Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

CONSULTATION PAPER

REGULATION OF HERBAL SUBSTANCES IN A JOINT AUSTRALIA NEW ZEALAND THERAPEUTIC PRODUCTS AGENCY

CALL FOR COMMENT

December 2004

CONTENTS

INTRODUCTION

This consultation paper outlines how herbal substances are currently regulated in Australia and New Zealand, and examines problems that have emerged under the existing regulations. A key aim of this paper is to seek comments on the mechanisms proposed to address these problems and the impact such changes may have on stakeholders.

The Australian and New Zealand Governments have agreed to harmonise the regulatory arrangements for therapeutic goods between both countries. Under the new joint Australia New Zealand therapeutic products agency (the Agency), complementary medicines will be regulated as medicines. This includes herbal substances and medicinal products containing herbal substances.

All medicines will be regulated by the joint Agency using a risk-based approach. This means that the level of control applied is consistent with the risk associated with the product. Medicines will be classified as either Class I or Class II medicines. The class will determine the level of regulatory control applied and the manner in which product licenses are obtained.

Class I medicines must:

- contain only ingredients from a published list of permitted ingredients;
- not contain scheduled medicines;
- not be required to be sterile; and
- not be intended to be used in the prevention or treatment of a serious disease.

Product license applications for Class 1 medicines will not be evaluated by the joint Agency prior to a product license being issued.

Class II medicines are higher risk medicines for which a product license can only be granted following evaluation by the joint Agency for safety, quality and efficacy of the medicine. However, within this class there is a continuum of risk and the product licensing process and data requirements applying to a Class II complementary medicine will be commensurate with the risks associated with the medicine.

This consultation paper outlines a number of core issues that have been identified with the regulation of herbal substances, and products containing herbal substances, and poses a number of questions in relation to these issues.

The TGA and Medsafe encourage stakeholders to give consideration to the issues raised in this paper, as responses will be used to inform the development of a risk-based regulatory framework for herbal substances, and medicines containing herbal substances. Stakeholders are also invited to provide any other comment that will assist in the development of appropriate regulatory arrangements for these medicines.

In finalising the regulatory arrangements for herbal substances, and products containing herbal substances, the joint Agency is mindful of the need to minimise the regulatory impact on the complementary medicines industry in Australia and New Zealand, while delivering an assurance that herbal medicines will meet appropriate standards of quality, safety and efficacy.

To provide context for the Consultation Paper, the current regulatory frameworks for medicines in Australia and New Zealand, and the current regulatory requirements for herbal ingredients, are described in Appendix 1.

HOW TO COMMENT ON THIS CONSULTATION PAPER

Submissions may be sent by post and/or email and, where possible, should be structured to address the specific questions posed in the consultation paper. In addition, stakeholders are encouraged to provide any other comments that will assist in the development of appropriate regulatory arrangements for herbal substances.

Submissions should, where possible, contain relevant evidence, and/or examples, to support the views expressed.

The Australian Self-Medication Industry (ASMI), the Complementary Healthcare Council of Australia (CHC), and the New Zealand Self-Medication Industry (NZSMI), have agreed to distribute the Consultation Paper: *Regulation of Herbal Substances in a Joint Australia New Zealand Therapeutic Products Agency,* and to coordinate responses on behalf of their members in Australia and New Zealand. Members of ASMI, CHC and NZSMI are therefore invited to provide written comment to their respective organisations.

Other stakeholders are invited to provide written comment on the Consultation Paper: *Regulation of Herbal Substances in a Joint Australia New Zealand Therapeutic Products Agency* directly to the postal and/or email address below.

Contents of submissions

It would be helpful if your submission included:

- your name and full contact details, including: address, telephone number and, if applicable, facsimile and email address
- the particular issue being addressed (eg. Issue 5 a. – Variation in solvent concentration)
- information and data concerning the impact of proposed changes on affected parties
- in the case of organisations, the level at which the submission was authorised.

In addition, submissions might:

- include any other relevant information eg. scientific and technical, economic, international obligations, business and consumer information
- identify and discuss any perceived omissions or alternative approaches, in addition to those already included in the consultation paper.

Confidentiality of submissions

If you wish any information contained in a submission to be treated as confidential, please clearly identify the information and outline the reasons why it is confidential.

Address for submissions

Electronic submissions should be emailed to

comp.medicines@jtaproject.com

Hard copy submissions should be addressed to

The Project Officer
Regulation Review Project
c/- Joint Agency Establishment Group
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606
AUSTRALIA

Questions relating to submissions

Any questions relating to submissions should be directed to the Project Officer, by email, at:

comp.medicines@jtaproject.com

Deadline for submissions

The deadline for receipt of submissions is **close of business, Friday 11 March 2005.**

ISSUES TO BE CONSIDERED

In considering appropriate regulation for herbal substances, and medicines containing herbal substances, in the joint Australia New Zealand therapeutics products agency (the joint Agency), it is essential that the matters of definition, quality, safety and efficacy be addressed. To provide context for these matters, the current regulatory requirements in Australia and New Zealand are described in Appendix 1.

The questions outlined below are not intended to be limiting, but rather a guide to the matters to be considered in the development of an appropriate system for the regulation of herbal medicines. Please indicate the source of any information/facts you provide in response to these questions, proposed changes, and any other points that are raised in your response (see page 4 HOW TO COMMENT ON THIS CONSULTATION PAPER).

The following core issues are considered in this consultation paper:

1. Definition of 'herbal substance'
2. Naming of herbal-derived substances which do not meet the definition of a 'herbal substance' (for the purposes of inclusion in Class 1 medicines in the joint Agency Register)
3. Regulation of complex and non-traditional herbal extracts
4. Expression of dry/fresh weight equivalence
5. Equivalence of extracts
    a. variation in solvent concentration
    b. variation in concentration ratio
    c. dosages of herbal medicines, and
6. Standardisation of herbal ingredients.

