Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM
Advisory Committee on Complementary Medicines

Extracted ratified minutes
Ninth meeting

9 March 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act* 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADRs	Adverse Drug Reactions
ARGCM	Australian Regulatory Guidelines for Complementary Medicines
ARTG	Australian Register of Therapeutic Goods
CMEC	Complementary Medicines Evaluation Committee
EP	European Pharmacopeia
FSANZ	Food Standard Authority Australia and New Zealand
GRAS	Generally Recognised as Safe
OCM	Office of Complementary Medicines
OPR	Office of Product Review
TGA	Therapeutic Goods Administration

The Advisory Committee on Complementary Medicines (ACCM) held its ninth meeting at the TGA from 10:45 am to 4:15 pm on 9th of March 2012.

TGA note: This document is the extracted minutes from the 9th 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
Ms Karen Martin
Professor Stephen Myers
Dr Marie Pirotta
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)
Ms Trish Garrett (Head, Office of Complementary Medicines)
Ms Diane Wilkinson (ACCM secretariat)

Present for part of the meeting

Mr Gerry Dendrinos
Dr Michael Dodson
Dr Linda Lenton
Ms Antoinette Schultz
Dr David Tattersall
Ms Jenny Mason

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 10:45pm, welcoming ACCM members and TGA staff.

1.2 Apologies

Dr Jason Ferla, Acting TGA Principal Medical Advisor.

1.3 Meeting declaration of interest

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

1.4 Options available to manage potential conflicts of interest

Background

Members were provided with an excerpt from the '*TGA advisory committee guidelines: Declarations of interests, managing conflicts of interests and confidentiality obligations*' (pages 12-18) which provides the options available for the committee to manage potential conflicts of interest, as below:

- allowing the member to participate fully in the deliberation by the committee and in any decision about making recommendations;
- excluding the member wholly from consideration of the matter;
- allowing the member to be present to answer questions or provide advice on particular matters or of a technical nature but not to participate in discussion or in making a decision about a recommendation; or
- allowing the member to participate in discussion but not to contribute to any decision to make a recommendation on the matter.

Outcome

Members noted the options available to the committee to manage members' declarations of interest. In general, Members agreed that the Committee should adopt a conservative approach to managing members' potential conflicts of interest, while ensuring the availability of expert advice to the Committee is not compromised. It was recognised that this may necessitate the sourcing of external expertise when required.

2. Minutes of previous meetings

2.1 Draft ACCM 8th minutes

Members requested some minor amendments to the draft ACCM 8 minutes and questioned the progress of action items arising from this meeting, as detailed at Item 3.

Recommendation 9.1

ACCM confirms that the draft minutes of its previous meeting ACCM 8 (2nd Dcember 2011), as amended, are a true and accurate record oft he that meeting.

3. Action arising from previous meetings

1.3 Meeting declaration of interest

Discussion

At ACCM 8 the committee considered a list of substances placed on a 'watching brief' by the ACCM and the Complementary Medicines Evaluation Committee (CMEC). At this time the TGA undertook to review the list to determine if any substances can be removed from a watching brief. Any substances identified for removal by the TGA would be tabled at an ACCM meeting, following which the revised list will be posted on Govdex. Members were advised that, to date, progress has not been made on this matter.

At ACCM 8 the Committee also considered new listable substance applications for betaine and betaine monohydrate. The Committee considered that, an appropriate dosage level, the safety profile of these substances were considered suitable for use in listed medicines. At the current meeting Members questioned whether the TGA had determined a suitable dosage level for these substances. A TGA officer advised that, as part of the process of finalising the evaluation of betaine and betaine monohydrate, the TGA will determine an appropriate maximum daily dose restriction, taking into account issues raised by the Committee.

In relation to other action items arising from ACCM 8, the Committee noted that these were to be addressed at the current meeting. In relation to action items from preceding meetings, the OCM undertook to provide the Committee with a status report.

4. Evaluation of new substances

4.1 Consideration of oral evidence of traditional use to support safety of complementary medicine substances

Background

A TGA officer introduced this item advising members that, in the evaluation of a new complementary medicine substance application for '*Ventilago viminalis* bark' an issue had arisen relating to the evaluation of oral evidence of traditional use. Members were asked to note that a reference to the need to provide photosensitivity data had been inadvertently omitted from the briefing paper.

