Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ACCM 4 ADVISORY COMMITTEE ON COMPLEMENTARY MEDICINES EXTRACTED RATIFIED MINUTES FOURTH MEETING 3RD DECEMBER 2010

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADRs	Adverse Drug Reactions
ARTG	Australian Register of Therapeutic Goods
BP	*British Pharmacopoeia*
CG	Compositional Guideline
DBPCFC	Double-Blind Placebo-Controlled Food Challenge
DoHA	Department of Health and Ageing
EU	European Union
MOU	Memoranda of Understanding
OCM	Office of Complementary Medicines
SATCM	State Administration of Traditional Chinese Medicine
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration
USP	*United States Pharmacopoeia*

The Advisory Committee on Complementary Medicines (ACCM) held its fourth meeting at the Sydney airport Stamford Hotel from 9:30 am to 4:00 pm on 3rd December 2010.

Members of ACCM present

Professor Alan Bensoussan (Chair)
Dr Lesley Braun
Ms Patricia Greenway
Ms Karen Martin
Professor Stephen Myers
Dr Richard Oppenheim
Mr Kevin Ryan
Professor Bill Webster
Dr Hans Wohlmuth

Present from the Therapeutic Goods Administration (TGA)

Mr Michael J Smith (Secretary)
Ms Jenny Burnett
Ms Diane Wilkinson

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 Ruth Lopert (TGA Principal Medical Advisor)
Dr Vicki Kotsirilos
Dr Gary Deed

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 3 (3 September 2010)

A Member suggested that if further discussions were required on the topic under discussion in Item 11.1 'The regulatory status of probiotic-derived non-viable microorganisms as ingredients in listed medicines', the Committee may benefit from additional external expertise.

In relation to an action item from Item 2, Members questioned what progress the TGA had made to foster communications with the State Administration of Traditional Chinese Medicine (SATCM). A TGA Officer responded that Memoranda of Understanding (MOU) enable Governments to confidentially share information. Currently, the TGA has MOU with the United States, Singapore and Canada, but does not have a direct MOU with China. However, the Department of Health and Ageing (DoHA) does have a MOU with SATCM, so it is possible for the TGA to liaise with SATCM via DoHA.

The Chair informed the Committee that he would be meeting with representatives of SATCM (in his own professional capacity) and offered, as Chair of ACCM, to facilitate the development of a communication link between the SATCM and the appropriate contact in DoHA.

> As an aside, a Member informed the Committee that the national regulation of TCM practitioners was on schedule to come in to effect in the middle of 2011.

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

Recommendation 4.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 3 (3 September 2010), as amended, are a true and accurate record of that meeting.

3. Action Arising from Previous Meetings

3.1

ACCM discussed one matter under this agenda item. As this matter is still under consideration by the Committee, the information relating to this item will be withheld until the Committee has concluded its deliberations.

3.2 Allura red as an excipient in therapeutic products

Background

A TGA Officer introduced this item, reminding Members that at ACCM 3, they had noted a cluster of minor adverse events associated with a product containing Allura Red AC as an excipient ingredient. At this time, Members commented that this ingredient had been reported to be associated with increased hypersensitivity. Members recommended that the OCM investigate the number of medicines containing Allura Red AC as an ingredient and determine if any Adverse Drug Reactions (ADRs) have been associated with these medicines.

Members were informed that Allura Red AC is a red synthetic azo dye that is known by several names including: Food Red 17 and FD&C Red 40. It is also used as a food dye and has the code number 129.

Another additive, Allura Red AC Aluminium Lake is prepared from aluminium hydroxide and Allura Red AC, producing a lake that is insoluble in water and more stable than the corresponding water-soluble dye.

The ingredient Allura Red AC is currently permitted for use as an excipient in Listed, Over the Counter and Prescription Medicines with no restrictions. The ingredient Allura Red AC Aluminium Lake is currently permitted for use as an excipient in Listed and Prescription Medicines.

Members noted that there are 157 medicines containing Allura Red AC and 40 medicines containing Allura Red AC Aluminium Lake currently in the Australian Register of Therapeutic Goods (ARTG) as excipient ingredients.

Members were informed that from November 2001 to March 2010, there have been 32 reports of ADRs for 10 medicines containing Allura Red AC as an excipient ingredient. As these are all multi-ingredient medicines, it is unclear if any of the ADRs are attributable to Allura Red AC. Further, the types of adverse reactions reported are highly variable, and given that all of the

ingredients are common to many other medicines, it appears unlikely that a cause and effect relationship exists.

