Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 3
ADVISORY COMMITTEE ON COMPLEMENTARY MEDICINES
EXTRACTED RATIFIED MINUTES
THIRD MEETING
3RD SEPTEMBER 2010

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ACNM	Advisory Committee on Non-prescription medicines
ACSOM	Advisory Committee on the Safety of Medicines
ADRs	Adverse Drug Reactions
ARTG	Australian Register of Therapeutic Goods
BSE	Bovine Spongiform Encephalopathy
CMEC	Complementary Medicines Evaluation Committee
ELF	Electronic Lodgement Facility
OCM	Office of Complementary Medicines
SATCM	State Administration of Traditional Chinese Medicine
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration

The Advisory Committee on Complementary Medicines (ACCM) held its third meeting at the TGA from 9:30 am to 4:00 pm on 3rd September 2010.

Members of ACCM present

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

Present from the Therapeutic Goods Administration (TGA)

Ms Jenny Burnett (Acting Secretary)
Ms Libby Kerr
Ms Diane Wilkinson

Present for part of the meeting

Dr David Tattersall
Ms Karen Longstaff
Mr Ian Stehlick
Ms Jenny Mason
Ms Nicola Powell
Ms Kara Lengyel
Ms Tahirih Mortal-Duff
Ms Barbara Rooks

1 Procedural Matters

1.1 Opening of Meeting

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

1.2 Apologies

Dr Lesley Braun
Dr Vicki Kotsirilos
Dr Ruth Lopert (TGA Principal Medical Advisor)
Mr Michael J Smith (ACCM Secretary)
Professor Bill Webster

1.3 Conflict of Interest

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

2. Confirmation of Draft Minutes of ACCM 2 (4 June 2010)

Members commented on Item 3.1 '*Carthamus tinctorius* update' noting that this had been a complex discussion which had been accurately recorded.

Also in relation to Item 3.1, a Member noted the Minutes stated that the OCM would liaise with relevant Chinese Government bodies. To this end, the Member advised that the NSW Health Department was meeting with the State Administration of Traditional Chinese Medicine (SATCM) in November and suggested that this might provide an opportunity for the OCM to foster communications with SATCM.

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

Members made the following recommendation:

Recommendation 3.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 2 (4 June 2010), as amended, are a true and accurate record of that meeting.

3. Action Arising from Previous Meetings

The ACCM discussed five matters under this agenda item. As these matters are still under consideration by ACCM, the minutes have not been released.

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

Nil items

5. Evaluation of New Substances

Nil items

6. Safety or Efficacy Reviews

Nil items

7. Herbal Safety Review Project

7.1 Implementation of recommendations arising from Plant Part Project and Herbal Safety Review Project

Background

A TGA Officer introduced this item advising Members that the OCM is finalising the details of a new Legislative Instrument which will list all active and excipient ingredients eligible for use in listed medicines. Only those ingredients mentioned in the Legislative Instrument, consistent with any associated restriction, will be able to be used in Listed medicines. Members noted:

- that herbal ingredients that have an identified safety risk, and are not currently, and have not recently been, used in listed medicines on the ARTG, will not be included in the Legislative Instrument;

- recommendations arising from herb safety reviews considered by CMEC will be incorporated as restrictions;
- where safety concerns have been identified by the TGA for a specific plant part or preparation (and the plant part or preparation is not currently in use in listed medicines) an appropriate restriction has been included in the Legislative Instrument; and
- some ingredients currently available for use in Listed medicines with no restrictions on plant parts or preparation type will be restricted to use as the appropriate part/preparation only (changes to ingredients have been made only where this is consistent with the current use of the ingredient).

Members also noted that some recently evaluated substances were inappropriately flagged on the Electronic Lodgement Facility (ELF) for possible use in both active and excipient roles. Inclusion in a medicine formulation will now be restricted to active use only, as this is the role for which the substance was evaluated.

Herbal species that are no longer available for use in listed medicines (other than those herbs with an identified safety concern that has been assessed by the OCM prior to removal) will remain in ELF with rules such that an application including those ingredients in a listed medicine will not validate. This will allow applicants to 'see' the ingredients and notify the TGA if they wish to include them in a new formulation. In such cases, the OCM would review the status of the herb.