Members noted that the safety aspects of the application for *V. viminalis* bark included a number of toxicology studies using an aqueous extract of the bark. The toxicology studies comprised acute oral and dermal studies in rats; an acute dermal irritation/corrosion study in rabbits; a local lymph node assay in mice; and an *in vitro* bacterial reverse mutation study in *Salmonella typhimurium.* Members noted that the *in vitro* mutagenicity study on its own is insufficient to establish the genotoxic potential of the substance. Though not a safety study *per se*, a wound healing study in rabbits was performed with the same substance. A human repeat insult patch test to determine irritation and sensitisation potential was also provided.

The TGA officer stated that none of the studies raised any safety concerns for the substance tested. However, the applicant had been asked to comment on the absence of a repeat dose toxicity study or clinical data to enable the assessment of the systemic toxicity of the substance when applied repeatedly *via* the dermal route, given that this is the proposed route of administration for future products. In response, the applicant stated that "the application relies on a history of traditional use, as applies to numerous herbal substances already permitted in listed medicines. As a formal written Aboriginal language does not exist, obtaining evidence of traditional use for substances used therapeutically in Aboriginal culture has particular challenges. There is no written history of Australian indigenous medicines, or published pharmacopoeia or *materia medica*. Knowledge of traditional medicine is passed orally down through generations usually by the senior women of the community. " To this end, the application included a report from an ethno-botanist who was commissioned to interview various language groups in the geographical area where this plant was traditionally used.

Evidence of traditional use provided in the application for *V. viminalis* bark comprised the ethno-botanist's report and extracts from a number of reference texts. However, the original sources referred to in the texts were not included in the dossier.

The report contains information gathered by the ethno-botanist from discussions held on one day with nine individuals on the preparation and use of *V. viminalis.* For the most part, the information provided by the interviewees was consistent with the information in the references with respect to preparation and medicinal use of *V. viminalis*.

These resources indicate that an extract of *V. viminalis* bark, prepared by soaking or boiling in water, has a history of use by the Aboriginal people from Kumumurra to Broome in Western Australia, mostly for the treatment of skin conditions and injuries, though it has also been used for a range of other conditions. A traditional preparation has usually been applied topically, though it may also be taken orally in some circumstances. In traditional use, aspects of extract preparation such as extraction ratio and time of

extraction appear to be variable, as is the dosage regime. The applicant proposes that listed medicines containing the substance, presented as liquid and semi-liquid topical dosage forms, are to be applied to the skin of adults and children (over two years of age), as required, for minor skin complaints such as cuts and bruising.

ACCM noted that, based on the information provided, the TGA is of the opinion that the safety of the substance has not been established for its intended use, and in order for this to be achieved repeat dose dermal toxicity and additional genotoxicity studies are required.

ACCM was asked to advise the TGA, with particular reference to the current new substance application, if an oral history of traditional use can compensate for gaps in the scientific data required to support the safety of the substance.

Discussion

Oral versus written

Members agreed that the consideration of oral history of traditional use in support of efficacy was an important issue, given that non-acceptance of oral histories may potentially present a barrier for preparations of Australian native plants being permitted for use in listed medicines.

The Committee agreed that oral histories of traditional use should be given due respect. Through life experience, insight, necessity, trial and error, and centuries of use, traditional cultures have gained knowledge of indigenous substances, using both nontoxic and toxic parts of plants, with traditional preparation methods developed to reduce toxicity and increase effectiveness.

Oral evidence to support safety

Members discussed the limitations of oral history and inherent difficulties with accepting this type of evidence to support safety. While an oral history can provide the manner of use, it does not give an indication of the extent of use, the prevalence of use or delayed effects. Further, there is the potential for bias or distortion in translation and interpretation. Conversely, it was argued that written histories can also be subject to bias and distortion, but there was agreement that, in general, writing a history necessitates caution and onerous precision due to an awareness it will be subject to scrutiny. Members acknowledged that a cultural bias exists, in that some cultures have a preference for a written history, whereas for other cultures, oral accounts of history is the norm.

Discussion ensued in relation to the different levels of confidence applicable to written documents, such as scientific documents, having greater credibility if they have been peer reviewed. Members agreed that there should be a weighting for oral histories as well, e.g. an isolated oral history of traditional use limited to one small community would have less weight than an oral history of extensive traditional use which is consistent across a wide range of diverse and discreet groups.