Note that it is not necessary to respond all issues and questions. However, it may help inform your response if you are aware of the issues raised in other questions.

1. The definition of a 'herbal substance'

The fundamental purpose for defining 'herbal substance' preparations in the *Therapeutic Goods Regulations 1990* (the Regulations) in Australia, was to identify those low risk herbal ingredients, prepared according to traditional herbal medicine, and/or established pharmaceutical practice, which could be included in Listed (low risk) medicines. The definition was intended to cover the more usual forms of traditional herbal preparations such as fresh and dry herbs, essential oils, tinctures, decoctions, infusions and simple extracts.

The rationale for this was that where there has been a history of traditional use, or use in established pharmaceutical practice, herbal medicines prepared and prescribed according to that tradition are likely to be of low risk to the public. Thus, where many practitioners have, over a long period of time, observed the therapeutic and adverse effects of using a herb, then the indications, preparation, dosage and formulation have been adapted to maximise the therapeutic effectiveness and minimise the risk.

It must be remembered that in this legislative or regulatory context, the definition of a herbal substance relates directly to Schedule 4 of the Regulations.

That is, the purpose of the definition is, effectively, to define the types of herbal substances that are eligible to be included in low-risk (Listed) medicines (see details in Appendix 2 - Schedule 4, Part 1, Item 3, of the Regulations).

Currently, as defined in Regulation 2, Interpretation:

> "**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.

The above definition of a herbal substance:

- excludes preparation methods involving fermentation and/or obtaining selected components through chemical reactions and precipitation;
- can include complex multi-step extraction processes using a wide range of solvents, provided that these are, in most cases, removed (water, ethanol, glycerol and permitted solvent residues may remain).

Proposed change to the definition of a 'herbal substance'

If adopted into the new joint regulatory scheme, the current definition of 'herbal substance', as described above, could exclude some traditional low risk preparations, such as traditional Chinese medicines prepared by steeping in wine and/or frying in vinegar or honey. It may also permit in low risk (Class I) products, some highly processed extracts whose component profiles may be significantly different from the original herbal material from which they were derived, to the point where (at least theoretically) they could be considered to be isolated chemical entities. It may not be appropriate to base the safety profile of these isolated or altered substances, on that of the traditional preparation of the herb on which safety was originally established.

The *British Pharmacopoeia* (BP) is an official standard, for regulatory purposes, in Australia. The current edition of the BP includes monographs describing 'herbal drugs' and 'herbal drug preparations'. However, the definitions included in these monographs are not sufficient to adequately define those herbal substances considered eligible to be included in Class I (low risk) medicines.

Using the BP definitions as a basis, possible definitions for 'herbal materials', 'herbal preparations' and 'herbal substance', are as follows:

> "**herbal materials** are mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, and lichen in an unprocessed state, usually in the dried form but sometimes fresh.
>
> Certain exudates that have not been subjected to a specific treatment are also considered to be herbal materials. Herbal materials are precisely defined by the botanical scientific name according to the binomial system (genus, species, variety and authority)"

"**herbal preparations** are obtained by subjecting herbal materials to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal materials, tinctures, extracts, essential oils, fatty oils, expressed juices and processed exudates.

Extracts obtained from herbal materials should comply with the BP monograph on *Extracts.*

Tinctures obtained from herbal materials should comply with the BP monograph on *Tinctures*.

Herbal teas should comply with the BP monograph on *Herbal teas"*

To fully define those herbal materials and herbal preparations eligible for inclusion in Class I medicines in the joint Agency, the following wording to define 'herbal substance' is suggested:

herbal substance, for the purpose of inclusion in a Class I medicine, means:

*a) a **traditional** preparation of a crude herbal material:*

i) obtained by the methods traditionally used to prepare that herb for therapeutic application, for example: drying, crushing, comminuting, cooking (charring, baking or frying), steeping in wine and frying in vinegar, honey, oil, or other herbal substances, traditional fermentation, or other processes identified and justified by the sponsor as being used traditionally to prepare crude herbal material; or

ii) obtained by a traditional extraction method such as infusion, decoction, maceroexpression, percolation, expression or distillation.

*b) a **non-traditional** preparation of crude herbal material:*

i) not obtained using a chemical transformation process; and

ii) justified as phytochemically equivalent* to a preparation of a crude herbal material currently included as an active ingredient in a product Listed in the ARTG

*The phytochemical equivalence of herbal preparations may be determined in a number of ways, and guidelines will be needed to assist stakeholders in making this determination.

Substances initially derived from herbs that do not meet the above criteria, may also be eligible to be included in Class I medicines following further evaluation via the joint Agency's expert complementary medicines evaluation committee, as is currently the case with the TGA's Complementary Medicines Evaluation Committee (CMEC). Following acceptance by the joint Agency, such substances would be permitted in Class I (low risk) medicines.

Stakeholder input

1.1 For regulatory purposes, how should a herbal substance be defined?

In suggesting a definition, consider whether there should be different definitions for different types of herbal substances (eg. traditional herbal substances, [modern] herbal derived substances). Please also consider issues such as consumer perception of herbal medicines, the impact of novel methods of preparation, synthesis of nature-identical compounds, etc.

1.2 Should traditional herbal preparations and novel preparations of herbs be differentiated on the basis of risk and hence, definition, for regulatory purposes?

If so, what factors should be considered? Do different levels of risk apply?

2. Naming of non-herbal substances

The issue of appropriate naming of substances initially derived from herbal materials, but which have been determined to be so different from the original material that naming or describing them as 'herbal substances or preparations' would be misleading, needs to be resolved.