Members were advised that the initial implementation phase will have minimal impact on medicines currently on the Australian Register of Therapeutic Goods (ARTG). Only 4 herbal species that are included in currently listed medicines will become 'not Listable' and require removal of the medicines from the ARTG.

ACCM was asked to note the incorporation of CMEC/ACCM recommendations on the use of relevant plant parts as approved ingredients in listed medicines; new restrictions placed on some ingredients in the list of ingredients eligible for use in listed medicines; and the removal of some previously available ingredients from the list of ingredients eligible for use in listed medicines.

Discussion

A Member questioned what will happen with substances that have previously been permitted for use in Listed medicines (and that are now suspended from use). A TGA Officer responded that a database will be established which will record the rationale as to why these substances are no longer permitted ingredients in Listed medicines. The onus will be on a sponsor to address these issues if they wish the ingredient's Listable status to be reinstated. It was conceded that, in some cases, a full evaluation may be required.

As part of the implementation of the '26BB List', Members noted the TGA's intent to correct a number of botanical names that are currently incorrect in the permitted ingredients list. Members questioned why there were incorrect names in the database. A TGA Officer responded that errors had been identified in the primary reference source historically used for botanical names (when the ARTG was first established). Also, as taxonomy is a dynamic environment, there have been taxonomic reclassifications of various plant species.

A Member commented on the current situation where, if a species is permitted in Listed medicines with no restrictions, any plant part and preparation of that herbal species can be used. The Committee agreed this was not acceptable practice, as ideally, plant parts and preparations should be limited to those traditionally used therapeutically. A TGA Officer agreed, stating that it

was now current practice to restrict new permitted ingredients to the appropriate plant part and preparation. Further, where safety concerns have been identified for a specific plant part or preparation, and the plant part or preparation is not currently in use in listed medicines, an appropriate restriction will be included in the Legislative Instrument. The Officer added that the task of restricting ingredients to the appropriate plant parts and preparations would be an ongoing project in the OCM.

A Member commented that the sponsor of a medicine including a preparation of a herbal species should have the evidence to support the use of the plant part and preparation included in their preparation.

Outcome

ACCM noted the incorporation of CMEC/ACCM recommendations on the safe use of certain herbal species in Listed medicines into the new Legislative Instrument providing ingredients eligible for use in Listed medicines.

8. Registration Applications

Nil items

9. Regulatory Reforms

Nil items

10 Adverse Drug Reactions associated with complementary medicines.

10.1 Further information on two ADRS reported at ACCM2

ACCM discussed additional information provided for two case reports of adverse events reported at ACCM 2.

10.2 ADRs associated with complementary medicines from May 2010 to July 2010

Background

Members discussed adverse events reported for complementary medicines from 1 May 2010 to 31 July 2010.

11. Matters Referred from within TGA

11.1 The regulatory status of probiotic-derived non-viable microorganisms as ingredients in listed medicines

Background

A TGA Officer introduced this item advising Members that, at present, there is no regulatory distinction between live probiotic ingredients and deliberately killed microorganisms of the same species/strain. Both live and killed probiotic microorganisms are known to confer therapeutic benefits, apparently acting through different, as well as similar, mechanisms of action.

Currently, there are no specific approved indications for killed/non-viable probiotic-derived ingredients and it is unclear if the standard indications for probiotics are appropriate for killed probiotic ingredients. In addition, there are no specific labelling requirements to distinguish between live and killed microorganisms, but general legislative requirements under the *Therapeutic Goods Act 1989* (the Act) stipulate that labelling must not be misleading.

Importantly, Schedule 4 of the *Therapeutic Goods Regulations 1990* (the Regs) does not specify that probiotic ingredients must be 'live' or viable, even though the OCM safety assessment of probiotic ingredients considered only live microorganisms. Therefore, at present, sponsors are able to legally list products with either live or killed microorganisms of the permitted probiotic species/strains, but there are no requirements for correctly describing the nature of the product when killed microorganisms are used. However, the sponsor must declare the true nature of the ingredient in therapeutic goods in order to comply with the legislative requirements for ensuring that a product's presentation is not misleading.