Members were informed that recent investigations into the safety of Allura Red AC, conducted by the European Union (EU) concluded that there is a shortage of large, well-controlled intervention studies with defined criteria following double-blind placebo-controlled food challenge (DBPCFC) principles which assessed the adverse effects of oral consumption of individual food azo-colours in humans. In addition, no data on sensitivity to Allura Red AC are available, and no documented cases of intolerance reactions have been reported after oral exposure to this colour. However, the EU Panel noted that the absence of data on adverse clinical reactions after oral exposure could be due to the lack of clinical awareness of this possibility and subsequent under-reporting. Only a few cases of intolerance reactions to colour mixtures including azo-dyes have been reported following DBPCFC procedures after exclusion diets. Intolerance reactions include urticaria, periorbital oedema, facial flushing, as well as higher hyperactivity scores in children. The EU Panel concluded that it is unlikely that oral consumption of the food colours under consideration, either individually or in combination, would trigger severe adverse reactions in human subjects at the current levels of use.

Given the EU conclusion and the fact that no strong causality could be identified linking ADRs to ingestion of Allura Red AC in reports submitted to the TGA since 2001, Members noted that while the TGA will continue to monitor the safety of this additive, no regulatory action will be taken at this stage.

Discussion

A Member commented that Allura Red was present in popular Australian biscuits at quantities far greater than would be present in a therapeutic good.

Members agreed with the TGA's conclusion that at present, there does not appear to be a safety concern in relation to the use of Allura Red in complementary medicines.

Outcome

ACCM noted the lack of a definitive link between the ADRs and Allura Red AC in medicines on the ARTG and the ongoing TGA monitoring for safety of this excipient ingredient.

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. Registration Applications

Nil items

8. Regulatory Reforms

Nil items

9. Adverse Drug Reactions associated with complementary medicines

9.1 ADRs associated with complementary medicines from 1 August to 31 October 2010

Outcome

ACCM noted the adverse events reported for complementary medicines from 1 August 2010 to 31 October 2010.

10. Matters Referred from within TGA

10.1 Krill oil compositional guidelines

A TGA Officer introduced this item, reminding Members that *Euphausia superba* (krill) oil was approved by the OCM for use as an ingredient in listed medicines in September 2007. As part of the application, a draft compositional guideline (CG) was provided for the substance and was subsequently published for comment on the TGA website.

During the comment period for the draft CG, a number of submissions were received by the OCM. These submissions noted the restrictive nature of many of the specifications included in the draft CG and raised concerns that some essentially similar oils would not meet these limits. A number of technical reports were submitted in order to support the case for widening limits on various constituents of krill oil.

As a result of the new data being submitted, the OCM investigated the possibility of a single CG being sufficient to control different types of solvent-extracted krill oil. Initial concerns were raised that appropriate justifications to assure both quality and safety would need to be provided for individual solvent processes. However, having reviewed the additional data, including expert safety reports, and in particular the European Commission decision to recognise two types of solvent-extracted krill oil (one the subject of original CG) as “substantially equivalent”, the OCM decided that a single CG would satisfactorily control the quality and safety of various types of solvent-extracted krill oils.

An update of the original draft CG was prepared and published for further comment. During the comment period for the revised CG, which incorporated wider limits for some specification parameters, an applicant submitted a counter-argument for retaining the original limits. The applicant argued that the revised CG allows the use of various types of solvent-extracted krill oil which have not been assessed by the OCM for safety and efficacy. The submission also noted that the USP was working on a monograph for krill oil as a dietary supplement, which, when published, would become a default quality standard, making the TGA CG obsolete. The principle changes included in the revised CG were summarised for ACCM as follows:

- Limits for oxidation markers have been extended, as both hot and cold extractions using various *British Pharmacopoeia* (BP)-compliant organic solvents have been allowed. It should be noted however, that these remain under the values stipulated in the BP and USP monographs for similar ingredients (e.g. fish oil).

- There are increased limits for content of copper and alpha-tocopherol, but these do not result in significant changes to the total daily intake, considering the recommended daily intakes for these components.
- Maximum limits of the main active components remain unchanged, but lower minimum limits allow compliance for a range of oils. As such, the safety profile of the krill oil is not affected.
- Removal of the separate value for esterified astaxanthin, in favour of retention of a single value for astaxanthin diol, is made on the basis of the latter being a more analytically valid parameter. This change in not considered to affect the quality of the substance.

ACCM was asked to consider the existing CG and the revised draft CG for krill oil; provide advice on the validity of the arguments for and against widening the specifications; and provide an opinion as to whether the OCM revised CG adequately controls the quality and safety of various types of solvent- extracted krill oil.

Discussion

Legal standing of compositional guidelines

Members noted that compositional guidelines have no legal underpinning and are therefore not enforceable. Krill oil is an approved Listable substance, irrespective of whether the substance complies with the compositional guideline or not. That is, there is nothing to stop a sponsor from including in their medicine krill oil that is not compliant with the compositional guideline.