It would appear reasonable that if an ingredient is determined not to be a 'herbal substance or preparation', the label should not represent that ingredient as a herbal substance. It may therefore be misleading to mention the plant species or plant part, or to represent the product to the consumer as a herbal product.

Stakeholder input

2.1 How should herbal derived substances that do not qualify as herbal substances, or herbal preparations, be named.

Consider the need for truth in labelling.

3. The regulation of complex and non-traditional herbal extracts

Increased access to novel preparations of herbs traditionally accepted as low risk, has highlighted the need for a mechanism for determining which herbal preparations may be regarded to be inherently low risk, and therefore eligible for inclusion in Class 1 medicines in the joint Agency.

There has been significant development and innovation in the herbal industry in recent years. As a consequence, the types of herbal ingredients available are becoming increasingly more complex and sophisticated. Technological development does not mean that some of the novel preparations available today are inherently unsafe. Many novel preparations have undergone significant research to establish quality, safety and efficacy. However, the provision of new and exciting herbal preparations must be supported by appropriate evidence for their quality, safety (particularly in the case of Class 1 medicines) and efficacy, and which has not been inappropriately 'borrowed' from evidence supporting other (sometimes significantly different) herbal preparations. Assurance of safety cannot be based solely on the fact that these substances were originally sourced from herbal material, as they may be very different in chemical (and therefore safety) profile.

What needs to be determined is, where, on the continuum between the raw herb and a single chemical derived from the herb, a preparation is so changed from the original material that it should be evaluated as a new substance by the joint Agency before its suitability for use in Class 1 medicines is decided.

In Australia, the Complementary Medicines Evaluation Committee (CMEC) has made a number of recommendations aimed at differentiating those herbal substances for which low risk status is recognised, from those herbal-derived substances for which further evaluation may be required (even if they have been derived from herbs that are permitted for use in low risk [Class I] medicines).

In considering this issue, CMEC recommended that non-traditional chemical transformation methods that alter the original herbal material (such as enzymatic processes, acid/base hydrolysis, saponification of lipids, fermentation and oxidation/reduction reactions), should be subject to pre-market evaluation.

However, it was noted that some herbs are traditionally processed with techniques which result in chemical transformation(s) (eg. fermentation of *Camellia sinensis* to black tea). These traditional preparations have been available in this form for a considerable period of time, with established safety.

More recently, precipitation of hydroxy-citric acid in the preparation of *Garcinia* species is also known, and regulators have received a number of enquiries relating to 'herbal' preparations that have been subjected to precipitation, enzymatic processes, or saponification steps. This highlights the desire of some sponsors/manufacturers to include these types of ingredients in low risk (Class I) products. Such non-traditional preparations are currently not eligible for inclusion in Listed therapeutic goods in Australia without further evaluation. However, as noted above, some chemical transformation techniques are used in the traditional preparation of some herbal materials, and it seems appropriate that this should be taken into consideration when determining eligibility for inclusion in Class I medicines.

The following table outlines a simple representation of a proposed system for the regulation of herbal substances. Phytochemical equivalence, for the purposes of this system, is taken to be where the final substance has a component profile 'equivalent' to the traditional preparation(s) on which the safety of the herbal substance was originally based.

Table 1: Simple representation of the Class I eligibility of herbal substances

MANUFACTURING PROCESS	OUTCOME
Traditional preparation - Crude herbal material[1] - Traditional extraction	Eligible for inclusion in Class I medicines
Non-traditional preparation - Chemical transformation	Requires evaluation[2]
Non-traditional preparation - Specific separation where phytochemical equivalence is demonstrated - Specific separation where phytochemical equivalence is **not** demonstrated	Eligible for inclusion in Class I 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.

Stakeholder input

3.1 The regulation of medicines is based on a framework of risk management. What are the essential elements that, for regulatory purposes, should be used to control the health risks associated with the use of herbal substances.

Consider factors such as dosage, history of use, degree and type of processing, similarity to herbal substances of established safety, suitability for self-administration, information required by consumers to use the herbal substance safely and appropriately.

3.2 Where, on the continuum between raw herb and purified component, is it no longer appropriate to refer to the substance as 'herbal'?

Consider factors such as preparation methods that transform the original herbal substance, specific selection/purification techniques, use of synthetic nature-identical compounds, etc.

3.3 For regulatory purposes, what factors should be considered in determining if a herbal substance is different from another similar one?

Consider factors such as differences in species, plant parts, preparation methods, solvents, and degrees of dilution or concentration.

4. Expression of dry/fresh weight equivalence

All ingredients entered into the joint Agency therapeutic products database will need to be expressed using approved names. In the case of herbal substances, most ingredients will require three parts to the approved name – the botanical name (eg. *Hypericum perforatum*), the plant part name (eg. herb flowering), and the plant preparation name (eg. dry, or oil infused).

Where a dry, fresh or powdered herb has been further processed, sponsors in Australia are currently required to include, in the expression, solvent and extraction details (where relevant), and the equivalent dry or fresh weight of the original herbal material used.

For example, an extract made from dried flowering *Hypericum perforatum* might be expressed as follows:

"*Hypericum perforatum* herb fl. ext. dry conc. (10:1 in 70% E:W)	x mg
Equiv. *Hypericum perforatum* herb fl. dry	y mg"

Two main issues in relation to the expression of dry/fresh weight equivalence have been identified:

1. Concern has been raised with regulators about consumer perception of the words "equivalent to" on the labels of herbal medicines. Although the term is meant to refer to the quantity of the herb from which the preparation was derived, the concern is that it may have the potential to mislead the consumer into assuming that it refers to equivalence of therapeutic effect or benefit of the original herb.

This concern is augmented by the fact that an extract, in most cases, does not include all the components of the original herb. In this context, the extract can never be equivalent to the whole or dried herb and consideration needs to be given as to whether an extract should be represented to consumers as such.

