Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM
Advisory Committee on Complementary Medicines

Extracted ratified minutes
Tenth meeting

1 June 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
ACSOM	Advisory Committee on the Safety of 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
CM	Complementary Medicine
CMEC	Complementary Medicines Evaluation Committee
DOSI	Drugs of Special Interest
OCM	Office of Complementary Medicines
OICG	Office of Complementary Medicines/ Industry Consultation Group
OPR	Office of Product Review
OTC	Over the Counter
PRR	Proportional Report Ratio
SIU	Signal Investigation Unit
TGA	Therapeutic Goods Administration
TMEC	Traditional Medicines Evaluation Committee

The Advisory Committee on Complementary Medicines (ACCM) held its tenth meeting at the Park Royal Melbourne Airport from 9.30 am to 4:00 pm on 1st of June 2012.

TGA note: This document is the extracted minutes from the 10th 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
Associate Professor Marie Pirotta
Dr Hans Wohlmuth
Dr Xianqin Qu
Dr Simon Spedding
Professor Bill Webster

Present from the Therapeutic Goods Administration

Ms Trisha Garrett (Head, Office of Complementary Medicines)
Ms Jenny Burnett (ACCM Secretary)
Dr Michael Dodson (Office of Complementary Medicines)
Ms Natalie Goodall (ACCM secretariat)
Ms Diane Wilkinson (ACCM secretariat)

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9.30 am, welcoming ACCM members and TGA staff.

1.2 Apologies

Professor Peter Williams
Dr Richard Oppenheim

1.3 Meeting declaration of interest

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

2. Minutes of previous meetings

2.1 Draft ACCM 9th minutes

Discussion

Members requested some minor amendments to the draft ACCM 9 minutes.

Recommendation 10.1

ACCM confirms that the draft minutes of its previous meeting ACCM 9 (9th March 2012), as amended, are a true and accurate record of that meeting.

3. Actions arising from previous meeting

3.1 Information from the OPR regarding analysis of ADRs and the use of advisory committees

Background

At ACCM 9, March 2012, a TGA Officer provided the Committee with an overview of the TGA's signal detection and investigation process relevant to the monitoring of adverse reactions associated with complementary medicines. At this time the Committee requested further clarification from the TGA in regard to:

- the formula used by the OPR to determine the causality rating for ADRs; and
- clarification as to whether the OPR monthly report on Proportional Reporting Ratio (PRR), which identifies potential signals for further investigation by the OPR, was an assessment of all ADRs or just those considered to be on a watch list.

In response, at ACCM 10, the ACCM was advised that when assigning a causality rating to ADRs reported to the TGA, a specific algorithm or formula is not used. The causality assessment is based on the World Health Organisation – Uppsala Monitoring Centre system for standardised case causality assessment.

The committee noted that the ADR database is analysed using the Proportional Reporting Ratio (PRR) formula on a monthly basis. All ADRs reported during the previous month are

included in the analysis and it was noted that the analysis is based on the 'generic' medicine term recorded in the ADR database. This is usually the active ingredient name. Where a medicine formulation contains two active ingredients, both are included as the generic medicine term. Therefore, in the case of complementary medicines (CMs), the PRR tool is only useful for detecting signals in CMs that contain two or less active ingredients. Where there are multiple active ingredients, the 'generic' medicine term may be a broad descriptive statement such as 'herbal medicine' or 'vitamin and mineral combination'. Where these medicines appear in the PRR analysis it is difficult to make further assessment as any signal cannot be attributed to a single product or active ingredient. Although the PRR analysis is a useful tool for detecting signals for CMs that contain two or less active ingredients, signals are rarely generated for CMs using this analysis, as the PRR is a ratio that takes into consideration all adverse reactions to all medicines. The number of ADRs reported for non-CM medicines far exceeds those reported for CMs.