It was added that an oral history of use of a medicine in a small community cannot lead to the assumption that use of the medicine is appropriate for the broader population. This led to discussion on native title law, where a traditional medicine or food, which might be subject to restrictions limiting or preventing its use, is permitted for consumption by a person/group within that traditional paradigm for their cultural use, but it cannot legally be used by persons outside this environment.

A member stated that inclusion of oral history of traditional use in a national pharmacopoeia implies a peer reviewed process. However, it was commented that, in

general, pharmacopoeias are quality standards only and are not accepted as evidence of safety or efficacy.

It was noted that there was a provision in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM) for well documented traditional evidence to be used in support of efficacy and safety. Members agreed there is a need for TGA guidance on differentiation between oral and written histories.

In relation to the current application, a member proposed that, given that the oral history of traditional use and the toxicology studies, while limited, show no safety concerns and, as the proposed product is to have a topical route of administration only, a lesser amount of evidence of safety may be acceptable. However, another member disagreed with the assumption that a topical route of administration would pose less risk than an oral route of administration, given that topical products can have an effect on sun exposure and promote skin cancer. Further, there is systemic absorption of substances applied topically. For these reasons, pharmaceutical products require significant toxicological testing when the route of administration is topical.

The comment was made that if an application for a registered pharmaceutical medicine had a similar lack of toxicity data it would not be accepted.

Ethno-botanist report

Members were critical of the ethno-botanical report provided in the current application. It was noted the report broadly summarises discussions held with nine individuals on the same day, from the same area, and it was not detailed. Members considered it regrettable that the report had been limited to the one area and population group, particularly given that it is likely that the herb is used by other Aboriginal populations across Australia in the same way and for the same therapeutic purpose. It was agreed that multiple sources of traditional evidence across different cultural groupings which demonstrate the same use and dose would contribute more to establishing the safety and efficacy of a substance.

While the Committee considered it appropriate for an ethno-botanical expert to collect an oral history of traditional use, there should be guidelines providing a framework for collecting such information and a methodology for reporting the collected information.

Conclusion

The Committee stated that it has previously accepted traditional evidence of efficacy when there is enough evidence to support the safety of a substance. It was important that the approach to accepting an oral history of traditional evidence is consistent with the approach applied to accepting a written history of traditional evidence. That is, an oral history of traditional use can be used to support efficacy, provided there is sufficient evidence to support safety.

With respect to the current application, the committee agreed that the oral evidence of traditional use was not sufficient to compensate for the inadequate data supporting safety.

Recommendation 9.2

ACCM advised the TGA that, in relation to the application, the oral history of use is not considered sufficient evidence to compensate for toxicological data absent from the submitted dossier.

Recommendation 9.3

ACCM advised the TGA that, in broad terms, the robustness oof evidence basedon an oral history can vary and the committee recommended that the tTGA consider drafting relevant guidelines to addresss this issue.

5. Registration applications

5.1

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

6. Safety or efficacy reviews

6.1 Safety review of *Nardostachys chinensis* and *Juniperus species* in listed medicines

Background

A TGA officer introduced this item, advising the Committee that the TGA had undertaken a review of seven herbal ingredients with potential safety concerns that are currently permitted for use in listed medicines with no restrictions.

With respect to *N. chinensis,* Members were advised that there are currently two listed medicines on the ARTG containing preparations of the herb – one oral medicine containing the root/ rhizome and one topical medicine containing the essential oil obtained from the root.

The root and rhizome of *N. chinensis* has a long history of use in Ayurvedic and Traditional Chinese medicine with few safety concerns. However, safety concerns relating to the hypotensive action of the essential oil of a closely related species, *N. jatamansi* (which is not a listable ingredient), have been raised.

Members were advised that the TGA proposes to restrict the plant parts of *N. chinensis* permitted for use in listed medicines to root/ rhizome only and the essential oil preparation of *N. chinensis* root restricted to topical use only. These restrictions are consistent with traditional usage and consistent with the plant part preparations currently included as ingredients in medicines on the ARTG.

With respect to *Juniperus* species, the officer advised that contraindications and potential safety concerns exist relating to the oral use of *J. communis* berries and the essential oil in pregnancy and chronic renal disease/ acute renal inflammation. Potential safety concerns

also exist for the topical use of *Juniperus* species extracts and essential oils with respect to dermatological reactions.

Members were advised that, of the 80 products on the ARTG containing *Juniperus* ingredients, 62 contain *J. communis* berries or essential oil (topical and oral use). There is one homoeopathic product containing *J. sabina.* The remainder are topical products containing *J. oxycedrus* or *J. virginiana* wood stem essential oil.