2. To date, sponsors in Australia have been given the option of expressing either the dry or fresh weight equivalent, to allow for those preparations that have been processed from fresh plant material. Sponsors are also permitted to include additional equivalence statements in ARTG applications and on labels, providing the essential details of the AAN are expressed first.

   For example, preparations of dry plant juice are not required to include an equivalent dry/fresh weight statement, however some sponsors may choose to do so, and this has been permitted providing the statement is truthful.

In addition to the possible consumer misunderstanding associated with dry/fresh weight equivalence statements for herbal substances, a related problem arises where labels include expressions of fresh weight equivalence for the herb, and then base the name of the product on this amount. For example, a garlic tablet which contains the expression *"5000 mg"* in the product name. The ingredient panel states that the ingredient is *"*Allium sativum *(garlic) extract equiv. fresh bulb 5g (5000 mg)"*. This situation may make it difficult for the consumer to compare products, as they may not be aware that, due to water content, a given amount of fresh herb will contain the same amount of components usually found in a much lesser amount of dried herb.

The international trend appears to be moving towards the use of dry weight equivalent statements when expressing and quantifying herbal ingredients that are not standardised, or which do not have established active components. This approach may allow much greater comparability between products, given that consumers are generally only made aware of the equivalent dry or fresh weight of any given herbal ingredient.

However, the above approach may be more difficult for sponsors who use preparations derived directly from fresh plant material. Whilst it is possible for manufacturers to determine water content of given batches of plant material, and extrapolate this information into the expression of the herbal substance in an application, this is an additional expense that must be taken into consideration. There are also supporters of true fresh plant tinctures; however, these preparations are not widely encountered commercially due to their comparatively short shelf life.

It is proposed that herbal ingredients be expressed as the **dried** weight equivalent of the plant material used, other than for products sold in the form of the fresh juice or as fresh plant tinctures. The joint Agency project team is interested in learning of examples of where such expressions may be inappropriate - please indicate how such preparations are manufactured and provide suggestions as to how they should be expressed.

Stakeholder input

4.1 How should herbal ingredients be expressed on the label?

Consider the needs of consumers for meaningful information.

4.2 How should herbal substances be quantified?

Consider factors such as quantitative expression (particularly of extracts), carriers and diluents in extracts, etc.

4.3 Please comment on the appropriateness of the use of the term 'equivalent to' on label of herbal medicines, and on the proposal that herbal ingredients be expressed as the dried weight equivalent of the plant material used, other than for products sold in the form of the fresh juice or as fresh plant tinctures.

The joint Agency project team is also interested in learning of examples of where such expressions may be inappropriate and whether consumers are likely to benefit from the introduction of the term dry weight equivalent.

5. Equivalence of extracts

Some areas of industry have previously expressed to regulators, the need to allow for certain variations in the concentration (extraction) ratio, and solvent concentration, for herbal extracts, without the resulting herbal preparations being considered separate and distinct therapeutic goods. Under a joint regulatory scheme, it is proposed that therapeutic goods will be considered 'separate and distinct' if they have:

- a different **formulation, composition** or design specification; or
- a different **strength** or size (disregarding pack size); or
- a different dosage form or model; or
- a different name; or
- different indications; or
- different directions for use; or
- a different type of container (disregarding container size).

It appears that some sponsors/manufacturers choose, at times, to accept extracts with different extraction profiles, due to fluctuations in price and availability. Given that different solvent concentrations and extraction steps can result in very different end substances, the question arises as to what variation could be permitted between slightly differing extracts of the same herbal substance, so that the stated (safe) ingredient is still adequately represented. If variation is considered appropriate, what are acceptable ranges in extraction ratio and solvent concentration?

a. Variation in solvent concentration

In the preparation of herbal extracts, different solvent mixes may be used. The CMEC has previously considered that, for extracts where the solvents are removed prior to completion of the manufacture of the ingredient, some degree of variation in the concentration of the solvents used to prepare the herbal extract, could be permitted. It is 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 ± 50% of the nominated value of the minor solvent. It is therefore proposed that a reasonable permitted variation in solvent concentration that will maintain the herbal ingredient profile is +/- 50% of the nominated concentration of the minor solvent in the solvent mixture. For example, 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 expected. Table 2 details proposed acceptable variations in solvent concentration.

Table 2: Proposed acceptable variation in solvent concentration

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%

Stakeholder input

5.1 Please comment on the proposed variation in solvent concentration permitted in the preparation of extracts.

b. 'Extraction ratio' vs 'concentration ratio'

The use of the term 'extraction ratio' in a regulatory context, appears to be interpreted in a variety of ways by different sponsors. To some, the term is taken to mean the ratio of the amount of herbal material used, to the amount of solvent used to extract it. This definition applies to the description of herbal tinctures (eg. 1kg herb extracted in 2 litres of alcohol would be termed a 1:2 tincture). For others, 'extraction ratio' has come to mean the ratio of the amount of herbal material originally used, to a given amount of extract.

However, in some instances, the amount of extract used may include a significant proportion of diluent or carrier. In such cases, the extraction ratio may not truly reflect the composition of the herbal material in the extract.

For example, 1kg of herb may be used to manufacture 100 grams of extract. This gives a ratio of 10:1 – 10 parts of herb to one part of extract. However, if 10g of herbal material was extracted from 1kg of herb (a ratio of 100:1), and this extract was then diluted with 9 parts of diluent, this would result in a final ratio of herbal material used to make a given amount of extract of 10:1. Ten parts of herb would be represented in one part of extract, but in this case the 'extract' contains an inactive portion. The chemical composition of the 10:1 extract would be significantly different to that of the 100:1 extract and yet a sponsor, for regulatory purposes, may currently represent them as the same extract.