The Officer informed Members that the OCM had recently received a request from an applicant for advice on the best way to express the quantities for a blend of two probiotic ingredients in an Electronic Lodgement Facility (ELF) listing of a new product. Some ingredient-specific manufacturing documentation was provided to illustrate how the material is processed, which indicated that the two probiotic *Lactobacillus* strains used in the medicine were deliberately killed in the process before encapsulation.

ACCM was asked to advise:

- If deliberate killing of probiotic microorganisms makes them different ingredients compared with live probiotics of the same species/strain?
- If the same general level indications are appropriate for probiotic ingredients regardless if they are live or killed?
- If killed probiotic ingredients should be recognised as distinct depending on what type of process, e.g., dry heat, moist heat, ionising irradiation, was used to kill the microorganism?
- What dose units should be used to express the potency/quantity of killed probiotic ingredients in a listed medicine?

Discussion

Therapeutic activity of live and non-viable probiotics

Members highlighted that there were different therapeutic uses for live and killed probiotic ingredients, commenting that live probiotics alter the bowel microbiota, whereas dead probiotics are used therapeutically for anti-inflammatory and immune modulatory therapeutic actions. Members agreed that this was an important distinction that clearly indicated that live and non-viable probiotics were two different substances.

A Member questioned if most listed products would predominantly consist of either live or non-viable probiotics. A TGA Officer responded that probiotics have historically been listed on the assumption that there are live organisms in the product. However, even with live probiotics there will always be dead organisms present and recent evidence has shown that in some cases both live and dead components contribute to the therapeutic effect. A Member added that some products may have a deliberate blend of both ingredients.

Members discussed whether live probiotics are degraded after consumption and therefore may act as a non-viable probiotic. A TGA Officer advised that any therapeutic effect or benefit is based on the species strain, dose and gut bioavailability. Not all strains have a beneficial effect; similar to *Escherichia coli* - some strains are beneficial, where other strains are not.

Quantification of the ingredient

A Member stated that it was relatively simple process to quantify live organisms, but questioned how quantification of dead probiotics occurred. A TGA Officer responded that while a plate count could not be used for dead probiotics, if the cell membrane is intact, it is possible to quantify the material using a solid-phase cytometry method incorporating a stain. However, as this method is very costly, an alternative way to quantify the material would be to quantify the input amount of raw material. This could be achieved by performing a microbial count prior to inactivation.

Members agreed that it would not be appropriate to use the term '*equivalent to...*' and proposed that '*derived from...*' was more acceptable.

Definition of a probiotic

Members agreed with the WHO definition of a probiotic, "*live microorganisms which when administered in adequate amounts confer a health benefit to the host*".

To address the issue of live versus killed probiotics the Chair suggested that killed probiotics be considered as a new ingredient.

Strain specific information recorded in the ARTG

Members commented that sponsors should hold strain specific evidence for the ingredient to support the type of claims promoted for the medicine. However, a TGA Officer stated that the ARTG does not have provisions for strain specific information to be recorded in the product entry and, hence, a manufacturer may infer that the same strain doesn't have to be used. However, the batch manufacturing of specific strains is picked up in Good Manufacturing Practice requirements, as this information is required in the raw material specifications. Members expressed their concern over this situation, considering it essential that this information be provided in the ARTG record.

Consumer expectations

Members discussed that it is common for consumers to self-prescribe probiotics when they have taken a course of antibiotics, as it is commonly accepted knowledge that probiotics have a role in re-establishing the bowel microflora. A Member clarified that not all antibiotics have a detrimental effect on the gut flora, it is a range of antibiotics that have this effect.

Members discussed that while probiotics that selectively decrease microflora (that might take over the bowel microbiota) should be alive when taken for this purpose, non-viable probiotics would also be beneficial in this situation as they act to boost the immune system.

It was noted that consumers look at probiotic medicines to achieve a particular outcome and may not be concerned that a combination of ingredients may be present. Members agreed that education of consumers and practitioners was important to understand the different types of probiotics, their therapeutic uses and the most beneficial time to take them.