Members noted that concerns relating to the use of *Juniperus* species appear to be based on inconclusive historical evidence and a preliminary investigation of available scientific data has also been inconclusive. In relation to use in pregnancy, the TGA considers that the risk/benefit posed by *Juniperus* ingredients is comparable to that posed by other herbs, such as *Achillea* species, for which no restrictions currently exist.

Overall, the TGA review concluded that the *Juniperus* species currently available for use in oral and topical listed medicines do not constitute a safety risk warranting additional restrictions, providing they continue to be used within traditional parameters.

Members are asked to comment on the outcome of the review of seven herbal ingredients that are currently permitted for use in listed medicines with no restrictions and the TGA's proposed approach to addressing these concerns.

Discussion

Nardostachys chinensis

Members questioned if *N. chinensis* has Generally Recognised as Safe (GRAS) status in the USA. A TGA officer responded this had not been ascertained. (*Post meeting TGA addendum: N. chinensis does not have GRAS status*).

The Committee noted that the reported hypotensive effects of *N. jatamansi,* a herbal species related to *N. chinensis,* refer to a study in 1958 involving an essential oil preparation administered intravenously to dogs at very high doses. The relevance of this to humans was not clear.

Members discussed the TGA's proposed restrictions on the plant parts of the herb and also the essential oil preparation of *N. chinensis,* noting the consistency with traditional use and the products currently on the ARTG. The Committee agreed with the TGA's proposed approach to ensure safety in use of preparations of this herbal species.

Juniperus species

Members noted that there are *British Pharmacopoeia* monographs for 'Juniper Berry' and 'Juniper oil'. The berries are commonly used topically and orally in western herbal medicine as well as widely used for culinary purposes and, as such, the herb is apparently non-toxic.

Members agreed that there was no apparent safety concern in relation to topical use. However, it was noted that there was some concern in relation to an abortifacient action of *J. communis* needles and berries and that *Juniperus* species were traditionally contraindicated in pregnancy. In literature, the abortifacient activity has been attributed to isocupressic acid, however the Committee noted that this component was present in *J. communis* berries at 0.00125%, which was considered a very low concentration. A Member questioned if there were currently any regulatory restrictions applicable to this toxic component and was informed that there was not.

It was noted that the studies demonstrating abortifacient activity were undertaken in cattle that were given large doses of *J. communis.* The Committee agreed that the relevance of these studies to humans was unclear.

The Committee noted some concerns related to the use in pregnancy, but were uncertain as to the relevance of this data and given the widespread use of the herb, considered that there were no apparent safety concerns associated with the use of *Juniperus* species in listed medicines.

Recommendation 9.5

ACCM agreed with the approach proposed by the TGA to minimise any potential safety concerns associated with the use of preparations of *Nardostachys chinensis* in listed medicines, as follows:

- restrict the permitted plant parts of *N. Chinensis* to root/rhizome only
- restrict the route of administration for the essential oil preparation of *N. Chinensis*

ACCM noted that these restrictions are consistent with tradityional use of the herb and with the formulations of the listed medicines currently on the ARTG.

Recommendation 9.6

ACCM noted the traditional contraindications associated with the use of the berries of Juniperus species in pregnancy, but given the uncertainty in relation to the relevance of the data and the widespread use of the herb, considered that there were no apparent safety concerns associated with the use of Juniperus species in listed medicines. The Committee therefore agreed with the TGA's proposal that preparations of Juniperus species remain eligible for inclusion in listed medicines with no restrictions on plant part, preparation or route of administration.

6.2 Chewing gum as a dose form for use in listed medicines

Background

A TGA Officer introduced this item, advising the Committee that the TGA has been approached by industry stakeholders to consider allowing chewing gum to be permitted as a dosage form in listed medicines, specifically for the systemic delivery of vitamin and mineral ingredients.

Currently, chewing gum as a dose form is only available for use in listed medicines when the route of administration is 'oral application' which limits the use of the products to dental type indications. There are listed medicines with the dose form chewing gum currently on the ARTG.

Generally, both in Australia and overseas, chewing gums are regulated as foods with the exception of highly researched products such as smoking cessation therapy gums or dental remineralisation products. Food Standards Australia New Zealand has a specific

Food Standard for chewing gum, which allows for the addition of calcium to some gums, but does not include other minerals or vitamins. There is an ambiguity as to whether chewing gums containing multivitamins and minerals would be regulated as foods or therapeutic goods.