To avoid confusion, it is proposed that the term 'extraction ratio' be changed to 'concentration ratio' with respect to the expression of herbal extracts. Concentration ratio should be taken to mean 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). This negates the diluent or carrier content in a given amount of extract, as this portion could be expressed as an excipient.

For example, the concentration ratio of the above herbal extract, (which contains 9 parts of diluent to 1 part of a 100:1 extract), would be expressed as a concentration ratio of 100:1 (which will more accurately reflect the component profile extracted from the herb).

Stakeholder input

5.2 Please comment on the need for a definition to unambiguously describe the amount of herbal material in an extract.

5.3 Please comment on the suitability of the term 'concentration ratio' and its definition to unambiguously describe the amount of herbal material in an extract.

c. Variation in concentration ratio

In some instances, variation in the equivalent dry weight of a herb used in a medicine can affect truth in labelling, as well as impacting on the recommended dose of the product. In Australia, the CMEC has considered this issue and recommended that, provided the equivalent dry weight remained the same for each batch of a particular product, some degree of variation in concentration ratio (ie. quantity of extract used) would 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). Table 3 (page 16) illustrates the effect a change in dry weight equivalence might have on the amount of extract.

Stakeholder input

5.4 Please comment on the proposal 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 +/- 20% (about a mean weight).

Table 3: Effect of variation in concentration ratio or dry weight equivalent

Variation permitted	Conc. ratio	Extract amount	Equivalent dry weight (edw) of herb
+/- 10% of concentration ratio	10:1 (9:1 – 11:1)	1mg (extract same) 0.9 - 1.1mg	9 - 11mg (range 2mg) 10mg (edw same)
	10:1 (9:1- 11:1)	200mg (extract same) 180mg - 220mg	1.8g – 2.2g (range 400mg) 2g (edw remains same)
	10:1 (9:1 – 11:1)	500mg (extract same) 450mg - 550mg	4.5g – 5.5g (range 1g) 5g (edw remains same)
	50:1 (45:1 – 55:1)	10mg (extract same) 9mg - 11mg	450mg – 550mg 500mg (edw same)
	50:1 (45:1 – 55:1)	300mg (extract same) 270mg – 330mg	13.5g - 16.5g (range 3g) 15g (edw remains same)
+/- 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)
+/- 30% of concentration ratio	10:1 (7:1 – 13:1)	1mg (extract same) 0.7 - 1.3mg	7 - 13mg (range 6mg) 10mg (edw same)
	10:1 (7:1- 13:1)	200mg (extract same) 140mg - 260mg	1.4g – 2.6g (range 1.2g) 2g (edw remains same)
	10:1 (7:1 – 13:1)	500mg (extract same) 350mg - 650mg	3.5g – 6.5g (range 3g) 5g (edw remains same)
	50:1 (35:1 – 65:1)	10mg (extract same) 7mg - 13mg	350mg – 650mg (range 300mg) 500mg (edw same)
	50:1 (35:1 – 65:1)	300mg (extract same) 210mg – 390mg	10.5g - 19.5g (range 9g) 15g (edw remains same)

d. Dosage

Dosage of herbal ingredients is an integral factor in the ultimate safety and efficacy of a herbal medicine. Where the herb is present in its raw form, or as a crude preparation, there are usually physical limits to the amount of the product an individual may ingest. However, with the advent of novel herbal extracts, there is increasing opportunity for the dose of particular herbal components to far exceed what individuals might receive in the traditional preparations on which the safety of that herb was based.

The issue of dosage of complex, concentrated, or novel herbal extracts, has been raised in a number of submissions received by the TGA in response to a previous Discussion Paper - *Identifying Low Risk Herbal Ingredients*. Submissions emphasised that the strength of the dose in the final product, as much as the extract itself, helps determine the product's final safety profile. The reasoning is that although a particular extract may concentrate components by a large factor, if the amount of extract used in the final preparation is reduced, the dosage of those components could be comparable to that received in a product containing a more traditional preparation. Whilst this may well be the case, there is potential concern that products may provide much stronger doses than the doses on which the safety and efficacy data were originally based

Stakeholder input

5.5 Please provide comment on ways to ensure that, where the dose of a complex, concentrated or a novel extract is based on its traditional preparation, the recommended dose will be safe and effective***.***

6. Standardisation of herbal ingredients

Despite widespread use, there is currently no regulatory definition for the term 'standardisation'. The variety of meanings currently attributed to the term, in Australia, New Zealand, and internationally, and the numerous approaches to implementing what is referred to as 'standardisation', has resulted in a term which is confusing, and provides little meaningful information for consumers, industry and regulators alike.

Lack of a definition has led to an apparent wide variety of so called 'standardised' ingredients in the market place, for any given herbal extract. 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. Any difference in analytical methods, and/or the use of different marker or active components, may result in inconsistencies, confusion and meaningless comparisons between herbal extracts.

Why standardise herbal ingredients?

The composition profile of herbal material may be highly variable, and this may be due to a wide range of factors which are controllable to varying extents. These factors include:

- genetic variation;
- environmental factors, such as climate, soil type, altitude and other growing conditions;
- maturity and time of harvesting;
- part of the plant used;
- post harvest treatment and storage conditions; and
- processing treatments.

Factors such as the method and degree of processing undertaken, the amount, concentration and type of solvent used in processing, and the time, temperature and pressure used, are all factors that can be specified and controlled. However, the plant material itself remains the most variable (in terms of 'uncontrollability') with regard to the ultimate composition of a herbal ingredient.

Generally, a standardised herbal substance[3] is a herbal preparation (usually an extract) made to a consistent, specified, level of an identified component, or group of components. The primary aim of 'standardisation' is to assist in delivering a specified level of one or more phytochemicals derived from the original herbal starting material. This should ideally, in turn, reflect a consistent phytochemical profile of the other non-standardised components.

