and Territory Rules that make it mandatory for health practitioners to report certain ADRs e.g. ADRs to vaccinations.

Under the Act, sponsors of medicines included on the ARTG have obligations to report serious ADRs associated with their medicines to the TGA.

An ACCM member commented that, in relation to complementary medicine sponsors, these are often small companies who may not be aware of their responsibilities or have an adequate system in place for reporting ADRs.

The TGA officer informed the ACCM that the TGA has recently developed pharmacovigilance guidelines that outline the responsibilities of sponsors in relation to reporting of ADRs. When these guidelines come into effect, they will be applicable to sponsors of all listed and registered medicines. Briefly, the guidelines state that sponsors are required to have an allocated person responsible for collecting ADRs, a system in place to record ADRs, serious ADRs must be reported within 15 days and records of non-serious ADRs should be kept for a period of 5 years. The TGA officer also advised that the complementary medicines professional organisations are exploring ways of providing assistance so that sponsors, especially smaller entities, had access to support to comply with these requirements.

Members asked what the best pathway was for consumers to report ADRs. It was advised that consumers can report ADRs to the sponsor (via the contact details on the medicine label) who then reports it to the TGA, or alternatively, a consumer can provide the information directly to the TGA by email, fax, telephone or mail. Members further questioned what response a consumer could expect when they have reported an ADR. It was stated that the reporter will receive an acknowledgment that the ADR has been received.

The information received by the TGA is entered into the ADR database to contribute to a body of knowledge. For an ADR database to be effective in generating signals, the database requires 250 to 300 thousand entries. Members questioned what the ADR threshold was that would generate a

signal. It was stated that a proportional reporting ratio number of three would generate a signal. Members expressed interest in understanding how signals are generated and safety issues identified. The officer undertook to provide this information to the committee.

Members questioned how ADRs for complementary medicines are monitored. The officer stated that ADRs for complementary medicines are reviewed by an OPR medical officer who assesses the risk/benefit and, if a safety signal is identified requiring further investigation, the issue will be allocated to a staff member with expertise in complementary medicine. If a particular concern is identified, this may go into the recall system.

Members discussed their concern that ADRs for complementary meds are grossly underreported. To increase the reporting of adverse events, the committee encouraged active engagement with general practitioners, complementary medicine practitioners, educational and professional organisations e.g. the Complementary Healthcare Council (CHC) and the Australian Self Medication Industry (AMSI) Education was required at the clinical interface on the importance of providing sufficient details relating to the product information. Members commented that TGA advertising seminars are well attended and it was suggested that information sessions on ADR reporting and pharmacovigilance be added to these sessions. The officer agreed, stating that the current TGA reforms have identified the need for increased communication with consumers and other health care professionals. Strategies to be implemented by the TGA to achieve this include TGA attendance at conferences and seminars and increased liaison with professional groups and consumer groups. In addition, the TGA is aiming for a more proactive approach that will alert consumers and industry to actual and potential safety issues. The committee expressed a willingness to help in any area, particularly with facilitating increased engagement with practitioners.

Role of the Advisory Committee on the Safety of Medicines

ACCM noted that the Advisory Committee on the Safety of Medicines (ACSOM) no longer considers all individual ADRs reported to the TGA. Rather, the OPR filters the ADRs through the database and only takes issues identified for products or types of products to the ACSOM for specific advice. The ACSOM may also be commissioned to give advice on risk management plans; on issues relating to education; and, robustness of TGA processes.

A member questioned if the ACSOM considered ADRs for complementary medicines, noting that there is not a member with expertise in complementary medicines on the ACSOM. The officer stated that ACSOM could refer matters to other committees if this was considered necessary.

Outcome

ACCM noted the business functions of the TGA's Office of Product Review, the development of the ADR database and the systems in place to detect signals for further investigation of ADRs.

9.2 ADRs associated with complementary medicines from 1 August to 31 October 2011

Outcome

ACCM noted reports for ADRs from 1 August 2011 to 31 October 2011, however, did not discuss individual cases.

A TGA officer advised the ACCM that in future, details of individual ADRs will not be provided to ACCM, as a synthesis of signals for ADRs for complementary medicines is considered to have a more practical application.

In future, the TGA will ask the committee for assistance where an issue of concern has been identified. These matters can be referred to the committee from the Advisory Committee on the Safety of Medicines or from the TGA as required.

10. Matters referred from within TGA

10.1 The committee considered one matter under this agenda item, but as this item remains the subject of further committee consideration, the minutes relating to this item have not been published at this stage.

11. For information

11.1 Advisory Committee on Non-prescription Medicines June 2011

Outcome

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

11.2 Medicines Safety Update bulletin Vol 2, No 5, 2011

Outcome

ACCM noted the Medicines Safety Update bulletin Vol 2, No 5, 2011.

11.3 For Information Advisory Committee on the Safety of Medicines meeting 8 minutes

Outcome

ACCM noted the Advisory Committee on the Safety of Medicines meeting 8 minutes.

12. Sponsor representations to ACCM

Nil items

13. Other business

Item 13.1 Regulatory reforms update and proposed publication of a list of evaluated registered comp meds

Discussion

A TGA officer provided an update on the progress of recent regulatory reforms and reviews occurring within the TGA.

Members noted a report (No. 3 2011-12) released in August 2011 by the Australian National Audit Office (ANAO) included 5 recommendations in relation to the regulation of complementary medicines and advertising. The officer advised that all these recommendations have been accepted by the Minister for Health and Ageing and a blue print for a significant and wide-ranging package of reforms has been developed. A TGA project team has established in the TGA to develop a business plan for the implementation of these reforms. The committee noted this with interest and requested details of the business plan when available.

Outcome

ACCM noted the completion of a number of reviews undertaken by the TGA which has resulted in a recent announcement by the Hon Catherine King MP of a blue print for a significant and wide-ranging package of reforms for the TGA.

Item 13.2 Govdex feedback

Discussion

Members were asked to provide feedback on the recent implementation of the Govdex database for the dissemination of ACCM agendas.

Outcome

Members provided feedback on the use of the Govdex database for the posting of the ACCM 8th agenda.

14. Recommendation record

Recommendation 8.1

ACCM confirms that the draft minutes of its previous meeting ACCM 7 (2 September 2011), as amended, are a true and accurate record of that meeting

Recommendation 8.2

ACCM advises the TGA that, at an appropriate dosage level (as determined by the TGA), betaine and betaine monohydrate have demonstrated the appropriate level of safety and quality for an ingredient considered suitable for use in listed medicines.

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