GUIDANCE ON THE USE OF THE TERM
‘QUANTIFIED BY INPUT’
FOR LISTED COMPLEMENTARY MEDICINES

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Guidance on the use of the term ‘Quantified by Input’ for Listed Complementary Medicines

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Background:
Under the Australian Code of Good Manufacturing Practice for Medicinal Products, it is a requirement that all active ingredients in medicines be tested to confirm that the content complies with prescribed standards. However, it is recognised that in some circumstances this may not be possible or practical to achieve. Where it is established that such medicines are manufactured in accordance with the principles of the Australian Code of Good Manufacturing Practice, and other criteria are met, quantitative testing of the active ingredient in the finished product may be omitted and the ingredient in the product ‘quantified by input’.

This guidance document should be read in conjunction with the accompanying Questions & Answers on the use of “Quantified by Input”

Scope:
This guidance document describes the criteria under which a manufacturer of a Listed complementary medicine would not be required to assay an active ingredient in a finished complementary medicine product. The document also provides wording that a manufacturer could use on a certificate where an active ingredient (see Note 1) has been ‘Quantified by Input’. Please note that the guidance provided in this document does not override or replace the need to comply with all relevant statutory requirements. This guidance does not extend to medicines other than complementary medicines nor is it applicable to other medicines containing a complementary medicine component.

It is intended that this document be used by manufacturers, in consultation with the relevant sponsor, as part of product development. It is most relevant where a quantitative claim (see Note 2) is made for a particular active ingredient in a complementary medicine. However, in certain circumstances, these principles may also be applied to excipients and/or components in ingredients that are considered to be ‘restricted ingredients’ (see Note 3). A Flow Chart has been provided to outline the assessment process that should be applied. The flow chart should always be considered in conjunction with this guideline.

Principles:
Consistent with the Therapeutic Goods Administration’s (TGA) risk-based approach to the regulation of medicines, it may be possible to justify certain situations where it is not necessary to assay an active ingredient in every batch of finished product. In such situations, the content of an active ingredient may be estimated from the amount dispensed during the manufacture of the product. This practice is termed ‘Quantified by Input’ (QBI). However, based on risk to consumers, it is not appropriate to apply this practice to all ingredients. The application of the principles of QBI to a particular active ingredient in a product is based on the following factors:

1. The manufacture of the complementary medicine product must be undertaken in a facility that is deemed by the TGA to have an acceptable level of Good Manufacturing Practice (GMP); and
2. The ingredient in the medicine is approved for use in Listed medicines. For ingredients that have quantity-based restrictions, it is expected that an assay in the finished product would be performed. However in some specific circumstances, where justified, rotational testing or the performance of a validated limit test may be acceptable.

Where a manufacturer does not intend to assay an active ingredient in a batch of a complementary medicine, this decision must be supported by written justification. The justification may be reviewed at a TGA GMP audit of the manufacturer or by the Office of Complementary Medicines (OCM). In justifying the use of QBI and therefore not undertaking an assay, the issue of what constitutes a reasonable attempt at performing an assay is difficult to judge with objectivity. It may often be a subjective judgement as to whether the justification for not assaying is sufficient. In such cases discussion with the TGA may help to resolve the issue.

**Assessing the suitability of an active ingredient in a batch of a Listed complementary medicine for quantifying by input:**

When determining whether the content of an active ingredient/component in a Listed complementary medicine could be quantified by input, the following points need to be addressed:

- the intent to make quantitative claims for the ingredient in the finished product;
- any restrictions applicable to the ingredient or any component in the ingredient, e.g. referred (see Note 4) to in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) or inclusion in Schedule 4, Part 4, Divisions 1 and 2 or Schedule 4, Part 5, Division 2 of the Therapeutic Goods Regulations 1990 (the Regulations);
- the performance of any relevant quantitative testing (assay) of the active raw material by a TGA licensed or approved manufacturer; and
- the availability of a valid assay method for the ingredient/component in the finished product.

Many ingredients of biological origin used in complementary medicines are not single component ingredients (e.g. shark cartilage, non-standardised herbal extracts). In these situations, where the ingredient/component is not subject to any restrictions and no associated quantitative claims are made in the finished product, the ingredient may be quantified by input. The words ‘Not assayed. Quantified by Input’, or words to that effect, may be used on the certificate of analysis of the finished product.