Where a signal is detected for a medicine, a safety filter is initiated and where this determines that a full safety review is not warranted, the medicine may be placed on a 'Drugs of Special Interest' (DOSI) list or there may be no further action required (for example, the reaction may already be included in the 'Product Information' sheet for the product). A TGA Officer explained that one of the core functions of the OPR is to monitor medicines in the post market environment, with a focus on safety. The committee specific to this function is the Advisory Committee for the Safety of Medicines (ACSOM). ACSOM's advice may be sought following the outcome of a safety review of a medicine by OPR. ACSOM is also provided with a list of issues currently under consideration by the Signal Investigation Unit (SIU) of OPR. This list is provided for information only and the committee may provide comment or request that a review be expedited, however the primary purpose of providing the list is to inform ACSOM of current issues under consideration, some of which may go to the committee for advice at a later date.

The ACCM noted that while ACSOM does not currently include a member with expertise in CMs, this is one of the selection criteria for membership to this committee, and is considered important during the assessment of applications for committee membership. In the meantime, should expertise in CMs be required, options are available to access such expertise.

Discussion

The Committee noted that the role of ACCM had been clarified as primarily associated with premarket issues, while adverse drug reactions for CMs arising in the post market environment would be referred to ACSOM in the first instance. Members discussed that previously the ACCM had considered all adverse events for complementary medicines, which had often enabled the early detection of potential signals. This was considered important given the under-reporting of ADRs associated with complementary medicines and the complexity of formulations.

Conversely, a member commented that it had been difficult in the past for ACCM to provide advice on these matters, given that the information provided to the committee on specific adverse events had often been too brief to enable meaningful analysis.

Members also noted that the PRR analysis was not sensitive to multi-ingredient CM medicines, and expressed concern that signals for these types of medicines may not be detected.

A TGA officer outlined internal processes relating to exchange of technical information between the OCM and the OPR when assessing the safety of ingredients and it was noted that naturopaths are employed in both Offices. Members also noted that specific expertise may also be sought from other advisory committees, including the ACCM.

The Committee reiterated that they would welcome the fostering of communication channels between the OPR, ACSOM and ACCM. In particular, ACCM would appreciate receiving regular reports summarising the types of ADRs occurring for CMs.

Outcome

ACCM noted the current processes of the TGA's OPR to determine causality ratings and signal detections for adverse drug reactions for complementary medicines.

ACCM expressed concern that the current OPR processes may not adequately capture ADR data for individual ingredients when those ingredients are included in multi-active medicines.

3.2 Review of substances on a watching brief

Background

At ACCM 7 (September 2011), a member requested information about substances currently on 'watching briefs'.

At ACCM 8 (December 2011), the Committee were provided a list of substances placed on watching briefs by ACCM, or its predecessor, the Complementary Medicines Evaluation Committee (CMEC). Members considered, among other issues, a process for retaining or removing substances from the watching brief; a formal procedure for monitoring substances on the watching brief; and a proposal for posting a revised list on Govdex for on-going consideration by ACCM members.

The Committee were advised that the TGA had reviewed the substances considered to be on a watching brief and three herbal species were identified for possible removal: *Larrea tridentata* (Chaparral), *Frangula purshiana* (ex. *Rhamnus purshiana) (Cascara sagrada),* and *Verbena officinalis*

ACCM was asked to advise if these three herbal species could be removed from the watching brief, given that safety reviews undertaken by the TGA on these substances indicated that current regulatory restrictions are adequate to address any potential safety concerns, and that there are no new safety data relating to ADRs.

Discussion

Members questioned the process of how substances were originally identified for inclusion on the list of substances on a 'watching brief'; how the substances included on the list are monitored; and what criteria should be used to ascertain that the substances can be removed from the list. Noting the previous discussion on ADR signal detection, a member postulated that signal detection for listed complementary medicines was particularly important as, potentially, the occurrence of one serious ADR could revise the 'low risk' status of an ingredient or medicine. After discussion it was agreed that maintenance of the 'watching brief' list was not solely to monitor safety issues as they arise, but also to 'fill gaps' in the evidence base – those gaps being the reason that some substances had originally been included on the list.