Another issue associated with the use of chewing gum as a dosage form relates to the systemic delivery of an active ingredient, which would rely on distribution *via* buccal absorption or release of the ingredient and dissolution into the saliva. While there is a *European Pharmacopeia* (EP) monograph for medicated chewing gums, there is little information available on the absorption *via* the alimentary tract of vitamins and minerals released from chewing gums. It is likely that absorption would be highly variable and difficult to quantify. While the EP makes reference to a requirement for dissolution testing to be carried out, this is not enforceable under the current Australian legislation for listed medicines.

While some of these issues may be overcome by the imposition of conditions of listing, mandating that dissolution testing must be undertaken for the product, the issues around the regulation of goods at the food/ medicine interface remain. Members were asked to consider these issues in advising if it is appropriate for chewing gum to be permitted as a dosage form for listed medicines.

Discussion

Issue with food/medicine interface

The Committee recognised that vitamins and minerals fall within a 'grey' area at the food/medicine interface. Vitamins and minerals are nutrients commonly added to food which is regulated by the Food Standard Authority Australia and New Zealand (FSANZ). Vitamins and minerals also have recognised therapeutic roles, such as alleviating perceived stress, so products containing these ingredients can make therapeutic claims. Vitamins and minerals in products presented as therapeutic goods are regulated by the TGA.

It was discussed that the amount of vitamins and minerals permitted to be added to food was restricted. Therefore a chewing gum providing a greater amount of vitamins and minerals can currently not be marketed as a food, but nor can it be marketed as a listed therapeutic good, given that chewing gum is not a permitted dosage form for listed medicines.

The Committee agreed that the dosage form 'chewing gum' also falls within a 'grey' area at the food/medicine interface. It is specifically mentioned in the definition of food and there is a FSANZ Food Standard for chewing gum containing calcium. Hence, under current legislation, these latter products cannot be therapeutic goods. However, the legitimate role of chewing gum was recognised by the Committee, who noted the EP general monograph for medicated chewing gum and also its use in smoking cessation products and dental products.

A Member expressed concern that permitting vitamins and minerals in chewing gum would be primarily for the purpose of a marketing tool, as this is not a recognised delivery system for these active ingredients, and also regarding the potential to promote a chewing gum that has therapeutic ingredients as being preferable to a chewing gum marketed solely as confectionary.

The issue of appropriate dosing was discussed, noting a potential for overdose or abuse of a medicated chewing gum. This was noted particularly given that this type of product would appeal to children and that some individuals continually chew gum.

A Member questioned the need for the new dosage form. Chewing gum was compared to lozenges which are currently a permitted dosage form in listed medicines and used for a local effect for inflammation/infection. It was also stated that chewable tablets are currently permitted as a dosage form, which was considered not that dissimilar to chewing gum. It was noted that chewing gum could serve as an alternative dosage form for individuals who cannot swallow tablets.

A Member asked why the current discussion was restricted to the use of chewing gum as an administration medium for just vitamins and minerals, considering that such a dosage form could also be used for other listable ingredients such as herbs. A TGA officer stated that the current enquiry related specifically to vitamins and minerals, however, if chewing gum is considered suitable as a dosage form for listed medicines, it would not be restricted to vitamin and mineral active ingredients.

It was questioned whether a therapeutic dose could be achieved with chewing gum and this was affirmed. The issue arose as to how quality control would be monitored and it was noted that the EP has dissolution requirements, which, while not enforceable under current Australian legislation, could be imposed as a condition of listing on relevant goods.

Discussion ensued as to when a medicine was considered a therapeutic good. A TGA officer stated that a good is considered therapeutic if it is presented as such and it is not the subject of a food standard. If a product makes a therapeutic claim, that doesn't necessarily make it a therapeutic good. It was added that declarations can be made under section 7 of the *Therapeutic Goods Act 1989* to identify specific instances where products that may be foods can in fact be regulated as therapeutic goods, e.g. fibre in tablets and capsules. A Member noted that foods can deliver therapeutic benefits without being considered therapeutic goods.

The Committee considered that, in principle chewing gum could be considered as a dosage form appropriate for use in listed medicines - if the need was demonstrable; consistent dosing could be demonstrated; and the finished goods were clearly distinguished as a therapeutic good with a therapeutic claim and the presentation of the goods was such that it could not be confused with foods. However, it was recognised that such controls were not currently achievable through the Electronic Lodgement Facility for listed medicines, and as such, the dosage form appeared more appropriate for a registered medicine, where the entire product including presentation is assessed prior to inclusion on the ARTG.