Standardisation may reflect either pharmacological activity and quality, or quality alone. In the former instance, the standardised component is linked to a clinical outcome (when supplied in an appropriate dose). In the latter case, a 'marker'[4] component is used for quality control purposes only.

Generally, four basic forms of standardisation appear to be recognised:

1. standardisation to one or more 'recognised'[5] active components;
2. standardisation to a marker component (compound), or group of components;
3. standardisation to a chromatographic fingerprint or profile; and
4. standardisation to biological activity.

Each of these forms of standardisation will help to deliver a herbal preparation with a more consistent phytochemical profile. This will, in turn, provide greater consistency in support of the safety of the preparation. These different forms of standardisation will also, to varying degrees, contribute to the efficacy of the preparation in that they allow for better quality control leading to more accurate dose determination and consistent clinical outcomes.

International situation

The American Herbal Products Association (AHPA) has revised their definition of the term standardisation:

> *"Standardisation refers to the body of information and controls necessary to produce material of reasonable consistency. This is achieved through minimising the inherent variation of natural product composition through quality assurance practices applied to agricultural and manufacturing processes."*

In the *British Pharmacopoeia (*BP), different types of extracts are described. Standardised extracts are defined as extracts that are adjusted within an acceptable tolerance to a given content of component with **known therapeutic activity**; standardisation is achieved by adjustment of the extract with inert material or by blending batches of extracts. Quantified extracts are defined as extracts that are adjusted to a **defined range of components**; adjustments are made by blending batches of extracts. Other extracts are essentially defined by their production process (state of the herbal drug or animal matter to be extracted, solvent, extraction conditions) and their specifications.

[3] In Australia, the preparation must first meet the current definition of a 'herbal substance' (see page 8).

[4] A 'marker' is a chemically defined component of a herbal substance which is of interest for control purposes, independent of whether it has therapeutic activity. A marker is generally selected because it is stable, easier to analyse for, and is characteristic or specific for the herbal ingredient.

[5] A 'recognised' active component, or group of components, is one that has been scientifically verified as providing the therapeutic activity that has been attributed to the herbal ingredient

The BP terminology would only permit preparations containing extracts that have scientifically validated active components to make a claim for 'standardisation'. Standardisation would always represent, in part, the pharmacological activity of the herbal preparation, rather than quality alone. This approach could be considered too restrictive given the current state of scientific knowledge of confirmed therapeutically active components in herbal substances.

In Australia, the CMEC has suggested that the term 'standardised' should refer primarily to the quantification of a particular component in an ingredient and could apply to a component(s) that is indicative of quality and/or efficacy. The CMEC proposed the following definition of standardisation:

> "*Standardisation refers to the manufacturing controls necessary to produce herbal ingredients of reasonable consistency. 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 (such as a monograph in the British Pharmacopoeia, United States Pharmacopoeia, WHO monographs on selected medicinal plants) or endorsed by a joint Agency evaluation process*."

The definition suggested by the CMEC allows flexibility for the components and analytical methods on which a 'standardisation' claim is based. Where a joint Agency-recognised monograph does not exist for the herbal substance, another monograph may be put forward to the Agency, justifying the use of the component as a quality marker and/or as an active component, together with the method of analysis. This information would need to be evaluated to ensure that the selected component is either linked to the pharmacological activity of the herbal ingredient, and/or is suitable for control of the herbal ingredient in question. Issues such as stability of proposed active components at expiry, and suitability and validation of the proposed method of analysis, could also be considered.

The definition given above might also be seen to cover those ingredients that do not currently claim to be standardised *per se*, but which still claim to contain a specified amount of a particular component. For example, the term 'equiv. hypericin x mg' might be used, with no reference to the term standardisation. How this component is determined, and the validity of the analytical method used, may vary depending on the sponsor of the product. It is not apparent from this expression of the ingredient whether or not the component (hypericin) has been quantified by analysis, or whether the 'x mg' has been estimated with regard to the average amount of the component found in a particular weight of the dry herb used to make the extract. To ensure that quantitation of a component between products is consistent, validated methods of analysis must be used for this purpose.

Stakeholder input

6.1 Stakeholder input is requested on whether products claiming standardisation should be regulated and, if so, the suitability of the BP and/or the proposed definition for this purpose.

6.2 Comment is also requested as to whether medicines using such terms as 'contains' or 'equiv. to' should be required to comply with the same requirements as for standardised ingredients, or whether these types of claims could be best managed another way.

APPENDIX 1

CURRENT REGULATION OF MEDICINES AND HERBAL INGREDIENTS

BACKGROUND

The Regulatory Framework for Medicines in Australia

The Therapeutic Goods Administration (TGA) is responsible for administering the provisions of the *Therapeutic Goods Act 1989* (the Act). The overall objective of the Act is to ensure the quality, safety, efficacy and timely availability of therapeutic goods, including medicines supplied, in or exported from, Australia. The Act is supported by the *Therapeutic Goods Regulations 1990* (the Regulations) and various Therapeutic Goods Orders (TGOs) and Determinations.

The TGA maintains the Australian Register of Therapeutic Goods (ARTG), a database that includes details of all therapeutic goods that are imported into, supplied in, or exported from Australia. It is a legal requirement that, unless specifically exempt or excluded, all therapeutic goods be included on the ARTG prior to their supply. Therapeutic goods cannot be included on the ARTG unless an application is lodged by a sponsor (the person or company responsible for applying to the TGA to have their goods included on the ARTG, who must be a resident of Australia or carrying on business in Australia). Based on risk, Australia has a two-tiered approach to regulation of medicines. Risk is determined by factors such as the ingredients in a medicine, the dosage form, indications and claims, the significance of side effects and the effects of prolonged or inappropriate use of the medicine.