One member proposed that, to ensure efficient use of resources, substances could be removed from the list if no 'negative' evidence arose over a significant time period. Members then discussed the level of evidence that would be required to change a substance's status, noting the grading of evidence undertaken by the NHMRC and the

possibility of utilising retrospective case studies when available for the substances in question. Another member proposed that the passing of time and the absence of ADR reports for a substance should not be the basis of its removal from the list. This was contrasted with the situation where the reason for inclusion on a watching brief is a gap in the toxicological evidence necessary to demonstrate safety for a particular substance, and over time a report becomes available, then at that time, the substance could be removed.

A member commented that if the protocol for placing a substance on the watching brief was that there were gaps in the evidence, then nearly every complementary medicine would be subject to a watching brief. Therefore there needed to be a more clearly identified concern, other than a 'safety gap', to warrant inclusion on the list. The member noted the existence of the OPR's 'DOSI' process and asked whether 'substances on a watching brief' could be managed in a similar way.

Members again noted the lack of sensitivity of the existing signal detection methodology in regard to multi-ingredient complementary medicines. It was suggested that the 'watching brief' list was an important resource that could in fact contribute to a 'signal' even if PRR criteria were not met. A TGA officer reiterated that the TGA regularly monitors issues associated with all complementary substances arising in literature or from international regulatory agencies. In the case of substances considered to be on a 'watching brief' the TGA undertakes a more proactive monitoring role.

However, a member commented that a watching brief is a pre-emptive rather than a reactive strike and that there should be two categories based on the methodology of the information being sought to have the substance removed from the brief. Categorisation could involve active review versus periodic assessment and should consider factors such as the reason for inclusion on the list. In cases where data were absent, a continuing lack of scientific data would result in the substance remaining on the list. If new data were available, the significance of this would need to be determined on a case by case basis. When following up on safety concerns resulting from previously reported ADRs, active review of the ADR database would be required. If a substance was placed on a watching brief *after* an adverse study came to light – it follows that subsequent positive studies would negate the need to keep it there.

A TGA officer clarified that substances on a watching brief continue to be monitored by other means, and that ADRs or the lack of them are not the sole reason for the retention or removal of substances. Members commented that the safety of a substance is more than ADRs and that more information should be used including the severity of the reaction and the frequency at which the substance is used.

Members further discussed the operation of the 'watching brief' list and the DOSI list, noting the gap in the information held in each resource and the unique nature of complex complementary medicine substances. It was stressed that the combined use was important, and the potential for better use of case studies and meta-analysis was identified.

It was identified that the safety concerns associated with a number of the substances on a watching brief had been addressed in part by the use of label advisory statements. A member questioned whether it would be appropriate for a substance to be removed from the watching brief if there was a warning label in place, and whether the label should be removed or remain in place.

A member commented that the watching brief appeared to present a contradiction to the fact that ACCM is not involved in the post market environment, to which a TGA officer responded that this a final step in a monitoring process which was previously raised by CMEC/ACCM.

Overall, members agreed they would like to see more research from the TGA in relation to individual substances before the Committee could consider recommending their removal from a watching brief.

Recommendation 10.2

ACCM advises that 3 herbal substances, *Larrea tridentata*, *Frangula purshiana* and *Verbena officinalis* should remain on the OCM list of substances on a watching brief.

3.3 Update to the herbal ingredient names

Background

As part of the Plant Parts Safety Project, initiated in 2006, the credibility and authenticity of hundreds of herbal ingredient names (originally 'grandfathered' onto the ARTG) were reviewed. Many of the names contained taxonomical, botanical and grammatical errors, and also provided erroneous information regarding synonyms and common names of herbs.

In 2009 the *Therapeutic Goods Act 1989* was amended to clarify the process for approving new ingredients for use in listed medicines on the Australian Register of Therapeutic Goods (ARTG). These amendments also allowed for the creation of a new legislative instrument detailing all ingredients approved for use in listed medicines.

During the development of the new legislative instrument, and using data generated by the earlier 'Plant Parts Safety Project', the names of herbal ingredients eligible for use in listed medicines were reviewed to ensure that all ingredients are correctly identified and defined by their authenticated names, requirements and references. Various resources have been utilised to verify botanical names.

