Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Complementary Medicines

Ratified Minutes of Meeting 20

16 November 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
BISS	Business Improvement and Support Section (of COMB)
CMES	Complementary Medicines Evaluation Section (of COMB)
COMB	Complementary and OTC Medicines Branch (of TGA)
CP	Chinese Pharmacopeia
EFSA	European Food Safety Authority
EMA	European Medicines Agency
LCS	Listing Compliance Section (of COMB)
PIs	Proprietary Ingredients
PSAB	Pharmacovigilance and Special Access Branch
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TCM	Traditional Chinese Medicine
TGA	Therapeutic Goods Administration

The Advisory Committee on Complementary Medicines (ACCM) held its twentieth meeting at the TGA Conference Room 1, from 9:30 am to 3:45 pm on 16 November 2018.

Members of ACCM present

[redacted] (ACCM Chair)

Staff from the Therapeutic Goods Administration present

[redacted]

First Assistant Secretary, Medicines Regulation Division
Assistant Secretary, Complementary and OTC Medicines Branch (COMB)
Director (A/g), Complementary Medicines Evaluation Section (CMES)
Director, Business Improvement and Support Section (BISS)
Director, Listing Compliance Section (LCS)
ACCM Secretariat
Assistant Director, Adverse Event and Medicine Defect Section (AEMDS) [afternoon attendance]
Assistant Director, Listing Compliance Section [afternoon attendance]
Scientific Evaluator, Listing Compliance Section [afternoon attendance]

1. Procedural matters

1.1 Opening of meeting

The Chair opened the meeting at 9:30am, 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 advised that the evidence guidelines for assessed listed medicines were published on the TGA website. V1.1 is the current version and was published in August. Committee comments as well as input from external stakeholders were considered in the current version. The CMES Director also advised that the TGA published a safety alert of the potential risk of harm to the liver associated with products that contain *Camellia sinensis* (green tea) extracts. The alert is directed to consumers and health professionals and encourages them to report adverse effects or other suspected medicine-related problems.

The BISS Director provided an update on the use of a claimer for efficacy assessed non-prescription medicines to address MMDR Recommendation 45. The TGA undertook public consultation and consumer usability testing. The outcomes of the public consultation and consumer usability testing are published on the TGA website. The claimer will be available for assessed listed medicines (with the exception of sunscreens) and registered complementary medicines. The TGA is finalising education campaigns to healthcare professional bodies and consumer bodies to ensure that the intent of the recommendation is achieved. The BISS Director also provided an update on the implementation of MMDR Recommendation 50 and that the TGA had implemented an electronic mechanism to allow applicants to exclusively use their new ingredient as well as enable other nominated sponsors to do so.

The LCS Director provided an update on the compliance status of green lipped mussel listed medicines that exceeded the arsenic limit specified in the Poisons Standard. The TGA consulted with FSANZ regarding their safety assessment of arsenic content. As there is no specific safety concern in relation to the non-compliant listed medicines, the TGA has not undertaken regulatory action and is looking into revising the requirement in the Poisons Standard.

4. Regulatory issues and updates

The BISS Director provided an update on the transition to permitted indications: 20% of listed medicines on the Australian Register of Therapeutic Goods (ARTG) have transitioned with no major issues.

Also, the TGA is introducing a post-market compliance rating scheme for listed medicines to address MMDR Recommendation 49. Listed medicines that have undergone a compliance review will be assigned a compliance rating as at the time of review. There will be a six-month transition period after which the overall outcome of the review including the compliance review rating will be published on the TGA website. The soft launch of the compliance rating scheme begins late November 2018.

5. Advice items

The committee started the discussion with item 5.4.

5.4 Requirements for oral caffeine in listed medicines

Background was provided by the CMES Director:

Caffeine is listed in the Therapeutic Goods Permissible Ingredients Determination (the Determination) as an individual ingredient and as a component within herbal ingredients.

When caffeine is used as an active ingredient in listed medicines, the medicine must not provide more than 100mg per maximum daily dose; however, there is no restriction on caffeine content when it is included as a herbal component.