In cases where the active ingredient consists of a single component, or where a quantitative claim is made for any component within an ingredient, it is usually expected that the ingredient/component would be assayed in the finished product. This is particularly important when, to ensure the safety of the medicine, an ingredient / component is subject to restrictions in any relevant legislative instrument.

However, in certain situations it may be justifiable to quantify by input such ingredient/components, including those that are restricted, and not assay the finished product. This could occur as part of a rotational testing program (see Note 5), where, for certain batches of medicine, the assay of a specified ingredient/component would not be performed. In these cases, words such as ‘Quantified by Input. This ingredient is part of a rotational testing program and was not assayed in this batch’ may be used on the certificate of analysis of the finished product.
Furthermore, the use of a validated limit test (see Note 6) may be able to be justified. The use of such a test may provide an acceptable level of assurance that the ingredient/component is present at a level which would exclude the medicine from a schedule of the SUSDP or restriction as defined in the Regulations.

In other instances, the formulation of the medicine may be of such complexity that a validated assay method for the ingredient in the finished product is unavailable or is difficult to achieve. To be able to apply the principles of QBI to the manufacture of these medicines, the potency of the ingredient/component must have been established by a TGA licensed or approved manufacturer prior to inclusion in the formulation. Once this has been done, the words ‘Not assayed. Quantified by Input’ may be used for the ingredient/component on the certificate of analysis of the finished product.

For multi-active medicines (e.g. multivitamin / mineral complexes) it may be justifiable to use QBI for ingredients for which a validated assay method for testing the finished product is available. If the quality and safety of the medicine is assured through other testing, the assay of certain ingredients may be put on a rotational testing program. Again, this can only be applied if the potency of the ingredient/component has been established by a TGA licensed or approved manufacturer prior to inclusion in the formulation. Once this has been done, the words ‘Not assayed. Quantified by Input’ or ‘Quantified by Input. This ingredient is part of a rotational testing program and was not assayed in this batch’ may be used for the ingredient/component on the certificate of analysis of the finished product.

Implementation:

The implementation of the principles outlined in this guidance document became effective on 1 January 2007. Consistent with the principles and guidance in this document, some testing must be performed on each batch of the finished product where a quantitative claim is made on the label. That is, there must be sufficient testing to provide assurance that the product is of intended quality (see Flow Chart).
Notes:

Note 1: An ‘active ingredient’ is the therapeutically active component in a medicine’s final formulation which is responsible for its physiological or pharmacological action (as defined in Section 52F of the Therapeutic Goods Act 1989).

Note 2: A ‘quantitative claim’ is a claim made for a medicine which states that a particular quantity of an ingredient, or component in an ingredient, is present in the medicine.

Note 3: An ingredient, or component within an ingredient, is considered to be ‘restricted’ where there is a quantity or concentration based restriction referred to in a legislative instrument such as the SUSDP, Schedule 4 of the Regulations, a condition of listing, etc (for full details, refer to the definition of ‘restricted ingredient’ below).

Where a quantity based restriction may apply to an ingredient or component it is generally not appropriate for that ingredient to be quantified by input because of the on-going need to confirm that the medicine meets the quantity based restriction and remains safe. This means that any ingredient referred to or mentioned in any of the legislative instruments may generally not be quantified by input, irrespective of whether or not the quantity based restriction applies.

Extract from the Regulations:

11(2) A substance is a restricted ingredient if:

(a) it is an ingredient in a relevant medicine; and

(b) for that medicine to be, or to remain, eligible for listing, the permissible quantity or concentration of the substance in the medicine is restricted by operation of any of the following:

(i) Schedule 4;

(ii) the Poisons Standard;

(iii) a condition imposed under section 28 of the Act;

(iv) a standard under section 10 of the Act;

(v) the Required Advisory Statements for Medicine Labels document;

(vi) any other provision in these Regulations or in the Act that deals with eligibility of medicines for listing.

11(3) In this regulation:

relevant medicine means a medicine that is listable goods or listed goods and that is not an export only medicine.