After identification of herbal ingredients that required name changes, and consultation with the OCM/Industry Consultative Group to obtain industry input to the proposed changes, the first phase of the project to update herbal ingredient names was carried out during 2010/2011. This phase comprised updating of ingredients that were not included in any current medicine formulations and therefore had no regulatory impact. To complete Phase II, industry cooperation was needed in order for the TGA to change the names of herbal ingredients which were included in formulations in current medicines.

In early March 2012, the TGA wrote to 350 sponsors seeking their authorisation for the herbal ingredient names to be changed. Information was also provided via the TGA website and eBS news to inform those stakeholders who sought to include the affected names in a new formulation.

The TGA provided a pro-forma and a generous time frame to ensure easy compliance and speed of response by sponsors. At the deadline date of 12th April 2012, the percentage of responses was approximately 67%. Following this, a further attempt was made to contact sponsors who had failed to respond initially. This increased the response rate to 90% and no sponsors disagreed to the proposed name changes.

In a coordinated effort with export and OTC medicines to ensure consistent coverage of all affected medicines, the OCM has corrected and updated a total of one hundred and seven herbal ingredient names used in listed medicines.

The ARTG will be re-examined for any new medicines entered since the beginning of April and not identified for the mail-out. The manual deactivation of all relevant redundant herbal ingredient names from the ELF and associated databases will proceed, after which date no redundant herbal ingredient names will validate using the eBS system.

Updating herbal ingredient names in the eBS system is now nearing completion. Details of the project are accessible via the TGA website.

Discussion

Members congratulated all those involved in the project and asked what procedures were in place to record and maintain the currency of herbal ingredient names.

A TGA officer advised that monitoring within the OCM is a continuous process and a specific policy may be implemented in the future.

Members commented on identified problems associated with different naming conventions of substances and a TGA officer advised that reliable data sources for this project included The Plant List (TPL) and the Germplasm Resources Information Network (GRIN).

Outcome

ACCM noted the significant progress of the TGA's project to update the Australian Approved Names for herbal species included as ingredients in medicines in the ARTG.

4. Evaluation of new substances

Nil items

5. Registration applications

Nil Items

6. Regulatory issues

6.1 Draft evidence guideline for listed medicines update

Background

A TGA Officer introduced this item, advising members that following the Auditor-General's report on Therapeutic Goods Regulation, the TGA undertook to update and include in legislation the *Guidelines for the levels and kinds of evidence to support indications and claims* in consultation with stakeholders. The Evidence Guidelines represents an attempt to provide increased clarity to sponsors regarding evidence required to support listed medicines. Comments on the draft Evidence Guidelines were sought and feedback on the document closed on 25 May 2012.

Forty-nine submissions were received – three quarters from industry and industry peak bodies; a quarter from consumer and health practitioner groups.

General points raised by industry and industry peak bodies included the fact that the model was onerous, costly and overly complicated; that experts were not needed and/or hard to source; that the approach was not in keeping with low risk medicines and that other aspects of the regulatory framework must be addressed. In addition ASMI/CHC submitted an alternative model which proposed the use of "established evidence" – for example monographs and texts. The model outlined the critique process of the evidence; it provided an option for abridged evidence to deal with indications falling outside "established evidence", and recommended that the document remain as guidance and be included in ARGCM.

General points raised by consumer and health practitioner groups were that, overall, they supported the revised document. However, they were of the opinion that a "tightening up" of the expert requirements was needed and that other aspects of the regulatory framework should also be addressed.