Caffeine is used in OTC medicines with a dose restriction of 100mg per dose which may be repeated at three hourly intervals, with a maximum dose of 600mg in 24 hours. The European Food Safety Authority (EFSA) and Health Canada have different limits for caffeine consumption.

As such, ACCM was requested to advise on options to clarify appropriate regulatory requirements for caffeine in listed medicines.

ACCM Discussion:

- ACCM considers it reasonable to align caffeine requirements in listed medicines whether caffeine is included as an ingredient or a herbal component. However, it is recognised that caffeine as a component of a herbal medicine may provide different caffeine doses when compared to ingesting caffeine as an ingredient.
- ACCM recognises the differences in people who metabolise caffeine and suggest that it is appropriate to include the equivalence to cups of coffee on labels e.g. 1 tablet contains x mg caffeine which is equivalent to x number of cups of coffee.
- ACCM considers the proposed warning statements reasonable and informative to consumers regarding the level of caffeine exposure given the additional habitual caffeine intake. The proposed warning statements were:

  80-100 mg caffeine is approximately equivalent to 1 cup of coffee (or words to that effect;

  Pregnant women should limit caffeine to under 200 mg caffeine per day (or words to that effect); and

  Not suitable for children.
- An ACCM member noted that some parents use caffeine to manage ADHD in their children, so it might be more appropriate for the warning statement to be '*Not recommended for children'*.
- ACCM considers it appropriate to set caffeine dosing intervals to limit consumers taking multiple tablets at a time: a dose to be repeated at three to four hourly intervals is considered reasonable. An ACCM member suggested that the warning may be clarified if worded as *'May be repeated at 3 hours intervals'.*
- An ACCM member suggested that 200mg may be appropriate as a single dose.
- ACCM also considered aligning caffeine requirements with others such as those for OTC medicines and prescription medicines, however, it is recognised that caffeine content in prescription medicines is subject to pre-market evaluation and that prescription medicines are regulated differently; based on their level of risk. Also, the use of prescription medicines is under the supervision of a medical professional who assesses the benefit-risk profile of the medicine for the

individual patient, an aspect that is not available in listed medicines which are self-selected medicines for self-treatment.

- On balance, ACCM considers aligning caffeine requirements in listed medicines with OTC medicines to be appropriate which would lead to the following requirements:

  A maximum of 100mg per dose* which may be repeated at 3-4 hours intervals with a maximum of 600mg in 24 hours.

  Label advisory statements:

  One dose is equivalent to X cups of coffee

  Pregnant women should limit caffeine intake to under 200mg caffeine per day

  Not recommended for children

  * However a maximum of 200mg per dose may also be appropriate

ACCM advice and resolutions

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

- It would be appropriate to consider aligning the requirements of caffeine content and label advisory statements in listed medicines with those for OTC medicines.

5.2 Risk-based scheme for implementation of changes to permissible ingredients used in listed medicines

Background was provided by the CMES Director:

The TGA makes regular amendments to the requirements for permissible ingredients in the Therapeutic Goods (Permissible Ingredients) Determination ('the Determination'). These amendments range from including new ingredients as an outcome of an application evaluation, correcting errors, and changes resulting from the outcome of safety reviews.

Initially, updates to the Determination proceeded on a 3 monthly basis with no public advance notice of the upcoming changes and little to no provision for existing ARTG medicines to come into compliance with the new ingredient requirements. The Determination update arrangement was revised later on to provide advance notice to sponsors to make necessary changes to their products to ensure compliance with the updated requirements.

The TGA proposes to implement a new process to manage changes to requirements for ingredients using a risk-based compliance transition scheme. This would provide systematic and transparent timeframes for sponsors to comply with the updated regulatory requirements.

The TGA advised that the Determination will be updated once per year to reflect 'low to negligible risk' changes. Sponsors of existing medicines on the ARTG will be notified of the upcoming amendments early and they will have a fair timeframe to adjust and bring their medicines into compliance with the updated requirements. New medicines would be required to comply straightaway with the updated regulatory requirement. Changes in the Determination rates as 'High to medium risk' would require immediate compliance.