Methods for producing non-viable probiotics

Discussion ensued in relation to the effect the method of killing probiotics had on therapeutic activity. In the paper by Adams (2010) '*The probiotic paradox: live and dead cells are biological*

response modifiers' viable and γ-irradiated killed probiotics (administered via an oral or subcutaneous route of administration) demonstrated an anti-inflammatory effect on Wistar rats with colitis, but heat killed probiotics did not have the same effect. The authors concluded that heat treatment may denature the probiotic DNA rendering the probiotic inactive in this instance. A Member commented that heat killed probiotics demonstrate an increase in Interleukin (IL) 6 and IL 8, γ-irradiated killed probiotics demonstrate and decrease in IL 6 and IL 8.

Another Member compared this to the pharmaceutical medicine Dukoral which is an oral cholera vaccine consisting of whole killed *Vibrio cholerae* cells and recombinant cholera toxin. It contains four cholera strains, two that are heat inactivated and 2 that are formaldehyde inactivated. This example could be considered as a precedent, establishing the case for recognising that mode of killing is important information. Furthermore, this could have relevance to any claims that could be made for a medicine.

Medicine labelling for probiotic ingredients

Members discussed that the different type of ingredient, strain and method of killing complicated the claims made on product labels and increases the onus on sponsors to ensure that they have the evidence in relation to the specific ingredient.

While the majority of Members agreed the method of killing was not required on a medicine label, it should be included in the ARTG entry. One Member disagreed stating that as consumers are concerned about irradiation, this information should be included on the medicine label. However, another Member contended that a large number of herbs are γ- irradiated and this is not stated on the product label.

Members agreed that the method of killing was not required on the medicine label, but that this information should be recorded in the ARTG entry for the product and perhaps made available to consumers in a product information sheet, or as product information provided on the internet.

Members agreed that truth in labelling must be established. Information such as the type of ingredient, colony forming units, condition of storage and shelf life should be provided.

Shelf life

A Member questioned the viability of probiotics over a product's shelf life, commenting that in the USA a study undertaken on probiotics had revealed the growth of *Escherichia coli* in some products.

A Member commented that the issue of shelf life was only applicable to live probiotics and was irrelevant for non-viable probiotics.

Recommendation 3.3

ACCM recommends to the TGA that killed microorganisms derived from probiotics are different ingredients to probiotics of the same species/strain and that appropriate indications and labelling requirements should be implemented for these ingredients.

Recommendation 3.4

ACCM recommends to the TGA that, in addition to Recommendation 3.3, killed microorganisms derived from probiotics should be recognised as different ingredients, including differentiation based on the method of killing (however, the method of killing will not be required to be stated on the medicine label).

11.2 Recognition of culture medium as a component of probiotic and non-viable microbial ingredients permitted for use in listed medicines

Background

A TGA Officer introduced this item advising Members that the OCM had received a query in relation to the need for 'fermented culture medium' to be recognised as a separate ingredient in preparations containing *Lactobacillus* strains (permitted for use in Listed medicines).It was noted that the status of probiotics as ingredients "was ill-defined" and suggested that "many of those probiotics contain some culture to support the live lactobacillus".

Probiotics are assumed to be microbial ingredients which, during processing for use, are separated from culture medium. It is recognised that the culture medium may remain in these ingredients in trace amounts. At present, there is no regulatory requirement to declare culture medium as a component of probiotic ingredients if it is present at levels exceeding trace amounts.

In 1991, two strains of *Saccharomyces cerevisiae* were permitted as grandfathered ingredients in listed medicines. In 1998, CMEC recommended that probiotics (a number of *Bifidobacterium* and *Lactobacillus* species/strains) previously approved for use in registered medicines should be available for use as ingredients in listed medicines. Since then, the OCM has evaluated and approved only one probiotic bacterium, *Streptococcus thermophilus*. Information retrieved from the evaluation report for this ingredient indicates that the culture medium was considered to be a contaminant. It was present only in trace amounts having been separated from the bacterial material using ultra filtration or centrifugation steps prior to lyophilisation.

Depending on the species/strain of the microorganism, a culture medium may contain various formulation components, some of which may not be permitted for use as ingredients in listed medicines. After fermentation, the final composition of a culture medium is likely to be quantitatively variable in terms of various microbial metabolites and other compounds released by the culture. This variation would be compounded by qualitative differences in the composition arising from differing manufacturing conditions for the same probiotic.