A TGA officer presented information on the draft document, pointing out that the guidelines will be implemented in legislation once they are finalised; and requested ACCM's advice in relation to:

- The protocol for literature searching. In particular, identifying relevant electronic databases such as MEDLINE, EMBASE, Web of Science, the Cochrane library, BIOSIS, SciVerse Scopus, Cab Health, AGRICOLA, and Food Science and Technology Abstracts, and whether the search should mandatorily utilise MEDLINE and involve one other relevant database. Whether searching of multiple databases was necessary and what was the Committee's view on the use of free services such as PubMed and Google Scholar.
- The need for an expert to review the evidence. In particular, whether a review of the evidence by an expert is necessary and if it is, whether the person responsible requires clinical knowledge, critical appraisal skills and competency – and for traditional medicine – also require knowledge of the paradigm. Whether 'modified' expert requirements should be considered, such as a minimum of tertiary degree of at least three years or post graduate qualifications from a recognised institution in a health related area and – for traditional evidence – whether the expert should also possess relevant experience as a practitioner, researcher, advisor, regulator or regulatory affairs associate in the area.

Discussion

General

Members commented that the name change of the document to "Evidence required to support indications for listed medicines" reflects the intention to include the requirement in legislation.

A member commented that the consultation period for the document appeared to be quite short at five weeks. The TGA officer clarified that there were several steps including another consultation and a regulatory impact statement to be completed before it can be enacted in legislation.

Evidence list

Discussion took place around the usefulness or otherwise of a list of resources which may be considered suitable for use as evidence for indications of listed medicines, and concerns

included whether the resources should be subjected to quality checks to determine their acceptability as determined by NPS or TGA, and also whether such a concept could be misleading.

Expert requirements

The Committee discussed the requirement for "experts" to review evidence.

While there was no overarching opinion, members agreed that it would be a valuable requirement and should not be merely a recommendation. However, there was some discussion as to what constitutes an 'expert' in this situation – and decided that a 'tertiary qualification' rather than a 'three-year degree' would be acceptable, and that the person would not necessarily need expertise in critical appraisal, etc.

An 'expert' may also ensure that the review would be properly completed and that it may discourage industry sales and marketing staff from developing proposed indications.

Outcome

ACCM noted the outcome of the recent consultation process on the 'Evidence required to support indications for Listed medicines (excluding sunscreens and disinfectants) - draft'.

6.2 TGA coded indications project

Background

Following the Auditor-General's report on Therapeutic Goods Regulation, the TGA undertook to make amendments to the ELF including the expansion of the list of existing coded indications. A TGA officer informed the Committee that this project would be implemented in two phases. The first, occurring this year, would be to expand the list of coded indications available to sponsors. The second, to occur in 2013, would be to remove the free text field and add a mechanism by which stakeholders can apply for new coded indications to be added to ELF. The officer explained that the object of the Coded Indications Project is to expand the list of coded indications so that there would be less incentive for sponsors to utilise the free text field.

Discussion

The TGA officer informed the Committee that the current 'free text field' used by listed medicines in ELF was reviewed, and that the use of common indications within this field could not be possible as a significant number of spelling errors and inaccuracies, including advertising claims, have been introduced, and it is apparent that not all sponsors have a clear understanding of what a 'listable claim' entails. In some cases a listing had as many as four pages of indications in its free text field.

Discussion took place on a mechanism for adding new standard indications and the potential for directly linking an ingredient to the specific indication. The use of monographs by Health Canada was noted and a question was posed as to whether the TGA would consider adopting the Canadian system. A TGA officer advised that the system would need to be reviewed as to its suitability within the Australian regulatory framework.

Outcome

Members noted the update from the TGA.

6.3 Bioavailability enhancing effects of excipients

Background

There has been increased interest from industry for the approval of new substances as excipients for use in listed medicines, whereby the role of the excipient in a formulation is to enhance the bioavailability of the active ingredient(s).

Under the current procedure for listing complementary medicines on the ARTG through the ELF, there is no opportunity to assess any potential interactions between the 'bioavailability enhancing excipient' and active ingredients (whether the active ingredient(s) is/are within the formulation or used concomitantly in the medicines) prior to entry onto the ARTG.

To date applicants have not been able to demonstrate the mechanisms of action of the proposed 'bioavailability enhancing excipients' in their intended formulations – hence the potential for selective interactions between these ingredients. As well, the interaction between components within complex herbal ingredients are also unknown and could result in changes in the safety and efficacy profile of substances.