ACCM was requested to advise on the merits of the proposed risk-based scheme for implementation of changes to permissible ingredients used in listed medicines.

ACCM Discussion:

- ACCM considers the 12-month period provided to sponsors for 'low to negligible risk' category changes appropriate. However, more clarification is required to better qualify what is in the 'high to medium risk' category.
- ACCM suggests providing examples to industry on each category and the type of data that may constitute the evidence for the update to the Determination, such as a safety signal from new animal studies, a clinical study or post-market surveillance, etc.
- ACCM acknowledges that sponsors will be provided advance notice prior to the 'low to negligible risk' changes coming into effect and that the 12-month transition to compliance period will start from the date of the registration of the amended Determination on the Federal Register of Legislation (FRL).
- ACCM considers that immediate compliance with the updated requirements when the changes are of a high to medium risk is appropriate and that the TGA may use recall or other compliance actions to ensure public safety.
- ACCM considers that the descriptors of 'likelihood' ratings need further clarification or quantification. For example, it might be useful, if possible, to describe the likelihood of the occurrence of an adverse event quantitatively e.g. 1:100, 1:1000, etc.
- ACCM considers that an ingredient with an 'almost certain' likelihood of 'insignificant' consequence of an adverse event to be of low to negligible risk, while an ingredient with a 'major' consequence and a 'rare' likelihood of an adverse event is of high to moderate risk. However, an ACCM member commented that 'superficial skin irritation' may not be considered as insignificant, although it was categorised as 'insignificant' in Table 3. ACCM suggested a conservative approach would be better.
- . ACCM suggests a grading system from 1-5 for the likelihood scale rather than descriptor terms like rare, possible, likely, etc.

ACCM advice and resolutions

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

- The proposed risk-based scheme for the implementation of 'low to negligible risk' changes in the Determination is appropriate. The 12-month transition period is reasonable to ensure medicines compliance with updated requirements.

- More clarity needs to be provided for the higher risk category changes to ensure sponsors understand the risk rating and their compliance obligations.

5.3 Outcomes of the TGA safety review of 'coumarin' for topical use in listed medicines

Background was provided by the CMES Director:

At ACCM Meeting 19, the TGA identified safety concerns with topical listed medicines that contain coumarin in fragrance proprietary ingredients (PIs). Following advice from ACCM Meeting 19, the TGA has completed a draft comprehensive safety review of coumarin for topical use.

ACCM was requested to discuss the draft safety review and advise whether the conclusions and recommendations within the report are appropriate.

ACCM Discussion:

- ACCM acknowledges that most of the coumarin-containing listed medicines included in Appendix 1 of the safety review are leave on products which include sunscreens and nappy rash creams.
- ACCM notes it appropriate to consider restrictions for coumarin as an excipient ingredient to mitigate the risk of skin sensitisation and/or hepatotoxicity. ACCM notes that the potential of skin sensitisation or hepatotoxicity is not dose-related. It could be appropriate to align with internationally established safety limits for coumarin.
- ACCM acknowledges under-reporting of Adverse Drug Reactions (ADRs) for listed medicines and that consumers are usually not aware of the presence of ingredients they may be allergic to in PIs.
- ACCM considers the risk of having coumarin in nappy-rash products (with high likelihood of systemic absorption in babies) is high and unacceptable for a listed medicine especially with concerns about its potential hepatotoxicity. ACCM acknowledges the 10 cases of hepatotoxicity associated with coumarin use for the treatment of lymphodema and the withdrawal of coumarin products from the market shortly after.
- ACCM also considers the risk of having coumarin in sunscreens that are usually applied liberally and for extended periods of time to be unacceptable for a listed medicine. Currently, there is no available data to set safe limits for skin sensitisation, phototoxicity or hepatotoxicity.
- ACCM acknowledges that many people experience skin sensitisation associated with sunscreens; declaring the presence of coumarin on sunscreens labels would be beneficial for consumers for better informed choices especially for those who are sensitive to coumarin.
- Some members of ACCM suggested not making coumarin available for use in listed medicines and to place the onus on industry to provide evidence to demonstrate its safety and suitability for use in listed medicines. Nevertheless, overall, ACCM considers the conclusions and recommendations within the safety review appropriate.
- ACCM agrees with the recommendations provided in the safety review:

  The concentration of coumarin in the medicine must be no more than 0.001%.

