



Consultation Paper:

Regulation of Herbal Substances in a joint Australia New Zealand therapeutic products agency

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Consultation Paper: Core issues

1. Definition of 'herbal substance'
2. Naming of herbal-derived substances that do not meet the definition of a 'herbal substance'
3. Regulation of complex and non-traditional herbal extracts
4. Expression of dry/fresh weight equivalence
5. Extracts
 - a. variation in solvent concentration
 - b. extraction and concentration ratios
 - c. variation in concentration ratio
 - d. dosages of herbal medicines, and
6. Standardisation of herbal ingredients



Herbal Regulation

- **Currently in Australia to be eligible for inclusion in a Listed medicine (Class 1) a herbal ingredient:**
 - must meet the definition of a ‘herbal substance’ as defined in the Therapeutic Goods Regulations 1990;
 - must not be subject to the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP); and
 - must not be subject to that part of the Regulations (Schedule 4, Part 4) that identifies hazardous herbal substances.



Current definition of a herbal substance

Regulation 2, Interpretation, states:

“**herbal substance**” means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

- (a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and
- (b) that is not subjected to any other treatment or process other than a treatment that is necessary for its presentation in pharmaceutical form.



Current definition of a herbal substance

The definition:

- **excludes methods of preparation such crystallisation, precipitation, chromatography and fermentation; and**
- **allows the use of solvents and extraction processes that may change phytochemical, safety and efficacy profiles from that of traditional preparations.**



Proposed definition of a herbal substance

herbal substance, means:

- a) a traditional preparation of a herbal material:**
- i. obtained by the methods traditionally used to prepare that herb for therapeutic application; **or**

For example:

drying, crushing, comminuting, cooking (charring, baking or frying), steeping in wine and frying in vinegar, honey, oil, or other herbal substances, fermentation, or other processes identified and justified by the sponsor as being used traditionally to prepare the herbal material.



Proposed herbal substance definition (contd)

- a. a traditional preparation of a herbal material (contd)**
 - ii. obtained by a traditional extraction method such as infusion, decocting, maceroexpression, percolation, expression or distillation.

- b. a non-traditional preparation of herbal material:**
 - i. not involving a chemical transformation process; and
 - ii. justified as **phytochemically equivalent** to a preparation of a herbal material currently included as an active ingredient in a product Listed in the ARTG (essentially, a Class 1 product license in the joint agency).



Proposed herbal substance definition contd

- **Phytochemical equivalence**
 - For the purposes of the Consultation Paper, is taken to mean that the herbal substance has a component profile ‘equivalent to’ or ‘not significantly different from’ that obtained traditionally and on which its safety was originally based.
 - Appropriate guidelines to establish ‘phytochemical equivalence’ will be developed in consultation with industry.



3. Regulating complex and non-traditional herbal preparations

- New methods of preparation of herbs traditionally accepted as low risk, have highlighted the need for criteria for determining which herbal preparations can still be regarded to be low risk (and eligible for inclusion in Class 1 medicines) and those which are not?
- On the continuum between herb and a single chemical derived from the herb, where is a preparation so changed from the original material, that it should be evaluated as a new substance by the joint Agency?



Herbal preparations and eligibility for inclusion in Class 1 medicines

PREPARATION	OUTCOME
Traditional preparation <ul style="list-style-type: none"> - Herbal material (1) - Traditional extraction 	Eligible for inclusion in Class 1 medicines
Non-traditional preparation <ul style="list-style-type: none"> - Involves chemical transformation 	Requires evaluation (2)
Non-traditional preparation <ul style="list-style-type: none"> - Where phytochemical equivalence to traditional preparation is demonstrated. - Where phytochemical equivalence is not demonstrated 	Eligible for inclusion in Class 1 medicines Requires evaluation (2)

1. Already supplied in approved low risk products.
2. Either a safety evaluation of the *substance* for eligibility to be included in a Class I medicine, or Class II evaluation of the *product* containing the substance.



2. Naming 'non-herbal' substances

- Ingredients derived from herbs may range on a continuum from herbal material to a single chemical entity.
- Ingredients meeting the definition of a herbal substance are named as a derivative of the herbal material. For example, *Ginkgo biloba* extract.

How should ingredients be named that are considered to be so different from the original herbal material, that naming or describing them as a 'herbal preparation' would be misleading?



Regulation of herbal extracts

4. Expression of dry/fresh weight equivalence
5. Equivalence of extracts
 - a. Variation in solvent concentration
 - b. Extraction and concentration ratios
 - c. Variation in concentration ratio
 - d. Dosage



Regulation of herbal extracts: naming

- All ingredients entered into the joint Agency therapeutic products database will be expressed using approved names.
 - Most herbal substances require the approved botanical name (eg. *Hypericum perforatum*), the plant part name (eg. herb flowering), and the plant preparation name (eg. extract).
- Where a dry, fresh or powdered herb has been further processed, the expression must also include solvent and extraction details (where relevant) and the equivalent **dry** or **fresh** weight of the original herbal material used.



