The Compositional Guidelines Officer
Office of Complementary Medicines
Therapeutic Goods Administration
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Dear Compositional Guidelines Officer

CHC Comments: Draft Compositional Guideline for Quercetin, Rutin trihydrate and Hesperidin

Thank you for the opportunity for the complementary healthcare industry to provide comment on the draft compositional guidelines for Quercetin, Rutin trihydrate and Hesperidin. The Complementary Healthcare Council (CHC) submits the following comments for consideration before each compositional guideline is finalised:

General Comments (these comments apply to all three drafts)
The CHC would like to suggest that for consistency, each of the compositional guidelines should be laid out in a similar format to that of a compendial monograph, as seen in approved default standards. For example, members have suggested it would be useful if similar section headings where used in the guidelines. The layout of a compositional guideline is very well explained in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM) Par III, Appendix 1; the CHC suggests these guidelines be followed when developing future compositional guidelines.

The CHC would like to further suggest that the compositional guidelines be linked to the substances Australian Approved Name (AAN) for industry's benefit. This could be included in '*Name of the Ingredient*' section or as a stand alone section under this.

Given that residual solvents are a legislated requirement to test for, and that these substances can be produced through solvent extraction/purification, the CHC suggests specifications be included into the compositional guideline as outlined in the approved default standards.

The CHC notes that infrared spectroscopy (IR) is listed as the method reference for identification for all three guidelines (thin layer chromatography (tlc) is included for Quercetin). The CHC requests there be other method references included such as melting point, retention time in a defined validated chromatography method, mass spectrometry profile etc.

The abbreviations for each compositional guideline are not user friendly. The CHC suggests listing each abbreviation down rather than running into each other. Furthermore, the abbreviation for 'tlc' is not included in the compositional guideline for Quercetin; if it is to be used, the abbreviation should be included for reference. The abbreviation for molecular weight is also used for Quercetin and Hesperidin; this should be expanded. Finally, some abbreviations are listed however not used in the document.

The loss of drying limits appear to be quite random, noting they vary from <1.0%; 9.0-12.0% and 5.0-8.5%. The CHC recommends these limits be reviewed before the guidelines are finalised. In addition, it appears that the limits for assaying also appear to be arbitrary, varying from 98.5-102% and 99-101%.

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The CHC strongly recommends that where related substances are required to be assayed, the actual substance should be listed within the compositional guideline. Furthermore, the CHC notes that the related substances in each guideline has limits of <0.1% for individual substances and a total of <0.3%. The CHC points out that these limits are tighter than what is required for a number of Over-the-Counter medicines. For example, the latest British Pharmacopoeia monograph for Rutin trihydrate has related compounds at NMT 2.0% for individual substances (e.g. Quercetin, Isoquercitroside and Kaempferol-3-rutinoside) and NMT 4.0% total related substances. As a comparison, Prednisolone Sodium Phosphate can have individual NMT of 1.0% (one related compound can be NMT 2.0%) and the total NMT 3.0% or Pseudoephedrine HCl which has Impurity A at NMT 1.0% and other impurities at NMT 0.5% with total NMT 1.0% (not including Impurity A). Based on this information, the CHC strongly recommends the limits for related substances be reviewed and amended.

Finally, the CHC notes that microbiology standards are the responsibility of the manufacturers/sponsor of the ingredients being used in a product and how these results are obtained for any given ingredient should be the responsibility and action of a TGA licensed manufacturer. Therefore, the CHC suggests that the reference to the Therapeutic Goods Order (TGO 77) be incorporated into the standards as a comment/reminder rather than being presented as a test specification.

Specific Comments

Quercetin

The CHC provides the following comments specific to the draft compositional guideline for Quercetin:

- The method reference has not been stated for loss on drying however, members have advised that Karl Fisher is more often used to determine water content rather than 'Loss on Drying'. The CHC therefore suggests that this test be amended with specifications of 9.5% to 12.5% (in place of 9.0% to 12.0%;
- The CHC questions the relevance in requiring both 'Residue on ignition' and 'Sulphated Ash' to be performed. The CHC notes that members are currently performing 'Sulphated Ash' with specification limits of NMT 0.2% with results generally falling between 0.1% and 0.2%;
- The definition of the substance states that the ingredient is '*Quercetin dihydrate'* however the molecular formula is for the non-hydrated form. The CHC requests that this be clarified;
- The CHC recommends that the related substances limit be set at NMT 1.0% for individuals and NMT 2.0% for total impurities. Quercetin is manufactured from Rutin which is extracted from the buds and flowers of Sophora Japonica and any related compounds are most likely going to be similar in nature to Quercetin or Rutin; and
- Some additional information that could be incorporated into the compositional guideline:
    - (M_r 338.2). *1138100.* 2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one.
    - Yellow crystals or yellowish powder, practically insoluble in water, soluble in acetone and in methanol.
    - *Water* (*2.5.12*): maximum 12.0 per cent, determined on 0.100 g.
    - *Assay*. Liquid chromatography (*2.2.29*) as prescribed in the monograph *Ginkgo leaf (1828)*.
    - *Content*: minimum 90 per cent (anhydrous substance) calculated by the normalisation procedure.
    - *Storage*: protected from light.

Rutin trihydrate

The CHC provides the following comments specific to the draft compositional guideline for Rutin trihydrate:

- There is no line formula or molecular weight stated on the guideline;

- The compositional guideline states a specification for 'moisture' however there is no method reference provided;
- The solubility: aqueous or specific solvent; has stated 'method' as the method reference instead of an actual process;
- The CHC notes again that there is doubling up of testing with both 'Residue on Ignition' and 'Sulphated Ash' listed – refer to comment above for Quercetin;
- Comments from members suggest Karl Fisher is being performed to determine water content with limits set at 7.5% to 9.5% rather than the 9.0% to 12.0% stated in the draft guideline for 'Loss on Drying';
- The CHC also suggests that the BP monograph be accepted for related substances with Impurity A, B and C all at NMT 2.0% and total impurities at NMT 4.0%. The CHC notes that Rutin is extracted from the buds and flowers of Sophora Japonica and any related compounds are most likely the result of extraction than as a result of manufacture and it is further notes that flavonoids are most likely present in the herbal starting material;
- There are a number of abbreviations missing from the end of the document that need to be included; and
- Some additional information that could be incorporated into the compositional guideline:
    - (M_r 665). *1075300.* [153-18-4]. Rutoside. 3-(*O*-6-Deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyloxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one.
    - Yellow, crystalline powder, darkening in light, very slightly soluble in water, soluble in about 400 parts of boiling water, slightly soluble in ethanol (96 per cent), soluble in solutions of the alkali hydroxides and in ammonia.
    - mp: about 210 °C, with decomposition.
    - *Absorbance* (*2.2.25*). A solution in *ethanol (96 per cent) R* shows two absorption maxima at 259 nm and 362 nm.
    - *Storage*: protected from light.

Hesperidin

The CHC provides the following comments specific to the draft compositional guideline for Hesperidin:

- No AAN is stated with the name of the ingredient;
- The CHC again points out that there is doubling up in testing with both 'Residue on Ignition' and 'Sulphated Ash' being listed. Members have advised that their limits for Sulphated Ash is NMT 0.4%;
- The CHC recommends the 'Loss of Drying' method be amended to 2 hours at 105^{o}C and with a specification of NMT 5.0%;
- In regards to related substances, the CHC recommends the limits be set at NMT 1.0% for individuals and NMT 2.0% for total impurities. Hesperidin is extracted from the Citrus Aurantium therefore it is expected that the 'impurities' in the Hesperidin would be the other flavonoids from the Citrus Aurantium. Based on this, the CHC questions whether there may need to be a reference to Synephrine instead of Quercetin for impurities with a NMT limit of 1.0%?; and
- Some additional information that could be incorporated into the compositional guideline:
    - (M_r 611). *1139000.* [520-26-3]. (*S*)-7-[[6-*O*-(6-Deoxy--α-L-mannopyranosyl)-β-D-glucopyranosyl] oxy]-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one.
    - Hygroscopic powder, slightly soluble in water and in methanol.
    - mp: 258 °C to 262 °C.

Noting that the compositional guidelines appear to be incomplete and of a very poor standard, the CHC suggests providing future drafts to the OICG (as previous process) before going out for broader consultation to assist in providing a high quality standard document for broad industry review.

If you would like to discuss any matters within this submission further, please feel free to contact me.

Yours sincerely

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Scientific & Technical Manager

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