  When coumarin is used as an excipient it must only be used in topical medicines for dermal application.

Label advisory statements:

Contains coumarin, may cause skin sensitisation

Do not use on broken, irritated or inflamed skin

- The TGA advised that the safety report will be provided to industry and scheduling committee prior any amendments to the Determination are made.

ACCM advice and resolutions

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

- The conclusions and recommendations within the draft safety review are considered appropriate.

5.1 Boron-containing compounds and safety in children/adolescents

Background was provided by [redacted] from the Adverse Event and Medicine Defect Section (AEMDS):

Safety concerns have been raised by the European Medicines Agency (EMA) on the use of boric acid and borates as excipients in medicinal products. The EMA identified the potential for boron to impair fertility, as well as being fetotoxic, teratogenic and fetolethal, as evidenced in animal toxicity studies. Consequently safe limits per age group were established by the EMA and requirements for a label declaration and warnings on the package leaflet were introduced. Current restrictions on boron containing ingredients in Australian medicines do not ensure exposure is below the EMA limits for certain age groups, particularly children/adolescents under 12 years of age. A TGA safety filter investigation concluded that modification of current requirements for boron-containing ingredients in listed medicines is warranted.

ACCM was requested to provide advice on whether it agrees that current requirements for boron-containing ingredients in listed medicines be modified to ensure that; EMA's age-related limits are not exceeded, and systemic absorption from topical use is avoided. ACCM was also requested to advise on appropriate regulatory options.

ACCM Discussion:

- ACCM notes that the maximum recommended daily dose of a listed medicine must not provide more than 6mg of boron which is lower than the maximum dose established by the EMA which may cause harm to the unborn child if taken during pregnancy (7mg). ACCM also notes that EMA assessment of reproductive toxicity was based on toxicity studies on mouse, rat and rabbit.

- An ACCM member provided a list that contains clinical and non-clinical studies that examined some therapeutic benefits of boron. The studies did not show any negative effects on fertility in the study populations. It was recommended that the TGA examine whether these studies were considered in the EMA report.

- ACCM acknowledges that the effect of impairment of fertility maybe delayed.

- An ACCM member raised concern on the use of boric acid compounded pessaries by pregnant women and the wide perception of their safety. The pessaries contain around 600mg boric acid and are used to lower the vaginal pH to help with thrush. There is a high likelihood of systemic absorption which could impact the fetus. It was suggested that a safety alert directed to health

professionals needs to be considered given the widespread use of boric acid compounded pessaries and the ramifications of their use by pregnant women. A follow up advice from the same member indicated that trans-vaginal absorption of boric acid from vaginal pessaries appears to be minimal according to the available evidence from literature and clinical experience.

- The TGA advised that sponsors who have medicines registered or listed on the ARTG must meet their pharmacovigilance reporting responsibilities. Sponsors are expected to monitor and take responsibility for the safety of their medicines and notify the TGA of any significant safety issues they identify.
- ACCM acknowledges the proposed amendments to boric acid, borax and borates entries in Schedule 5 of the Poisons Standard to include warning statements 'not to use the product in children under 3 years' and 'not to use the product on peeling or irritated skin'. The inclusion of other warning statements such as 'may cause birth defects' or 'contains boric acid which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with boric acid' are also proposed.
- ACCM considers label advisory statements for listed medicines to warn consumers not to use in children under 12 is appropriate :

  For medicines that provide more than 1mg boron/day

  Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future

  For medicines that provide more than 3mg boron/day

  Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future
- ACCM acknowledges the potential of systemic absorption associated with the use of topical preparations on broken, inflamed or irritated skin and therefore, considers a warning statement for topical preparations is warranted:

  Do not use on broken, irritated or inflamed skin (or words to the effect of the Poisons Standard warnings)

ACCM advice and resolutions

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

- The inclusion of label statements to warn consumers not to use a listed medicine in children under the age of 2 or 12 (depending on the amount boron provided by the medicine) is considered appropriate.

