Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Complementary Medicines

Ratified Minutes of Meeting 19

22 March 2018

TGA Health Safety Regulation

Abbreviations

ACCM	Advisory Committee on Complementary Medicines
ADRs	Adverse Drug Reactions
AEMDS	Adverse Event and Medicine Defect Section
ARTG	Australian Register of Therapeutic Goods
As	Arsenic
CMES	Complementary Medicines Evaluation Section (of COMB)
CMRS	Complementary Medicines Reform Section (of COMB)
COMB	Complementary and OTC Medicines Branch (of TGA)
LCS	Listing Compliance Section (of COMB)
PIs	Proprietary Ingredients
PSAB	Pharmacovigilance and Special Access Branch
TGA	Therapeutic Goods Administration

The Advisory Committee on Complementary Medicines (ACCM) held its nineteenth meeting at the TGA Executive Boardroom, from 10:00 am to 3:00 pm on 22 March 2018.

Members of ACCM present

[redacted] (ACCM Chair)

Staff from the Therapeutic Goods Administration present

[redacted]

Chief Medical Adviser
First Assistant Secretary (A/g), Medicines Regulation Division
Assistant Secretary (A/g), Complementary and OTC Medicines Branch
Director (A/g), Complementary Medicines Evaluation Section
Director, Complementary Medicines Reforms Section
Director (A/g), Listing Compliance Section
ACCM Secretariat
Assistant Director, Adverse Event and Medicine Defect Section [afternoon attendance]

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 10:00am, welcoming ACCM members and TGA staff.

1.2 Apologies

[redacted]

1.3 Meeting declarations of interest

Members declared no conflicts of interest.

2. Minutes of previous meeting

Accepted.

3. Update on matters previously considered by ACCM

The CMES Director provided an update on the public consultation on the TGA proposal to discontinue pre-market evaluation of Herbal Component Names (HCNs). The TGA has received comments from the public and Industry and is considering the feedback received. The CEMS Director also provided an update on the application submitted for FEFOL IRON Capsules and advised that the application was withdrawn by the sponsor.

The CMRS Director provided an updated on the permitted indications list in relation to the exclusion of indications relating to cellular actions and biomarker indications from the list. The permissible Indications list came into effect on 6 March 2018.

4. Regulatory issues and updates

The CMRS Director advised that the Therapeutic Goods Amendment Bills passed the Parliament and therefore, the reforms started to be implemented. The key reforms in the complementary medicines space are: the implementation of permitted indications list, assessed listed medicines pathway and market exclusivity for new ingredients approved for use in listed medicines.

5. Discussion and advice items

5.1 MMDR Implementation Recommendation 39: Assessed Listed Medicine – supporting Assessed Listed Medicines Evidence Guidelines

The CMES Director provided background information on TGA's updated version of the Assessed Listed Medicines Evidence Guidelines that will be published on the TGA website shortly.

ACCM was requested to comment on the clarity of the guidelines particularly in relation to the biopharmaceutic and pharmacokinetic data requirements and whether there are any concerns or issues that can be addressed in future revisions.

ACCM Discussion:

- ACCM considers the guidelines are comprehensive and provide good guidance on the data requirements for the assessed listed medicines pathway.
- ACCM suggested more examples on the different types of applications may be useful for sponsors.
- Minor edits were also noted – eg terminology used to describe indications may benefit from some clarification/examples e.g. the distinction between indications that reduce/relieve or alleviate a disease. Similarly, consistency of terms may need review eg 'sponsor' *vs* 'applicant' and 'reference medicine' *vs* 'reference product'.
- ACCM considers the requirement set out in 5.4.1 'Level of evidence' of publication of clinical trials in a peer-reviewed journal with at least an impact factor of 5 might not be achievable for complementary medicines. Very few journals in nutrition, nutraceuticals and complementary medicines have that

high impact factor. ACCM recommends the accepted evidence should include well-conducted clinical trials published in high ranked journals e.g. top quartile journals in the discipline without an emphasis on the journal's impact factor. The CMES Director advised that the next revision of the guidelines will be updated accordingly.