Note 4: A substance may be ‘referred’ to or mentioned in the SUSDP, but it may not be ‘included’ in a Schedule. That is, it may not be subject to the requirement of the SUSDP entry because the quantity/concentration of the ingredient is below that specified in the entry. It should be noted that, by definition, a Listed medicine cannot contain any substance that is included in a Schedule.
For example, Vitamin D preparations are referred to in the SUSDP for internal human therapeutic use, although preparations containing 25 micrograms or less of vitamin D per recommended daily dose are not subject to restrictions in the SUSDP. Therefore:

- medicines which contain vitamin D at levels that provide a daily dose of more than 25 micrograms are included in Schedule 4 and cannot be used in Listed medicines; and
- for Listed medicines which provide 25 micrograms or less of Vitamin D, a Vitamin D assay of the finished product must be performed.

In instances where reference to an ingredient in a legislative instrument only relates to a requirement for a warning statement (e.g. *Hypericum perforatum* in Schedule 4, Part 4, Division 2 of the Regulations), that ingredient may, subject to the principles of this document, be eligible for quantitation by input. Please note that this would not be the case if the warning statements are quantity dependent.

**Note 5:** Rotational testing is the performance of specified tests on pre-selected batches and/or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not fully tested must still meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should be supported by written justification. This justification may be reviewed at a TGA GMP audit of the manufacturer or by the OCM.

**Note 6:** A ‘limit test’ is a semi-quantitative assay for a component in a product. It generally provides a pass / fail result for the component. It should be developed with suitable specificity, precision and accuracy, but it is not expected to provide an exact value.

The use of a validated limit test may provide an acceptable level of assurance that a particular ingredient or component is present in a product at levels consistent with low risk and, subject to the principles of this document, be eligible for quantitation by input. In instances where restrictions in the SUSDP or in Schedule 4 of the Regulations apply to an amount of an ingredient / component in a recommended daily dose, the application of a limit test will require knowledge of the recommended dose. In instances where this is not known, manufacturers should liaise with the product’s sponsor to ascertain this information.
Flow Chart: Determining the requirement for assay of an active ingredient in a batch of a Listed complementary medicine

(this does not replace the need to comply with relevant statutory requirements)

Is the active ingredient primarily a single component ingredient?

YES

e.g. a vitamin

NO

e.g. herbal extract

Is a quantitative claim made for any component in the documentation for the product?

YES

e.g. standardised herbal extracts

NO

e.g. shark cartilage with no equivalency statements or a simple herbal extract stated as being equivalent to the fresh herb.

Is the ingredient, or any component in the ingredient, referred to in a schedule of the SUSDP or otherwise restricted?

YES

Any ingredient or component subject to a restriction or referred to in the SUSDP should be assayed in the finished product. Rotational testing may be acceptable where supported by documentation. In such cases, with suitable justification, the ingredient can be quoted on the certificate for the finished product as 'Quantified by Input. This ingredient is part of a rotational assay program and was not assayed for this batch' (or words to this effect).

NO

Has the potency of the active ingredient/component been tested by a TGA licensed or approved manufacturer?

YES

Ingredient or component can be quoted on the certificate for the finished product as 'Not assayed. Quantified by Input' (or words to this effect1). Rotational testing for this ingredient/component should be considered. In all cases, some testing must be performed on each batch of the finished product. That is, sufficient testing to provide assurance that the product is of intended quality should be carried out.

NO

Is a valid assay available for the ingredient or component in the finished product?

YES

The ingredient should be assayed in each batch of the finished product.

NO

The finished product manufacturer should assay the ingredient at input. The ingredient should be quoted on the certificate for the finished product as 'Not assayed. Quantified by Input' (or words to this effect). In all cases, some testing must be performed on each batch of the finished product. That is, sufficient testing to provide assurance that the product is of intended quality should be carried out.

1 Any alternative wording must clearly indicate that an assay of the ingredient in the finished product has not been performed.

2 The use of a validated limit test to establish that an ingredient, or component in an ingredient, is not subject to a quantity based restriction, may provide suitable justification to permit the ingredient to be quantified by input.