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Addendum to Submission to the TGA Consultation on the draft evidence guidelines for Listed Medicines.

1st April 2022

Complementary and OTC Medicines Branch
Therapeutic Goods Administration
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Dear Complementary and OTC Medicines Branch,

In addition to the submission made yesterday 31st March 2022, we wish to provide an addendum with reference to Section 3.1.2.1. The proposed guidance states "When the medicine contains a herb or herbal substance... The method of preparation and processing … of active component described in the evidence source should also be comparable to that in the medicine."

Per our previous submission, a lack of clarity exists with regards to establishing comparability, and we therefore recommended that a rational guidance in this area be developed.

The following table reflects a proposed **draft** matrix which may be used by sponsors to establish comparability, which we believe is rational, user-friendly and considerate of the intricacies of herbal medicine practice.

Scientific: "extract-specific"	**Scientific: "active component specific"**
Scientific research of a very specific extract; may be characterised by one or more of the following: • A defined quantitative and/or qualitative profile of a range of constituents (for example, a patented extract) • A standardised extract where one or more components is standardised to contain particular quantity of component efficacy and/or quality marker(s). • An extract that is defined by very specific manufacturing and extraction techniques, including the use of the proprietary extract defined as the test material in the evidence. Note: For the above, any unspecified components are generally accepted to have natural plant variation unless there is a **known reason** related to safety, quality or efficacy that a particular component must not vary (for example, an upper limit restriction on a component specified in the Poisons Standard / 26BB Ingredients Determination, or specification in a default standard or evidence sources). *Examples:* Any patented extract, *i.e.* Withania KSM, Longvida Curcumin, Meriva Curcumin, Chaste Tree Agnucaston, Chaste Tree ZE 440, Milk Thistle Silophos, Ginseng G115, Black Cohosh Ze450.	The action of the herb is supported by one or more specific active components whose therapeutic activity is characterised by scientific data. • Other components in the extract may vary in quantity provided there is no known safety or quality issue with the content of other components that would cause the extract to be unacceptable for use. *Examples:* - Extract containing specific amount of sennosides (or curcuminoids, etc) based on therapeutic evidence profiling known action of sennosides (or curcuminoids, etc) - *Salix alba* extract containing salicin based on evidence supporting known actions of salicin at a specific dose; - Milk Thistle extract containing flavanolignans; - St Johns wort extract containing hypericin and/or hyperforin; - Panax Ginseng extract containing ginsenosides.

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Scientific: "preparation-flexible" (usually for non-specific indications)

Extract aligns with the scientific herbal monograph or evidence based text, extract and dose requirements:

- ESCOP, Expanded Commission E, Health Canada, WHO, Globinmed scientific herbal monographs don't always specify a standardised extract, or specific extraction requirements but plausibly support an effect of herb and its extracts.

This type of evidence could be used for non-specific, scientific herbal claims evidence.

Examples:
Health Canada Panax ginseng monograph; non standardised extract, 0.5 - 9 grams dried root/rootlets, per day. Helps support cognition.

Traditional: "preparation-specific"

- An ingredient with a preparation based on a specific, narrowly defined traditional preparation using solvent and extraction techniques relevant to the paradigm. Any minor processing into modern dosage forms are not expected to change the therapeutic quality or effect of the substance (such as drying into a powder and inclusion into a capsule for better stability, shelf-life, and convenience).

Examples:
- Kava water-based extracts or dried and encapsulated kava water-based extracts
- Certain dried, ground Ayurvedic herbs or dry TCM water extracts
- Extracts whose profile and/or activity is known to be dependent upon a traditional vinegar-based solvent rather than common traditional solvents.

Traditional: "traditional-formula-specific"

- Medicine's active ingredients based on a known traditional formula, and any changes are justified as part of the evidence package (for example, replacement of a herb with one with an equivalent action).

Examples:
- TCM formulations which may be exact or have some modifications.
- Commission E Approved Fixed Combinations.

Traditional: "preparation-flexible"

- Use is consistent with the ingredient within the paradigm
- Type of preparation (solvent, herbal quantity) is consistent with the range of recognised preparation types for that ingredient within that paradigm.
- Any minor processing into modern dosage forms that are not expected to change the therapeutic quality or effect of the substance (such as drying into a powder and inclusion into a capsule for better stability, shelf-life, and convenience).

Examples:
Herb that is validly used in a variety of preparations and extractions in traditional use including powdered root, water-based extracts (infusions, decoctions), a variety of ethanol-

Traditional: "altered/modern ingredient preparations"

- Modern preparations and formulations have therapeutic properties that may also draw on the known properties of the ingredient based on its tradition of use. Where there is processing or changes to the profile of a traditional extract, this requires increasing scientific evidence or justification depending on the nature of the change.

Examples:
- Milk thistle, Ginseng, any extract with a cross-base of evidence from scientific (75 years used) and traditional. Some TCM herbs/preparations
- Ayurvedic herbs with ground herb references if they now extracted in ethanol-water.

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water based extracts, etc. Herbs per EMA monographs, BHP, WHO, British Pharmacopeia etc.	

This matrix was originally prepared by the CMA with input from industry (ourselves included).

We are hopeful that this is of use in consideration of the draft evidence guidelines.

Thank you for your consideration.

Best Regards,

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