- Section 5.4.2 Clinical Significance might need examples on how clinical significance could be assessed e.g. validated instrument, assessments, etc.
- Section 5.4.5 External validity and extrapolation of results – may benefit from recognising the importance of clinical judgment.
- Information on the currency of evidence in the literature search report might be of value.

ACCM advice and resolutions

ACCM advised that:

- The guidelines are comprehensive and provide clear guidance to sponsors on the data required for the assessed listed medicines pathway.

- A few comments were provided on individual sections for consideration in future revisions.

5.2 MMDR Implementation Recommendation 45: Assessed Listed Medicine – claimer that efficacy of the product has been independently assessed for the approved indications

Background was provided by CMRS Director:

Where a medicine is listed on the ARTG under the assessed listed pathway, the sponsor would be able to publish a 'claimer' on all promotional materials and on the product label, that the efficacy of the product has been independently assessed for the approved indication(s) (Recommendation 45). The TGA consulted on implementation options for the claimer in February 2017 which was strongly supported by consumers and industry. Some sponsors requested that the use of the claimer could be extended to all self-selected medicines to include Schedule 2 OTC medicines.

The TGA will consult publicly on: the types of products that could use a claimer on their labels and promotional materials, claimer design and the labelling requirements for the use of the claimer.

ACCM was requested to advise on the options proposed by the TGA in the consultation paper provided to ACCM.

ACCM Discussion:

- ACCM considers the ARTG identifier on the label important to distinguish different types of medicines; however, consumers and many healthcare professionals are not familiar with the ARTG identifier. More education and public awareness campaigns need to target consumers to ensure they understand what is written on medicines labels.
- ACCM acknowledges that label statements should be easy to understand by an average consumer. The TGA advised that consumer testing of claimer design and label statements will be conducted as a part of the public consultation.

- ACCM considers that the use of the claimer should be available for all self-selected medicines that meet the efficacy requirements set out by the TGA.
- ACCM considers the term 'efficacy' is not understandable by an average consumer and may be misinterpreted as TGA endorsement of safety and effectiveness unless education campaign accompanies the implementation of the recommendation.
- An ACCM member suggested that the Health Star Rating system could be an alternative claimer design.
- ACCM considers the term 'evidence assessed' unclear and not well understood by consumers.
- ACCM considers the term 'TGA Assessed' misleading as it implies TGA assessed all aspects of the medicines.
- ACCM suggests the term 'TGA Efficacy Assessed' as a symbol in a box without additional label statement provided that guidance and education for both consumers and sponsors will accompany the release of the claimer.

- ACCM considers the claimer would provide an incentive for sponsors to use the new assessment pathway as it provides greater consumer certainty about the product efficacy being assessed by the TGA. The visual identifier would make the product easily identifiable amongst others.
- An ACCM member suggested using similar terminology used by Standards Australia e.g. certified, etc.
- An ACCM member raised concern on the potential disadvantaging of traditional medicines in the new pathway.

ACCM advice and resolutions

ACCM recommended to the TGA Delegate of the Minister and Secretary that:

- All pre-market efficacy assessed self-selected products should be allowed to make an optional claim that the product efficacy has been assessed by the TGA on their product label and promotional material.

- A visual symbol 'TGA Efficacy Assessed' may be used on the label; there is no need for additional label statements to describe the claimer.

- The claimer is likely to be included on the front panel of the product label at the discretion of the sponsor. The claimer is optional; sponsors may choose not to include it on their medicines labels.

5.3 MMDR Implementation Recommendation 50: Market exclusivity for new ingredients approved for use in listed medicines

Background was provided by CMRS Director:

The TGA is currently preparing to implement a mechanism to incentivise innovation for the complementary medicines industry. The TGA has developed a draft approach to implement market exclusivity for new ingredients approved for use in listed medicines.

ACCM was requested to comment on the TGA proposed approach and the proposed criteria for new ingredients for granting market exclusivity.

