



The QBI Project Officer
Guidance on the Use of the Term 'Quantified by Input' for Listed Complementary Medicines
Office of Complementary Medicines
Therapeutic Goods Administration
PO Box 100
WODEN ACT AUSTRALIA

Dear Sir/Madam

CHC Submission:

- **Draft Guidance on the use of the term 'Quantified by Input' for Listed complementary medicines**
- **Questions and answers on the use of 'Quantified by Input'**
- **Explanatory note: Draft Guidance on the use of the term 'Quantified by Input' for Listed complementary medicines**

Thank you for the opportunity for the complementary healthcare industry to provide comment on the Draft Guidance on the use of the term 'Quantified by Input' for Listed complementary medicines and associated documents, dated October 2009. The CHC acknowledges that there has been significant work carried out on these documents by TGA and industry.

The Complementary Healthcare Council (CHC) provides the following comments on the consultation documents:

Draft Guidance on the use of the term 'Quantified by Input' for Listed complementary medicines

Background

The CHC recommends that the second paragraph under the heading 'Background' be expanded to include a reference to the "Explanatory note: Draft Guidance on the use of the term 'Quantified by Input' for Listed complementary medicines" as well as the Q&A.

Scope – responsibility of the sponsor:

The CHC notes that, unlike the third paragraph of the Q&A document, the scope does not emphasize that the sponsor has ultimate responsibility for the product, and therefore for the correct use of QBI. The CHC suggests that the scope incorporate that fact so that both manufacturer and sponsor are clear about the line of responsibility. This could be done by the addition of the following to the first sentence of the second paragraph under Scope:

"It is intended that this document be used by manufacturers, in consultation with the relevant sponsor **(who has ultimate responsibility for the product and therefore for the correct use of QBI),**".

Scope – excipients, page 2, Scope paragraph 2, line 4:

The CHC suggests that given that some restricted ingredients may be excipients, as mentioned in line 4, that any reference to "active ingredients" in the document be replaced with the term "ingredients" to cover both types. The CHC notes that this is a new requirement. Most ingredients that may be used as 'excipients' and which have a restricted component (for example the essential oils) are better controlled at the raw material

stage, not at the finished product. Excipients with restricted components should not form part of a QBI justification which is focused on finished product testing.

Rotational testing

The CHC recommends that a common interpretation of the term “rotational testing” be developed that incorporates the understanding given in the QBI document and that is used by auditors of the Office of Manufacturing Quality.

There are a number of references to “rotational” testing of batches of the finished product throughout the QBI document and there is concern about possible differences in the interpretation of the term between the QBI document and the auditors of the Office of Manufacturing Quality.

"a TGA licensed or approved manufacturer":

The Guidance document refers to "a TGA licensed or approved manufacturer" in a variety of places, including the Flow Chart. This change is not acceptable to the CHC. The TGA argue that this brings this document in line with the PICS Code 2009. We disagree. The Code actually states (Annex 8) that *'nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry.'* It is not acceptable to us that our members cannot accept raw material CoA results except those results which have been tested in TGA laboratories, even if the supplier has passed vendor assurance/validation. The original wording should be re-instated.

- In the event of the continued use of this term, the CHC suggests that as the difference between “TGA licensed manufacturer” and “TGA approved manufacturer” may not be obvious to many readers unfamiliar with TGA terminology, that a footnote be appended to this statement, referencing the reader to the “Explanatory note: Draft Guidance on the use of the term ‘Quantified by Input’ for Listed complementary medicines”.

“Note 3”, page 5

The CHC requests that consideration be given to the effect of the use of the term ‘restricted ingredient’ and the extent to which this could affect ingredients or components for which a QBI procedure may be needed. In particular, there could be significant difficulties in carrying out assays or limit tests for some of the herbs in Schedule 4 that have dosage restrictions, particularly where there may be either no specific components to assay or a mixture of minor components to assay.

Flow Chart: Determining the requirement for assay of an active ingredient in a batch of a Listed complementary medicine (page 7)

The CHC notes that the flow chart is not consistent with the guidance provided in Question 9 of the document ‘Questions and answers on the use of ‘Quantified by Input’ and recommends that the flow chart be revised to incorporate this guidance and prevent confusion.