Recommendation 9.7

ACCM noted that, while 'chewing gum' was a recognised delivery system for therapeutic goods, chewing gums with added minerals were regulated as foods both in Australia and overseas. ACCM considered that therapeutic goods based on chewing gums should be required to provide specific active ingredients at an appropriate therapeutic dose and be presented in such a way as to minimise confusion with fortified foods or confectionery. ACCM advised the TGA that specific conditions may be required to allow use of chewing gum as a dosage form in listed medicines and recognised that such rules would not be able to be built into the current Electronic Lodgement Facility.

7. Regulatory activity

7.1 TGA Blueprint

Background

A TGA officer provided the Committee an overview of the recent reviews, reports and reform activity occurring within the TGA, namely the:

- Transparency review
- Auditor General's Report on Therapeutic Goods Regulation: Complementary Medicines
- Informal Working Group Examining Complementary Medicines Regulation and Reasons for Low Compliance Rates
- Advertising consultation
- Working Group on Promotion of Therapeutic Products
- Medical Device Reforms

In response to the various reviews, the Government has developed a comprehensive package of reforms entitled 'TGA Reforms: A blueprint for TGA's future'. It is anticipated that these reforms will improve the Australian community's understanding of the TGA's regulatory processes and decisions. The reforms will be implemented in various stages and have been grouped under the following themes: communications and stakeholder engagement; advertising of therapeutic products; complementary medicines; medical devices; and promotion of therapeutic products.

In relation to the regulation of complementary medicines, the blueprint highlights the following issues:

- a poor rate of compliance with the regulatory requirements
- a lack of incentives for sponsors to comply with the legislation
- a lack of clarity and understanding of the regulatory requirements; and
- community concern that the labels of complementary medicines fail to inform consumers that listed medicines have not been assessed against efficacy criteria.

In general, the flow-on effect of these issues is a reduction in community confidence and understanding of the existing regulatory framework for complementary medicines. The reform measures identified to address these issues include:

- The TGA will update the 'Guidelines for the levels and kinds of evidence to support indications and claims' to improve compliance by sponsors. This reform has been identified as the first priority for implementation.
- The Electronic Listing Facility will also be amended to review coded indications, remove/restrict sponsors' access to free text to provide increased guidance for sponsors to increase their compliance.
- The Government will examine options for enhancing, applying and enforcing sanctions and penalties for breaches of compliance requirements, including those relating to advertising breaches.

- The TGA will work with stakeholders to develop options to improve labelling and packaging to help educate and assist consumers to make informed decisions on the use of complementary medicines.

In general, the need to provide more information and education relating to the regulation of complementary medicines to industry and consumers is recognised.

Outcome

Members noted that the outcomes of a number of recent TGA reviews have been summarised and a comprehensive reform package developed in the document: 'TGA Reforms: A blueprint for TGA's future'.

7.2 Draft evidence guideline for listed medicines

Background

A TGA Officer introduced this item advising members that, in relation to reforms to the regulation of complementary medicines, the first priority is the revision of the TGA's guidance document for the levels and kinds of evidence required to support efficacy for listed medicines. A revised document entitled 'Evidence guidelines for listed medicines' was provided for Member's input prior to broader consultation. It was noted that there was a tight timeframe for the development, consultation and publication of the document. Members were asked to provide a high level view of the document at ACCM 8, following which they could provide their detailed comments to the TGA out of session.

Discussion

General comments

Members acknowledged the complexities involved with the development of the draft 'Evidence guidelines for listed medicines' and congratulated the TGA on achieving a document which was considered to be a practical, evidence based guide and a significant improvement on the current guidelines.

Members commented that the document would have a variety of interested stakeholders including industry, consumers, health care providers, experts as well as regulators. As such, it was important the information included in the document adequately addressed the needs of all these groups. A TGA officer agreed, stating that the need for a comprehensive consultation process with all interested stakeholders was important prior to the finalisation and publication the document.

A Member questioned how the document addressed the assessment of the safety of medicines. A TGA officer responded that the guidelines were applicable to listed medicines only, for which only low risk ingredients approved by the TGA could be used.

Another member stressed that the document is a guidance document only, providing information on how to consider evidence. The relevance, quality and population used in obtaining evidence are important factors. If a sponsor holds a particular type of evidence, the guidelines should provide guidance on whether this information is adequate and more practical examples to this effect would be useful.

