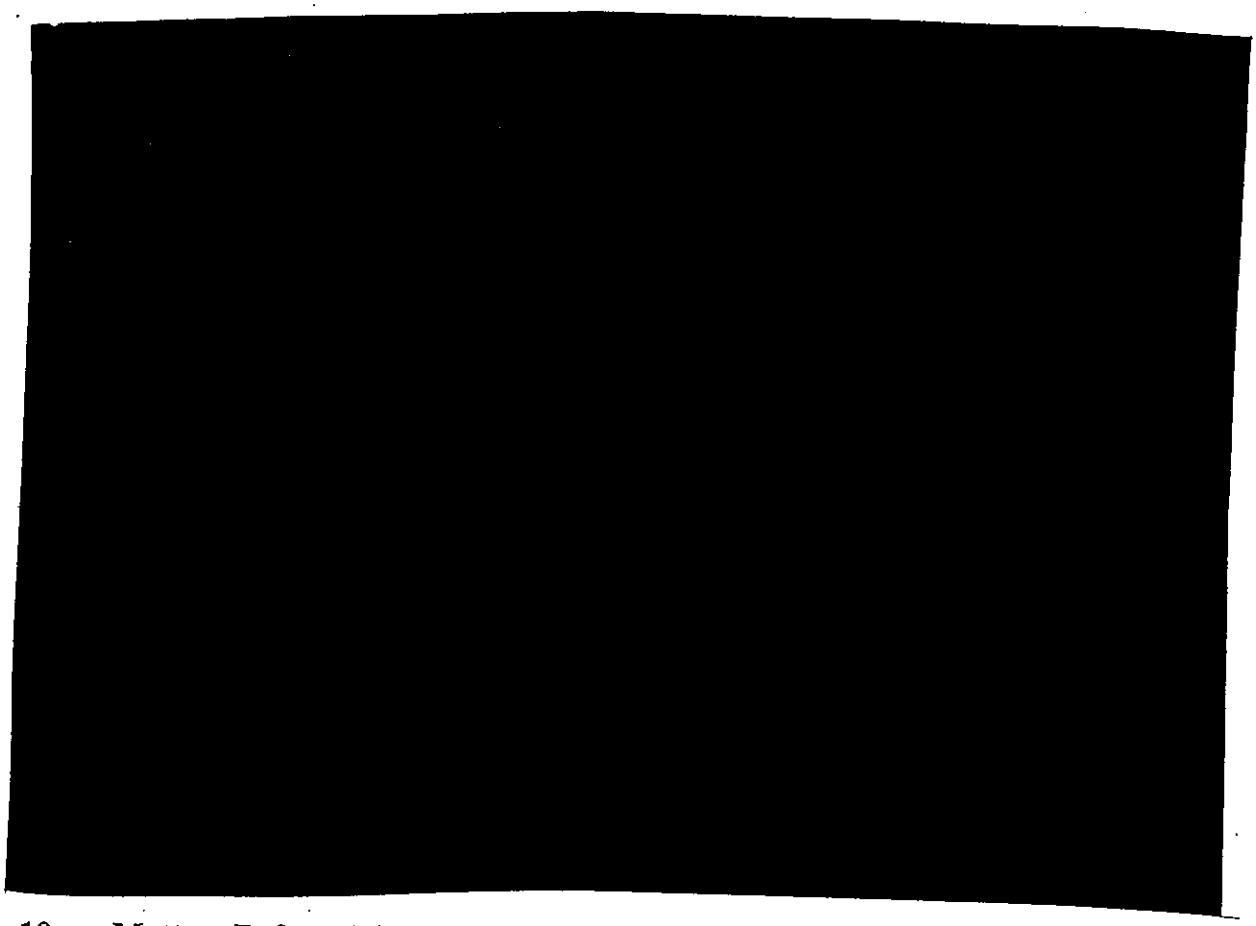

10. Matters Referred from within TGA

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, submissions from several competitor suppliers of krill oil 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 their 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, the original applicant submitted a counter- argument for retaining the original limits.

In their submission opposing the relaxation of 'their' CG, the original applicant has 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 compared with their *Euphausia superba* (krill) oil (Neptune krill oil). The submission also claimed 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. However, the TGA Officer advised ACCM that if the USP includes a monograph for krill oil, the OCM considers it likely that it would provide broader specification limits than the current TGA CG, thus capturing the various types of krill oil available.

The principle changes included in the revised CG that are relevant to the case put forward by the original applicant, 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 a 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, other than establishing that the substance is an active ingredient.

Differences in the two compositional guidelines

Members noted the EU considered the two materials, Neptune krill oil and Aker Bioamarine to be the same ingredient.

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 the applicant's comment that a monograph for krill oil was being developed by the USP. 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 *British Pharmacopoeia*.
- 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.

Action Items

- OCM to reinvestigate the role of compositional guidelines.

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.

Action Items

- ACCM to be presented the summary of ACCM considerations on a regular annual basis.

11.1 Advisory Committee on Non-prescription medicines August 2010 minutes

Outcome

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