The Officer stated that the risks associated with the use of various culture media as components of probiotic ingredients are unclear. ACCM was asked to advise if probiotic culture medium should be recognised as a component of probiotic and/or non-viable microbial ingredients permitted for use in listed medicines.

Discussion

A TGA Officer clarified that retaining 1-2% of the probiotic culture medium may increase the stability of the probiotic organism in a product. Furthermore, this trace amount of medium is often difficult to remove without affecting the probiotic organism's viability.

In the current case, the culture medium is proposed as an ingredient, deliberately retaining or adding it to the product. The culture medium would not present in trace amounts.

<u>Expression of a culture medium</u>

Members discussed the difficulty in qualitatively defining a culture medium post-culture, due to the presence of metabolites of microbial growth. Different metabolites may be beneficial, but some may be undesirable.

In addition, the composition of culture media is typically considered a trade secret and, as such, this information is not readily divulged by sponsors. Different culture media may be used for different strains and every fermentation batch could result in different levels of metabolites. The metabolite end products would be difficult to identify and quantify, and achieving consistency and stability of metabolites from batch to batch would be difficult.

Therapeutic activity

Members questioned: the nature of the therapeutic activity claimed for the media 'ingredient'; if there was a therapeutic effect; and how this could be consistent between batches? Members commented that even if present at 1-2% the material would potentially not be inert.

Contaminants of culture medium

Discussion ensued as whether culture mediums could contain other substances, for example, bovine-derived products or lactose and if so, whether this should be declared on the product label to inform consumers.

TGA Officer clarified that only products that claimed they were lactose free were required to justify the claim. Otherwise, it cannot be assumed that a product is dairy/lactose free.

The question of Bovine Spongiform Encephalopathy (BSE) arose. TGA Officer stated that when the culture medium for a new probiotic organism was assessed, and it contained a component of bovine origin, the media was required to be sourced from countries clear of BSE.

In addition to contaminants of animal origin, Members noted that culture medium may also contain inhibitory substances, such as antibiotics, to suppress the growth of undesirable substances. Other media may be sterile and contain only pure culture, with no need for antibiotics.

Members expressed concern that there were a large number of potential allergens present in culture media of which consumers would be unaware. These may pose a health risk or lead to unwitting exposure. Members commented that this information should be declared on the medicine label.

Comparison to pharmaceutical medicines

Members questioned whether pharmaceutical medicines such as vaccines declare a culture medium. A TGA officer noted that in USA, at the suppliers' discretion, products such as Rotarix included a statement that it may contain traces of culture medium.

Conclusion

Members considered that there was not enough information to determine if culture media were suitable as active ingredients in listed medicines and agreed that the each culture medium needed to be evaluated as a new Listable ingredient. Members agreed further information was required and additional expertise would be useful.

Outcome

ACCM makes a preliminary recommendation to the TGA that culture media should only be present in trace amounts (amount to be determined) in both probiotic and non-viable (killed) microbial ingredients used in Listed medicines.

12. For Information

12.1 Advisory Committee on Non-prescription medicines May 2010 minutes

12.2 Advisory Committee on the Safety of Medicines 1st meeting minutes

12.3 Advisory Committee on the Safety of Medicines 2nd meeting minutes

12.4 Medicines Safety Update No 4 bulletin

Background

ACCM was provided with the minutes of ACNM and ACSOM and the Medicines Safety Update bulletin.

Outcome

ACCM noted the minutes of ACNM and ACSOM and the Medicines Safety Update bulletin.

13. Sponsor Representations to ACCM

Nil items for consideration

14. Other Business

Nil items for consideration

15. Recommendation Record

Recommendation 3.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 2 (4 June 2010), as amended, are a true and accurate record of that meeting.

Recommendation 3.3

ACCM recommends to the TGA that killed microorganisms derived from probiotics are different ingredients to probiotics of the same species/strain and that appropriate indications and labelling requirements should be implemented for these ingredients.

Recommendation 3.4

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The Chair closed the meeting at 4pm.