Registered medicines

Medicines that are assessed to be of higher risk are individually evaluated for safety, quality and efficacy before they can be released onto the market.

If, following evaluation, a higher risk medicine is approved by the TGA for use, it is included on the ARTG as a Registered medicine. Registered medicines include both prescription medicines and non-prescription medicines.

Listed medicines

A different process is applied to low risk medicines, which includes most complementary medicines. Low risk medicines are included on the ARTG as Listed medicines. These medicines are not required to be evaluated for safety, quality and efficacy before they are released onto the market, but are checked to ensure they comply with certain legislative requirements. For example, that:

- the medicine only contains substances previously approved by the TGA as suitable for use in low risk medicines;
- each step in the manufacture of the medicine has been carried out by a licensed manufacturer and to an acceptable standard; and
- the presentation is acceptable.

In addition, sponsors[6] must certify to the TGA that they hold information or evidence to support any claim made in relation to the Listed medicine.

The Australian Code of Good Manufacturing Practice

Australian manufacturers of medicinal products are required to comply with the *Australian Code of Good Manufacturing Practice for Medicinal Products* (16 August 2003). The code is based entirely on the international standard, *Guide to Good Manufacturing Practices for Medicinal Products*, published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S). The Australian code was implemented on 21 August 2003 and applies to all medicines manufactured in Australia, including complementary medicines.

Compliance with the code is ascertained by carrying out pre-licensing audits and, thereafter, regular on-site audits of manufacturers of medicinal products. The TGA has good manufacturing practice (GMP) inspection agreements with some other countries and organisations to obtain inspection reports, GMP certificates and other GMP-related information about overseas manufacturers exporting, or wishing to export, medicinal products to Australia.

Dispensed or extemporaneously compounded herbal medicines

Medicines (other than medicines used for gene therapy) that are dispensed, or extemporaneously compounded, for a particular person, for therapeutic application to that person by a complementary healthcare practitioner, such as a herbalist, are not regulated by the TGA. The exemption applies to medicines prepared for individual patients, either following consultations with that particular patient, or to fill a prescription for that particular patient. The exemption does not cover situations where the practitioner makes up medicines in advance, in anticipation of patients who may come onto the premises and ask for that medicine.

Regulation of Herbal Medicines in Australia

In Australia, medicines containing herbal substances are regulated under the *Therapeutic Goods Act 1989.* Products containing herbal substances must be included on the ARTG, unless specifically exempt from this requirement.

The current regulatory system provides for Listed medicines to contain of a wide range of herbal substances, provided that it can be adequately demonstrated that the herbal substance is safe, and the product is low risk. Meeting the requirements of a herbal substance, as defined in the Regulations, is an important step for supporting the safety of these substance.

The TGA's Approved Terminology for Medicines[7] classifies herbal ingredients as 'herbal substances'. Herbal substances are preparations of plants and other organisms that are treated as plants in the International Code of Botanical Nomenclature, such as fungi and blue-green algae. The definition of a 'herbal substance' in the Regulations includes details of acceptable production processes.

[6] A sponsor of a therapeutic good is the person or company responsible for applying to the TGA to have their goods included on the ARTG. The sponsor must be a resident of Australia or carrying on business in Australia.

[7] Therapeutic Goods Administration Approved Terminology for Medicines
http://www.tga.gov.au/docs/html/aan.htm

In a regulatory context, 'herbal substance' is referred to in Schedule 4 of the Regulations. This schedule refers to therapeutic goods required to be included in the part of the ARTG for Listed goods. 'Herbal substance' is defined in Regulation 2, Interpretation, of the Regulations). The definition effectively describes the types of herbal substances that are eligible to included in Listed medicines on the ARTG. Registered medicines may also contain herbal substances.

Criteria for Including Herbal Ingredients in Listed Medicines

To be eligible to be included in a Listed medicine, a herbal ingredient[8] must meet four criteria[9] set out in the Regulations, Schedule 4, Part 1, Item 3 (see Appendix 2 for details):

1. the herbal ingredient must have been *"present in therapeutic goods included in the Register (ARTG) for supply in Australia"*; that is, must have been included in a product accepted for supply in Australia;
2. the preparation must meet the definition of a 'herbal substance' as defined in the Regulations (see *The definition of a 'herbal substance'* on page 6);
3. the ingredient must *not* be a scheduled poison, that is, it must not be subject to the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP); and
4. the ingredient must *not* be included in that part of the Regulations (Schedule 4, Part 4) that identifies more hazardous herbal substances, unless the herb meets the conditions specified to enable it to be considered low risk.

The first and second criteria were intended to provide a practical means of allowing herbal ingredients or herbal preparations that have a history or tradition of use, and/or use in established pharmaceutical practice, to be identified as low risk. Where herbal ingredients and preparations have been identified as unsuitable for use in low risk medicines, they are excluded by the third and fourth criteria. If a herbal ingredient has not been included in a product accepted for supply in Australia, it must undergo assessment by the regulator to determine its suitability for use in Listed medicines.

Details of the requirements for quality, safety and efficacy of both Listed and Registered herbal medicines, and the evaluation of new herbal substances for use in Listed medicines, are included in the Australian Regulatory Guidelines for Complementary Medicines (ARGCM). The ARGCM comprises five parts, all include details of TGA regulatory processes and indicate the minimum requirements to support quality, safety and efficacy of Registered and Listed complementary medicines containing herbal substances:

PART I - Registration of Complementary Medicines

provides guidance on the regulatory process and the requirements for quality, safety and efficacy for the Registration of complementary medicines.

PART II - Listed Complementary Medicines

provides guidance on regulatory process and the requirements for quality, safety and efficacy for Listed complementary medicines.

[8] An 'ingredient' refers to a herbal substance in the formulation, and a 'component' is a chemical constituent of an ingredient.