ACCM Discussion:

- ACCM acknowledged the objectives of market exclusivity for new ingredients; however, it noted complexity around the protection of new ingredients.
- An ACCM member suggested that the TGA also consider 1) applying the period of exclusivity to claims for novel health indications for either new or existing ingredients based on proprietary evidence; 2) reviewing the approach adopted by the European Food Safety Authority (EFSA) which provides a 5 year-period of data protection for novel claims.
- The TGA clarified that the proposal to provide a 2-year period of market exclusivity was modelled on the provision for exclusive permissions for novel foods in the Australia New Zealand Food Standards Code – Standard 1.5.1 – Novel foods that grants 18 months market exclusivity. The 2-year period is commensurate with the level of investment listed medicines sponsors put for the new ingredients.
- An ACCM member clarified that different plant parts with different composition will not be subject to market exclusivity under this scheme.

ACCM advice and resolutions

ACCM recommended to the TGA Delegate of the Minister and Secretary that:

- The proposed approach and criteria for new ingredients for granting market exclusivity is considered appropriate.

5.6 Green tea extract (*Camellia sinensis*) and hepatotoxicity

Background was provided by the Adverse Event and Medicine Defect Section (AEMDS):

There have been several reports of hepatotoxicity associated with the use of *Camellia sinensis* in complementary medicines. TGA's safety review of this matter concluded that the reviewed information, including 20 liver-related adverse reaction reports in Australia, and a Health Canada Signal Assessment of this issue, shows a consistent association between green tea extract consumption and rare and unpredictable cases of hepatotoxicity.

Currently, there is no restriction on the *Camellia sinensis* dose or a mandatory label warning statement for products containing *Camellia sinensis*. Considering the apparent widespread availability of green tea in supplements on the market and its common use as a beverage, the hepatotoxic events would appear to be rare and unpredictable.

ACCM was requested to provide advice on the possible association between hepatotoxicity and the green tea herbal ingredient and whether the adoption of risk mitigation strategies is deemed appropriate.

ACCM Discussion:

- ACCM notes that the product involved in the 2015 case of liver injury was not included on the ARTG.
- ACCM notes that Health Canada has warning statements and quantity restriction in place for *Camellia sinensis*.
- In response to a question from a member, a TGA officer advised that disproportionality analysis had not been conducted for this review due to the complex nature of listed medicines and the difficulty in applying standard disproportionality algorithms to multi-ingredient medicines.
- It was unclear to ACCM whether the hepatotoxic component in *Camellia sinensis* is EGCG or other substance(s) in green tea extracts.
- ACCM members agreed that the available information suggests there might be a link between *Camellia sinensis* and liver injuries. However, it was noted that the reactions appear to be idiosyncratic and appear to have occurred at low doses, therefore would be difficult to set an upper dose limit. ACCM members agreed that continued monitoring of the ADRs is warranted and that label warning statements should be considered.
- ACCM members agreed that based on the available information a link appears possible between hepatotoxicity and *Camellia sinensis* and is sufficient to warrant a precautionary approach. ACCM advised that it would be appropriate for the TGA to give further consideration to Options 1 and 2. This includes continued monitoring (Option 1) and risk communication (Option 2) such as publication of a web advisory statement and incorporation of warning statements e.g. *Take with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice*, on the labels.
- Given the nature of the herbal ingredient, ACCM members agreed that the TGA should consider consulting with Food Standards Australia New Zealand (FSANZ) over the issue.

ACCM advice and resolutions

ACCM recommended the TGA Delegate of the Minister and Secretary that:

- There is no conclusive evidence that confirms the association between hepatotoxicity and *Camellia sinensis*, although the available information suggests a link is possible

- It would be appropriate for the TGA to give further consideration to risk mitigation strategies such as ongoing monitoring and suitable risk communication, including publication of a web advisory statement and label warning statements.

-it would be appropriate for TGA to consult with FSANZ

5.4 Green Lipped Mussel

Background was provided by LCS Director:

Recent TGA Laboratory testing of 30 Green Lipped Mussel containing listed medicines found that 28 medicines contained total arsenic concentration above the limit specified in the Poisons Standard (1 ppm). However, further testing of the selected products showed that the inorganic levels were below 1 ppm. Since the Poisons Standard does not distinguish between organic and inorganic arsenic, these products—and potentially many other shellfish-containing products currently on the ARTG—are ineligible for listing.