Definition of an expert

Members acknowledged the criteria provided for the determination of an expert, agreeing this was an important factor and well articulated in the document. However, members stressed that there should be some flexibility as to the professions considered to fit in this category i.e. it should not be limited to the medical profession only, other health paradigms should also be acknowledged. Further the stipulation of a '4 yr degree' may preclude experts who have extensive experience obtained by other means.

Tradtional evidence

The issue of traditional evidence was recognised as a problematic area, particularly in relation to identifying appropriate sources for traditional evidence. The draft guidelines state that references in textbooks must be traced back to the primary historical references and do not constitute evidence of traditional use in their own right (unless the authoritative text is a primary source). Members discussed that this requirement attempts to reduce the ability of three different texts being considered independent sources of evidence when, in reality, they may just repeat the same primary reference and add no value. However, Members considered that this statement was not reflective of the fact that herbal medicine is an empirical skill developed over centuries. In all probability, the primary source of evidence for an indication could be from ancient Egyptian or Greek literature. A herbal text can be considered to be a summation of the empirical knowledge available at that point in time i.e. while the primary evidence may originate from an ancient text, a latter text may be a representation of a 1000 more years of use and experience. Examples of such texts include Culpepper, which dates to the 16th century and was a major source of information for a long time; and Grieve, which was written in 1945 and is considered a summation of the empirical knowledge at that point in time.

Also, while liking the hierarchal formula provided in the guidelines for distinguishing traditional evidence, Members questioned the exclusion of such sources as research focused journal articles and ethno-botanical journals. It was noted that these sources could be the only written document evidence of indigenous medicine use.

The TGA officer agreed that the issue of traditional evidence had been the most difficult area to include in the guidelines. Members questioned whether there could be a list of authoritative texts included in the guidelines and the officer responded that the feasibility of this was being investigated.

A further question raised was whether traditional use should be limited to traditional users. A TGA officer responded that this was not the intent of the guidelines, rather, the intended purpose is to ensure that consumers are aware of the evidence base for the medicine they may choose to consume.

Oral history

It was noted that the current version of the guidelines did not address the issue of oral evidence of traditional use. Members agreed that guidance should be provided as to as to how oral evidence should be collected and noted that consistency of use could be demonstrated by establishing that discreet traditional populations use the same substance in a similar way.

Consultation and implementation

Members requested clarification on the approach to the consultation process for the guidelines. A TGA officer responded that there was already a statement on the TGA website advising the public that a consultation process would commence in April and

further, relevant industry associations had also been informed. The document would also be provided to the OCM/ Industry Consultation Group.

Members questioned if there will be a trial period of implementation and what education sessions are proposed, recognising that the requirements included in this document are significantly greater than the previous guidelines. A TGA officer responded that, once the documents are finalised, a reasonable transition period would be appropriate.

Outcome

Members noted the 'Draft Evidence guideline for listed medicines' and considered the document was practical, well articulated and a significant improvement on the TGA's existing evidence guidelines. Members welcomed the opportunity to provide specific feedback on the document prior to broader consultation.

8. Reports to ACCM

8.1 OPR signal detection

Background

A TGA Officer provided the Committee with an overview of the TGA's signal detection and investigation process relevant to the regulation of complementary medicines.

One component of this is analysis of the adverse drug reaction (ADR) database. When assessing reports of ADRs, a TGA triage officer determines if the event is serious or non-serious. Coding terms and reports of non-serious ADRs e.g. nausea, injection site reactions, are entered into the ADR database by professional officers. Reports of serious ADRs are assessed by medical officers who undertake a causality assessment and follow up where required. ADRs that are of the most interest are serious ADRs requiring hospitalisation or a visit to the doctor/death/disability or sequelae/certain conditions, and new (unexpected) ADRs.

The officer reiterated that the goals of the ADR database is to complement other sources of information and provide a sample of ADRs that are occurring, rather than a registry of all ADRs that occur.

Analysis is conducted using the Proportional Reporting Ratio, which is undertaken by professional staff on a 4 weekly cycle and identifies potential signals that require further investigation. Assessment and evaluation of a particular medicine can be provided to committees for advice when required.