The TGA has requested that ACCM take into consideration that:

- Listed medicines undergo no pre-market evaluation
- Safety of listed medicines is based on the inclusion of only those ingredients already approved by the TGA (noting that any specific known safety concerns of a particular ingredient have been appropriately addressed)
- Generally, an approved ingredient is available through ELF for use in association with any other listed ingredients, and
- Approval of a 'bioavailability enhancing excipient' could lead to unrestricted use of that ingredient.

Currently, the TGA has before it an application for the use of d-alpha-tocopheryl phosphates (TPs) as an excipient in both topical and oral products. The excipient is claimed to promote transdermal and oral uptake of active ingredients. A preliminary report of the toxicology evaluation has indicated several deficiencies in the submission package, including the claim for enhanced bioavailability of active ingredients.

While the data available remains unclear on whether TPs have a 'bioavailability enhancing effect' on active ingredients, the question before ACCM is whether approval of such an ingredient as an excipient is acceptable if the role is proven.

Betadex (AAN)(synonym: Betacyclodextrin) is an ingredient available for use as an excipient on the ARTG and is included in a number of listed medicines.

Betadex monographs are included in both the *United States Pharmacopoeia* (USP) and the *British Pharmacopoeia* (BP). While no role has been assigned to it in the USP, its action and use is stated as a 'carrier molecule for drug delivery system' in the BP.

In November 2011, two applications for Active Herbal Extracts (AHEs) proprietary ingredients (PIs) were received. Both AHEs are mixed with betacyclodextrin (Betadex) which was claimed to be an excipient.

During the assessment, it was noted that the manufacturing process had a registered trademark, and the supplier promotes Betadex and the BetaSorb® technology as being able to "improve the absorption and bioavailability of these specific components, and therefore potentially increase their efficacy".

At the time, an internet search of the trade name gave the following information from the link – http://www.zinova4pain.com/betasorb

"Many active components found in herbal and chemical substances have been found to be poorly absorbed. Some are also unstable. The Betasorb® technology has been developed to improve the absorption and bioavailability of the specific components, and therefore potentially increase their efficacy. BetaSorb® technology involves a proprietary process which binds together the required components with the β-cyclodextrin to form a stable structure know as an inclusion or host-guest complex. β-cyclodextrin is a natural starch molecule treated with an enzyme. The β-cyclodextrin molecule has a truncated cone shape with a lipophilic inner area known as a cage.

Key active components, such as phyto chemicals, that are enveloped in this cage as a complex, are automatically transported to the surface of the mucosa in the intestine where the complex is then dissolved and the components more readily available for absorption.

Unlike other cyclodextrins, β-cyclodextrin as Betadex is the only cyclodextrin approved for use in listed medicines by the TGA. A specific Betadex monograph is included in both the European and the US pharmacopoeias, where it is listed as a pharmaceutical excipient (CAS No. 68168-23-0). All ingredients in the BetaSorb® range have been individually approved by the TGA for listing as proprietary ingredients.

Betadex is also well known as a common food excipient and is approved by FSANZ without restriction."

In light of this information, TGA sought data to establish the safety of *Vaccinium macrocarpon* BetaSorb®. The applicant commented, "The purpose we use the Betadex for in each extract or compound can also differ depending on the nature of the original ingredient it is mixed with." When sufficient data could not be supplied by the applicant, the AHE application was rejected. The applicant then withdrew the second AHE application.

Under the current process for listing complementary medicines, once approved for use, an ingredient, whether active or an excipient, could be used in any combination with other ingredients. In theory, restrictions could be imposed limiting the use of a particular ingredient in certain formulations. However, this would not be a practical option in this instance, considering the range of possible ingredient combinations and/or interactions between bioavailability enhancing excipients and active ingredients.

Of particular concern is that the safety profile of approved herbal ingredients could be altered by the addition of such excipients. The basis of the safety of approved ingredients, either through consideration of traditional use or after scientific evaluation, may no longer be valid. In the absence of pre-market evaluation the safety of a medicine whose formulation included a 'bioavailability enhancing excipient' would not be established prior to supply of the listed medicine.