- For topical medicines that contain boron, a label statement to warn consumers not to use the medicine on broken, irritated or inflamed skin is warranted. It was suggested to align with the proposed warning statements in the Poisons Standard for boric acid, borax and borates.

5.5 Comparability of traditional methods of preparation and modern manufacturing processes

Background was provided by [redacted] from LCS:

The Evidence Guidelines for listed medicines state that where sponsors hold evidence of traditional use for a given listed medicine and indication, this should take into account the method of preparation of the medicine. However, methods of preparation reported in traditional evidence provided to the TGA usually differ markedly from those used in modern manufacturing practices for listed medicines. Hence, there is a possibility that the efficacy of a good may differ significantly from what is reported in the traditional evidence. The TGA therefore seeks to ascertain what aspects are critical for comparability, or how sponsors of listed medicines can justify differences in method of preparation. This will allow the TGA to clarify for sponsors how the regulatory requirements for listed medicines with traditional indications are to be met.

ACCM was requested to discuss and provide advice on several regulatory options presented in the paper that are available to the TGA going forward. ACCM was also requested to advise on how to develop criteria to ensure sufficient comparability.

ACCM Discussion:

- An ACCM member advised that:
  - In Traditional Chinese Medicine (TCM) there is no clear definition of a "traditional method of preparation". This is due to the fact that traditional methods have never been standardised and the description of methods of preparation recorded in traditional literature are often vague (e.g. stir-fry in salt until golden brown) and rely on the experience of the person conducting the processing (taste, smell, appearance, etc.).
  - The main purpose of processing raw materials into decoction pieces is to modify the nature, flavours and enhance the therapeutic action of the decoction pieces as well as removal of toxicity. The decoction pieces can either be supplied to consumers *via* a TCM practitioner or processed further into finished goods in the form of granules, powders, pills or liquids. Any step in this process (raw material to decoction pieces to finished goods) potentially impacts on the quality, safety and efficacy of the finished good.
  - The Chinese Pharmacopeia (CP) is the national standard in China and sets out the minimum quality requirements (such as minimum water content, ash weight, etc.) for decoction pieces. Since raw herbs grown in different geographical locations have been shown to result in different amounts of active components, the quality of herbs may vary, thus resulting in differing levels of efficacy even when the CP requirements are followed. Nevertheless, as long as the decoction pieces or finished good meet CP requirements, a minimum level of efficacy is to be expected.
  - For TCMs, China is starting to invest in research to support the standardisation of processing methods.
- ACCM members all agreed that some level of scrutiny of method of preparation should occur due to ramifications on quality, safety and efficacy of the finished good. It was advised that the focus should be on the end product rather than comparing traditional and modern methods.
- ACCM considers that information on phytoequivalence could help ascertain the comparability of the traditional preparation with the listed good.
- ACCM considers that collaboration with other regulators could be beneficial to ensure quality, safety and efficacy of traditional medicines.
- ACCM suggested that the TGA seeks advice from specialist groups such as the

Chinese Medicine Board of Australia, academic institutions such as RMIT University (Chinese Medicine Program) or the World Health Organisation (who are set to publish a chapter in ICD-11 for traditional medicines) to determine how comparability can be demonstrated.

ACCM advice and resolutions

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

- The TGA seeks further information from specialist groups, overseas regulators and academic institutes to determine the criteria that are considered within traditional paradigms to be important for comparability of different methods of preparation.

6. Other business

NIL

7. Proposed schedule for 2019 meetings

Proposed dates:

Thursday 28 March

Friday 26 July

Thursday 21 November

8. Close

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

Meeting ended at 3:45 pm.

Chair's certification

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

[redacted]

ACCM Chair

December 2018

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