4. Expression of dry/fresh weight equivalence

- Concern has been raised about consumer perception of the words “*equivalent to*” on the label of herbal medicines.
 - Consumers may interpret the term to mean the preparation is equivalent in therapeutic effect or composition to the stated quantity of the herb.
 - The use of both dry and fresh weight equivalence may make it difficult for consumers to compare products
 - the international trend appears to be towards the use of dry weight equivalent statements for expressing and quantifying herbal preparations that are not standardised.



4. Expression of dry/fresh weight equivalence

Comment is sought on:

- the appropriateness of the term ‘equivalent to’ on label of medicines containing herbal preparations; and
- the proposal that herbal ingredients be expressed as the dried weight equivalent of the herb used (other than for products sold in the form of the fresh juice or as fresh plant tinctures).



5. Equivalence of extracts

- Some areas of industry have expressed the need to allow for variations in:
 - concentration (extraction) ratio, and
 - solvent concentration, for herbal extracts

without the resulting preparations being considered separate and distinct therapeutic goods.

If variation is considered appropriate, what are acceptable ranges?



5. (a) Variation in solvent concentration

- It is considered unlikely that the component profile of a herbal extract will be significantly changed if the concentration of solvents in a solvent mix, varied by no more than $\pm 50\%$ of the nominated value of the minor solvent.
 - eg. if the solvent mix is 40% ethanol / 60% water, the ethanol percentage could vary from 20% to 60% (the water component would then range from 40% to 80%) with little expected change in the profile of components.



**Proposed acceptable
 variation in solvent
 concentration (± 50%)**

Solvent concentration	Acceptable solvent range
1%	0.5-1.5%
5%	2.5 – 7.5%
7.5%	3.75 – 11.25%
10%	5 – 15%
15%	7.5 – 22.5%
20%	10 – 30%
30%	15 – 45%
40%	20 – 60%
50%	25 – 75%
60%	40 – 80%
70%	55 – 85%
80%	70 – 90%
85%	77.5 – 92.5%
92.5%	88.75 – 96.25%
90%	85 – 95%
95%	92.5 – 97.5%
99%	98.5-99.5%



5. (b) Extraction vs concentration ratio

- The use of the term ‘extraction ratio’ in a regulatory context, appears to be interpreted in different ways. Some sponsors include a diluent or carrier in the expression.

It is proposed that *Concentration Ratio* be the ratio of the weight of herbal material in the extract, to the weight of dried material used to make the extract (sometimes called ‘native extraction ratio’ or ‘native extract’ ratio).

- The diluent or carrier content in a given amount of extract would be expressed as an excipient.



5. (c) Variation in concentration ratio

- Provided the equivalent dry weight remains the same for each batch of a particular product, some degree of variation in concentration ratio (ie. quantity of extract used) may be acceptable.

It is proposed that, providing the dried weight equivalent of the original herbal material remains constant, the quantity of extract used in a formulation be permitted to vary, if necessary, up to +/- 20% (about a mean weight).



Effect of variation in concentration ratio or dry weight equivalent

Variation permitted	Conc. ratio	Extract amount	Equivalent dry weight (edw) of herb
+/- 20% of concentration ratio	10:1 (8:1 – 12:1)	1mg (extract same) 0.8 - 1.2mg	8 - 12mg (range 4mg) 10mg (edw same)
	10:1 (8:1- 12:1)	200mg (extract same) 160mg - 240mg	1.6g – 2.4g (range 800mg) 2g (edw remains same)
	10:1 (8:1 – 12:1)	500mg (extract same) 400mg - 600mg	4.0g – 6.0g (range 2g) 5g (edw remains same)
	50:1 (40:1 – 60:1)	10mg (extract same) 8mg - 12mg	400mg – 600mg (range 200mg) 500mg (edw same)
	50:1 (40:1 – 60:1)	300mg (extract same) 240mg – 360mg	12g - 18g (range 6g) 15g (edw remains same)



5. (d) Dosage

- Although some preparations may concentrate herbal components by a large factor, if the amount of extract used in the final preparation is appropriately reduced, the dosage of those components should be comparable to that received in a product containing a more traditional preparation.

Where highly concentrated preparations are used, can safety (and effectiveness) be assured if the dose is based on the traditional preparation?



6. Standardisation of herbal ingredients

- For a given herbal preparation, the lack of a definitive meaning for the term standardisation has led to an variety of ‘standardised’ ingredients in the market place.
 - For example, different sponsors may use different substances as a marker of ‘potency’ for the same herbal ingredient, and may quantify them using different analytical methodologies.
- Differences in analytical methods and/or the use of different marker components, may result in inconsistency and make comparisons between products confusing and meaningless.



6. Standardisation of herbal ingredients

Comment is sought on the need for and proposed definition:

Standardised herbal ingredients are ingredients that are adjusted within an acceptable tolerance of a given content of a recognised therapeutically active component(s) or a recognised quality marker(s).

- A claim for standardisation may be made for a herbal ingredient where:
 - a validated analytical method for the ingredient or a component in the ingredient is included in a joint agency-recognised monograph;
or
 - endorsed by a joint agency evaluation process.



Conclusion

- This consultation paper provides an opportunity for all stakeholders to have input into the development of appropriate regulation for herbal substances under the joint Agency.
- We welcome responses to the issues proposed in the Consultation Paper, and any other matters related to the development of appropriate regulation for herbal substances.