[9] Where a herbal ingredient is homoeopathically prepared, separate criteria apply (see Regulations Schedule 4 Part 1 Items 4A and 5).

PART III - Evaluation of Complementary Medicine Substances

provides guidance on the evaluation of complementary medicine substances for use in Listed medicines including excipients.

PART IV- General Guidance

provides general guidance in relation to complementary medicine modalities such as homoeopathy, traditional herbal medicine, and aromatherapy. This part also provides information on exempt medicines, combination complementary / pharmaceutical medicines, and the food / medicine interface, and contains a glossary of terms.

PART V - Policy Documents and Guidelines

provides details of TGA policy guidelines relevant to complementary medicines.

To meet the needs of all stakeholders requiring guidance on the regulation of complementary medicines, the ARGCM is structured to provide different levels of detail, ranging from broad overviews to, for example, specific technical guidance on the selection and quality of individual studies to support the safety of complementary medicine substances.

Additional guidance has also been developed to supplement the ARGCM, and to provide more specific advice. Guidance documents of relevance to the quality, safety and efficacy of medicines containing herbal ingredients include:

Guidance on the use of the term 'Quantified by Input' for Complementary Medicines

Using a risk-based approach, it may be possible to justify some situations where the assay of an active ingredient in every batch of finished product is not necessary. In such situations, the content of active ingredient may be estimated from the amount dispensed during the manufacture of the product. This practice is termed 'Quantified by Input'. However, based on risk, it is not appropriate to apply this practice to all ingredients. This guidance document describes the criteria under which a manufacturer of a complementary medicine is not required to assay an active ingredient in a finished complementary medicine product.

Questions & Answers on Stability Testing of Listed Complementary Medicines

The approach taken by TGA in relation to stability testing of herbal and certain other Listed complementary medicines, recognises the differences between these complex therapeutic products and pharmaceutical products that usually contain a single, chemically defined, active ingredient. The approach also recognises the technical difficulties that may be associated with stability testing of complex multi-ingredient complementary medicines.

Questions & Answers for the Identification of Herbal Materials and Extracts

The overarching principle for the identification of herbal starting materials and extracts used in complementary medicines is traceability to a primary source or certified herb. Identification testing must discriminate between related species and/or potential adulterants/substitutes that are likely to be present.

Guidelines for Levels and Kinds of Evidence to Support Indications and Claims for Non-Registerable Medicines, Including Complementary Medicines, and other Listable Medicines

When submitting an application to the TGA for Listing, a sponsor must certify to the TGA that they hold the evidence to support all indications and claims made in relation to the product.

To facilitate compliance with this requirement, these guidelines assist sponsors to determine the appropriate level and kind of evidence necessary to support the indications and claims made for a product.

Guide to interpretation of the Australian Code of Good Manufacturing Practice for Medicinal Products (16 August 2002) applicable to the manufacture of complementary medicines

The purpose of this document (developed in collaboration with the Australian complementary medicines industry, developed) is to clarify the requirements of the *Australian Code of Good Manufacturing Practice for Medicinal Products* applicable to the manufacture of complementary medicines.

Regulation in New Zealand

The regulatory framework for medicines in New Zealand is based on the *Medicines Act 1981.*Many products that would fall within the definition of "complementary medicine", including herbal medicine, are currently sold as dietary supplements, which are regulated under the *Dietary Supplements Regulations 1985* under the *Food Act 1981*. The *Dietary Supplements Regulations 1985* impose some restrictions on what a dietary supplement can contain, and therapeutic claims are prohibited. The current legislation does not adequately regulate complementary medicines, and New Zealand has for some time recognised the need to develop new legislation to regulate complementary medicines.

APPENDIX 2

GOODS REQUIRED TO BE INCLUDED IN THE PART OF THE REGISTER FOR LISTED GOODS

Schedule 4 of the Australian *Therapeutic Goods Regulations 1990* outlines those goods required to be included in the part of the Register for Listed goods. Schedule 4, Part 1, Item 3 states:

"preparations containing as their therapeutically active ingredients only vitamins, minerals, herbal substances, a substance mentioned in Part 5 of this Schedule, or a combination of those substances where:

a) the preparation:

   i) is not included in a Schedule to the Poisons Standard; and

   ii) is not of a kind required to be sterile; and

b) the vitamins consist only of vitamins or their salts specified in Part 2 of this Schedule; and

c) the minerals consist only of minerals or their salts specified in Part 3 of this Schedule; and

d) the preparation

   i) does not include a herbal substance derived from plant material mentioned in Divison 1 of Part 4 of this Schedule; and

   ii) if it contains a herbal substance derived from plant material mentioned in an item in the table in Division 2 of that Part – is consistent with the qualification mentioned in column 3 of that item; and

      (A) does not include the substance in a quantity that exceeds, for the recommended daily dose of the preparation, the equivalent of 1 mg of the dry herbal starting material; or

      (B) is not inconsistent with the qualification mentioned, in relation to the substance, in column 3 of the table in that Division; and

e) the herbal substance is present in therapeutic goods included in the Register for supply in Australia;

f) if a substance mentioned in Division 2 of Part 5 is an ingredient – the preparation is not supplied:

   i) in a form that contains the substance in excess of the maximum amount per dosage for that form, as mentioned in column 3 of the table in that Division for that substance; and

   ii) without the information about daily dosage mentioned in column 4 of the table for that substance; and

g) if a substance mentioned in Division 3 of Part 5 is an ingredient – the preparation is supplied:

   i) in accordance with the qualification (if any) mentioned in relation to the substance in that Division: and

   ii) with a label that complies with the requirements of the required Advisory Statements for Medicine Labels for that substance;

unless the indications proposed by the sponsor of the preparation are in the treatment of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 to the Therapeutic Goods Advertising Code."