Discussion

While acknowledging that the products related to this agenda item had not moved onto the approval stage as yet, Members considered splitting this item into two parts – one part dealing with the safety of the actual ingredient and the other dealing with the overall safety of the 'complex' (the ingredient in conjunction with the 'bioenhancer') – at the same

time assessing the therapeutic window effect, as the frequency of dosage for an ingredient would potentially alter in relation to sustained delivery or bioavailability.

Questions from members included whether information had been provided in regard to the safety of the excipient itself; what the action of the excipient is - in terms of raising the efficacy of the active and the resulting toxicity, and if there was any impact on serum levels. It was noted that there is control on dosage of listed medicines only in specific instances – in general this was not controlled.

Bioavailability was discussed in terms of its natural variation and whether the addition of a bioavailability enhancing agent may or may not be significant with respect to this natural variation. In relation to commercial advantage, a TGA officer advised that any marketing claims may be considered to be misleading should evidence not be provided under the Therapeutic Goods Advertising Code (TGAC) to support such claims.

In terms of proving safety, a TGA officer advised that if an excipient has a history of use it would be considered "safe", and in relation to proving safety of a new substance, the TGA officer responded that in the case of a herbal extract complexed with a bioenhancing excipient, this may be considered to be a new ingredient and therefore it could not rely on traditional use as evidence of efficacy.

A member commented that FSANZ had approved excipients that increase bioavailability in any product.

Members agreed that they did not have any safety concerns about excipient ingredients that claimed to enhance bioavailability.

Recommendation 10.3

ACCM advises that the effect of bioavailability enhancing excipients on active ingredients in listed medicines is not expected to be greater than the natural variability in herbal ingredients and, given the wide therapeutic window associated with listed medicines, the use of these excipients do not pose a safety concern.

7. Papers for information

Item 7.1 MSU Bulletin Vol.3 No 2, 2012

Outcome

Members noted the MSU bulletin Vol 3, No 2, 2012.

Item 7.2 ACSOM 10th meeting minutes

Outcome

Members noted the ACSOM 10th Meeting Minutes

Item 7.3 ACSOM 11th meeting minutes

Outcome

Members noted the ACSOM 11th Meeting Minutes

8. Labeling and packaging review

Background

The TGA is conducting a review of the requirements for labels and packaging of medicines marketed in Australia. The review is focused primarily on the presentation of information on medicine labels, emphasising any visual aspects that contribute or otherwise to the usability of textual information provided and promote the safe use of a medicine by consumers.

The proposed changes were developed jointly with an external reference group representing consumers, health care professionals and industry. Previous consultations on labelling requirements, feedback and reports from consumer groups and industry, and consultation with key stakeholders all contributed to the determination of the changes.

The TGA is interested in receiving the views of all the above-mentioned stakeholder groups on the proposed regulatory changes, with a consultation period open until 24th August 2012. The TGA has requested feedback from ACCM in relation to these changes and the ACCM secretariat has agreed to post the relevant papers on Govdex and thereafter to collate all comments received from members and submit these to the Project Manager.

Outcome

ACCM noted the invitation to participate in the TGA's Labelling and Packaging Review.

9. Recommendation record

Recommendation 10.1

ACCM confirms that the draft minutes of its previous meeting ACCM 9 (9th March 2012), as amended, are a true and accurate record of that meeting.

Recommendation 10.2

ACCM advised that 3 herbal substances, *Larrea tridentata, Frangula purshiana* and *Verbena officinalis,* should remain on the OCM list of substances on a watching brief.

Recommendation 10.3

ACCM advises that the effect of bioavailability enhancing excipients on active ingredients in listed medicines is not expected to be greater than the natural variability in herbal ingredients and, given the wide safety margin associated with listed medicines, the use of these excipients do not pose a safety concern.

Chair's certification

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

Professor Alan Bensoussan
ACCM Chair
September 2012

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