Members agreed that the role of compositional guidelines should be reviewed and ideally, compositional guidelines should be monographs and legally enforceable.

While acknowledging that compositional guidelines are not enforceable, a TGA Officer stated that any requirements can be included in the definition of the ingredient and therefore, can be enforced as a condition of Listing.

Members considered that the current issue was in essence, an issue in relation to the original sponsor's proprietary rights to the ingredient.

Consideration of efficacy and dosage

Members discussed that when assessing a product, the Committee could consider dosage and efficacy of the medicine but for a new Listable substance efficacy is not evaluated.

Differences in the two compositional guidelines

Members noted the variation in the two TGA Krill oil CGs, noting that the original CG contained significantly higher amounts of essential fatty acids and tighter allowances for the active component, astaxanthin. Members debated if the broadening of the criteria in the CG was a compromise on the safety of the substance. It was agreed that while there was no real safety concern, there was a difference in quality between the substances, but whether this resulted in two different ingredients was questionable. Member considered that the two materials were essentially the same ingredient, just different classes or grades. As one material has more biological activity than the other, this would have to be reflected in different recommended dosages for the two materials, which could be confusing for consumers.

Members questioned when it was appropriate to separate an ingredient into two different ingredients. Members compared krill oil to fish oil, noting that there are many different compositional guidelines for fish oil and questioned whether this could be the same for krill oil.

However, Members could see little advantage in this, and considered it would cause considerable consumer confusion.

Natural substance variation and differentiation

Members discussed that natural products were inherently variable (e.g. analogues, different processing, natural variation) and that different solvents would create different preparations e.g. acetone extracts fatty acids and would result in a different chemical profile to an alcoholic extract.

It was noted that this was the same for herbal ingredients, where use of different plant parts or preparations resulted in different ingredients. Members questioned how herbal ingredients were differentiated. A TGA Officer responded that the complete herbal name consisted of the botanical name plus the plant part plus the preparation. Members questioned if this could be applied to differentiate the different types of krill oil, but again, Members could see little advantage in this and considered it would cause considerable consumer confusion.

Potential USP monograph

Members noted that in the event that a monograph was included in the USP, this would be the standard adopted by the TGA and would override any compositional guidelines for the material.

Conclusion

Members considered that while the two compositional guidelines for krill oil resulted in two substances of differing quality, there were no safety concerns for either material. While the Committee considered allowing two compositional guidelines for krill oil, it was agreed that there would be little advantage in this and it would be confusing for consumers. Members agreed that the broader compositional guideline for Krill oil should be adopted and any differences in material quality would be reflected in different product dosages.

Recommendation 4.2
ACCM recommends to the TGA that the revised compositional guideline, which includes broader specifications, be adopted to control quality and safety of all solvent-extracted krill oils.

Outcome

In making the above recommendation:

- ACCM recognises that krill oil is an approved listable substance irrespective of whether the substance complies with the compositional guideline.
- Based on the presented data ACCM identified no safety concerns in either of the two compositional guidelines, providing the krill oil is identified and the solvents used are compliant with the requirements in the BP.
- ACCM recognises that different raw material processing methods may result in different constituent profiles in the final material. However, this is not uncommon in natural substances and is therefore not a strong argument for the existence of more than one compositional guideline. Further, ACCM noted that variations in the active constituent profile may be reflected in the final dosage instructions for the therapeutic product.
- Finally, ACCM also notes the possibility of a relevant monograph being included in a TGA recognised standard in the future and that this may impact on the need for a krill oil compositional guideline.

10.2 Summary of ACCM considerations to date

Outcome

ACCM noted the attached consolidated list of ACCM items considered, recommendations and action items from 2010.

11 For information

11.1 Advisory Committee on Non-prescription medicines August 2010 minutes

Outcome

Members noted the Advisory Committee on Non-prescription medicines August 2010 minutes.

11.2 Advisory Committee on the Safety of Medicines 3rd meeting minutes

Outcome

Members noted the Advisory Committee on the Safety of Medicines 3rd meeting minutes.

11.3 Advisory Committee on the Safety of Medicines 4th meeting minutes

Outcome

Members noted the Advisory Committee on the Safety of Medicines 4th meeting minutes.

11.4 Medicines Safety Update No 5 bulletin

Outcome

Members noted the Medicines Safety Update No 5 bulletin.

12. Nil Items

13. Sponsor Representations to ACCM

Nil items for consideration

14. Other Business

Nil items for consideration

15. Recommendation Record

Recommendation 4.1

ACCM confirms that the draft Minutes of its previous meeting ACCM 3 (3 September 2010), as amended, are a true and accurate record of that meeting.

Recommendation 4.2

ACCM recommends to the TGA that the revised compositional guideline, which includes broader specifications, be adopted to control quality and safety of all solvent-extracted krill oils.