Members noted that signals are generated from multiple sources including: analysis of the Australian ADR database; overseas regulatory agencies (e.g. Europe, United Kingdom, USA, Health Canada, New Zealand, Hong Kong, Singapore etc.); medical literature; sponsor referrals; referral from within TGA; complaints; medicine problem reports; and media reports. The TGA assesses the significance of signals by using a filter process, which assesses the safety concern; the source of the safety concern; the products involved; if the issue has been previously considered by the TGA; if the safety concern is valid; and further, if the safety concern is relevant in an Australian context.

If further investigation is warranted, a safety review is undertaken which involves product/substance identification; investigation of the background; data overview;

investigation of pharmacology, efficacy and safety issues; investigation of current risk mitigation activities; determination of risk of harm *versus* probability of benefit; and options to manage risks.

Discussion

Signal detections and investigation of adverse drug reaction reports

Members noted with interest that a Proportional Reporting Ratio of 3 is required to generate a signal and asked if this report was only on a select number of ADRs, considered to be on a watching brief, or whether it was applied to all ADRs. A TGA officer undertook to confirm this for the committee.

The Committee sought clarification as to how causality was determined for ADRs and if this process involved the use of an algorithm. The TGA officer stated that a TGA medical officer determines and assigns the causality ratings of 'unlikely; certain; possible and likely'. The officer undertook to ascertain if an algorithm or formula was utilised in this process.

Members also questioned if drug interactions were reported in the ADR database and this was confirmed.

Members sought details of what signals are currently being investigated for complementary medicines. The officer provided a presentation of current issues under investigation by Office of Product Review (OPR), which includes the use of caffeine containing ingredients combined with oxedrine containing herbs in weight loss products and party pills.

Outcome

Members noted the OPR presentation on signal detection and investigation for complementary medicines.

9. Papers for information

9.1 ACNM September 2011 minutes

Outcome

Members noted the ACNM September 2011 minutes

9.2 MSU bulletin Vol 2, No 6, 2011

Outcome

Members noted the MSU bulletin Vol 2, No 6, 2011

9.3 MSU bulletin Vol 3, No 1, 2012

Outcome

Members noted the MSU bulletin Vol 3, No 1, 2012

10. Other business

Nil items

11. Recommendation record

Recommendation 9.1

ACCM confirms that the draft minutes of its previous meeting ACCM 8 (2nd December 2011), as amended, are a true and accurate record of that meeting.

Recommendation 9.2

ACCM advised the TGA that, in relation to the current application, the oral history of use is not considered sufficient evidence to compensate for toxicological data absent from the submitted dossier.

Recommendation 9.3

ACCM advised the TGA that, in broad terms, the robustness of evidence based on an oral history can vary and the committee recommended that the TGA consider drafting relevant guidelines to address this issue.

Recommendation 9.4

As this item remains the subject of further consideration, this recommendation has not been published at this stage.

Recommendation 9.5

ACCM agreed with the approach proposed by the TGA to minimise any potential safety concerns associated with the use of preparations of *Nardostachys chinensis* in listed medicines, as follows:

- restrict the permitted plant parts of *N. chinensis* to root/rhizome only; and

- restrict the route of administration for the essential oil preparation of *N. Chinensis* root/rhizome to topical use only.

ACCM noted that these restrictions are consistent with traditional use of the herb and with the formulations of the listed medicines currently on the Australian Register of Therapeutic Goods.

Recommendation 9.6

ACCM noted the traditional contraindications associated with the use of the berries of *Juniperus* species in pregnancy, but given the uncertainty in relation to the relevance of the data and the widespread use of the herb, considered that there were no apparent safety concerns associated with the use of *Juniperus* species in listed medicines. The Committee therefore agreed with the TGA's proposal that preparations of *Juniperus* species remain eligible for inclusion in listed medicines with no restrictions on plant part, preparation or route of administration.

Recommendation 9.7

ACCM noted that, while 'chewing gum' was a recognised delivery system for therapeutic goods, chewing gums with added minerals were regulated as foods both in Australia and overseas. ACCM considered that therapeutic goods based on chewing gums should be required to provide specific active ingredients at an appropriate therapeutic dose and be presented in such a way as to minimise confusion with fortified foods or confectionary. ACCM advised the TGA that specific conditions may be required to allow use of chewing gum as a dosage form in listed medicines and recognised that such rules would not be able to be built into the current Electronic Lodgement Facility.

Chair's certification

I certify that this is an accurate record of proceedings of the meeting.

Professor Alan Bensoussan
ACCM Chair
June 2012

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Reference/Publication #