ACCM was requested to provide advice on the arsenic entry in the Poisons Standard to whether a separate entry for inorganic arsenic should be included. ACCM was also requested to advise whether the TGA should be taking regulatory action against listed medicines that exceed the current scheduling limit of 1 ppm total arsenic or whether the responsibility lies with sponsors to demonstrate that organic arsenic presents less of a safety concern for consumers than inorganic arsenic.

ACCM Discussion:

- Some organic arsenic (As) compounds are metabolisable and bioavailable and therefore would impose similar safety risk to inorganic As compounds. Multiple organic As could have additive toxicity when combined. Speciation of organic As should be combined with information on the level of bioavailability of the organic form.
- ACCM recommends liaison with FSANZ on the levels and distinction of different As salts.
- In relation to the As entry in the Poison Standards, considering the bioavailable form of As would be more appropriate than the reference to organic/inorganic form of As.
- It might be useful to consider the quality standards for Green lipped mussel in the Japanese or European pharmacopeia.

ACCM advice and resolutions

ACCM recommended to the TGA Delegate of the Minister and Secretary that:

- Having the entry of As in the Poison Standard relating to the bioavailable form of arsenic might be more appropriate than the reference to the inorganic form.

- Consultation with FSANZ on the levels and forms of As.

5.5 Coumarin as a topical excipient ingredient in listed medicines

Background was provided by CMES Director:

Coumarin is not currently listed in the Permissible Ingredients Determination for use as an excipient ingredient in listed medicines. However, it was historically available for inclusion in proprietary ingredients (PI) notified as fragrances. Coumarin is included in Schedule 4 of the Standard for Uniform Scheduling of Medicines and Poisons (SUSMP) when used for therapeutic use but is not scheduled when used as an excipient. Preliminary assessment of coumarin by the TGA Toxicology section found that it is a frequently reported allergen and skin sensitizer. It is also hepatotoxic and carcinogenic and readily absorbed through the skin (60-95%). Comparable Overseas regulators have restrictions on its use as a food additive and require a declaration on the label when it is available in topical preparations at levels 0.001% or higher in leave on products.

ACCM was requested to provide advice on whether coumarin should be included in the Determination at a level not more than 0.001% in line with the current restriction for its inclusion as a component in *Cinnamomum spp.* and a homeopathic active ingredient or it could be used without a restriction in coumarin-containing fragrance PIs. Also, ACCM was requested to advice whether warning statements declaring its presence are required on medicines labels.

ACCM Discussion:

- ACCM notes that most of the topical preparations on the ARTG that contain coumarin in PIs are sunscreens.
- ACCM also noted that in the Australian context, sunscreens should be applied liberally and regularly to achieve protection against skin cancer. Having an allergenic, carcinogenic excipient that is absorbed through the skin that is applied liberally and regularly also raises the possibility of cumulative toxicity.
- The quantity of coumarin in sunscreen PIs may not be exactly known. However, based on the information provided about coumarin's allergenic potential, a label warning statement about its presence would appear warranted.
- The allowable concentration of coumarin as an excipient should be aligned with an in- depth toxicology evaluation of the ingredient.
- Consultation with FSANZ as to the use of coumarin as a food additive would also appear warranted.

- ACCM also noted that it may be appropriate to approach the Scheduling committee about whether the use of coumarin as an excipient is appropriate without restriction, considering that it has concentration restrictions as an active?

ACCM advice and resolutions

ACCM recommended to the TGA Delegate of the Minister and Secretary that:

- Coumarin is a contentious ingredient and in depth assessment of its safety profile might be warranted.

- Depending on the outcome of a safety assessment, warning statements declaring its presence and its potential allergenicity may also be warranted on the labels.

- Consideration be given to also discussing the coumarin entry with the Scheduling Committee

6. Other business

An ACCM member raised the issue of regulation of raw herbs and the potential of adulteration and contamination of these unregulated herbs. Regulation of raw herbs is outside the remit of the TGA.

7. Next Meeting

The next meeting is scheduled for 26 July 2018.

8. Close

The Chair thanked ACCM members and TGA staff for their contributions.

Meeting ended at 3:00 pm.

Chair's certification

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

[redacted]

ACCM Chair

March 2018

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