It is suggested that the following question be added to the flow chart “Is a valid assay available for the ingredient or component in the finished product?” after the answer “Yes” to the question “Has the potency of the active ingredient/component been tested by a TGA licensed or approved manufacturer?”, refer to the revised flow chart in Appendix 1 for further detail.

- The CHC understands that the testing of the potency of the active ingredient/component by a qualified manufacturer is not a replacement for assaying the active ingredient/component in the finished product, although this could appear to be the case from the current flow chart.
- The answer to the question in the flow chart “Has the potency of the active ingredient/component been tested by a TGA licensed or approved manufacturer?” appears to allow a situation of ‘permanent’ QBI as long as the active ingredient/component has been tested by a TGA licensed or

approved manufacturer. The current answer being “Ingredient or component can be quoted on the certificate for the finished product as ‘*Not assayed. Quantified by Input.*’”

- In addition, the CHC recommends the replacement of the term “TGA licensed or approved manufacturer” with the original wording of the QBI document.
- The important step of asking whether a valid assay is available has been left out resulting in a contradiction to the answer to Question 9.
- The answer to Question 9 confirms that where a valid assay is available for a non-restricted ingredient in a finished product, testing must be performed on each batch, unless QBI is used as part of a rotational testing program.
- Given that this is one of the fundamental principles for a ‘permanent’ QBI situation, the inclusion of this guidance in the flowchart would appear to be crucial.

Flow Chart - answer to the restricted ingredient question:

The CHC recommends that to prevent confusion and to maintain consistency with Note 3, the answer to the flow chart question “Is the ingredient, or any component in the ingredient, referred to in a schedule of the SUSDP or otherwise restricted?”, which begins with “Any ingredient or component subject to a restriction or referred to in the SUSDP ...” be replaced with the following words, or similar:

“Any ‘restricted’ ingredient or component (refer Note 3) subject to a quantity or concentration restriction”.

Last Flow Chart box:

The CHC suggests that the word “at” in the first sentence in the flow chart box at the bottom of page 7 be replaced by the words “prior to”, or similar meaning, to prevent confusion about the timing of assaying an ingredient. A finished product manufacturer would usually assay the active ingredient on receipt into the company and assign the appropriate shelf life.

“The finished product manufacturer should assay the ingredient **prior to** input.”

Questions and answers on the use of ‘Quantified by Input’

First paragraph, page 1:

The CHC recommends that the first paragraph on page one be expanded to include a reference to the “Explanatory note: Draft Guidance on the use of the term ‘Quantified by Input’ for Listed complementary medicines” and to the Code of GMP, in addition to the Q&A and the ARGCM.

Question 4. (a), Note 2:

The CHC strongly supports the development of the list of ingredients, components and matrices where experience has established that a validated assay is not feasible, and recommends that priority be given to the development of this list.

- There will be real benefit for industry in the availability of such a list for the development and assessment of products and tests methods for QBI.

In addition, the CHC recommends that guidance be given on the requirements and process for adding new information to the list.

Question 6, Note 4:

The CHC strongly supports the development of the list of ingredients, components and matrices where a validated limit test has been established, and recommends that priority be given to the development of this list.

- There will be real benefit for industry in the availability of such a list for the development and assessment of products and tests methods for QBI.

In addition, the CHC suggests that the introduction to such a list provide guidance that industry is not restricted by this list and can use other limit tests where it has been established that a validated limit test is feasible in accordance with the TGA document 'Finished Product (Medicine) Analytical Procedure Validation'.

The CHC also recommends that guidance be given on the requirements and process for adding new information to the list.

Question 7. (a):

The CHC recommends the inclusion of the words "of a herb" in the question for 7. (a) and a change from "herbal extract" to "herb" in the answer to 7. (a) for consistency. Note that a restricted component could be part of a raw herb or herbal extract and the use of the word "herb" would encompass both.

Question 9:

The CHC suggests that a minor rewording of the last sentence to the answer to Question 9 may provide further clarity between QBI as part of a rotational testing program and QBI used on a permanent basis.

"The use of QBI **on a 'permanent' basis** is based on the inability to assay the ingredient at all".

Question 10:

The CHC suggests that the phrasing of Question 10 with the use of the word "particular active(s)" could be confusing for industry and proposes that the word "particular" be replaced and that the word "same" be used, as follows:

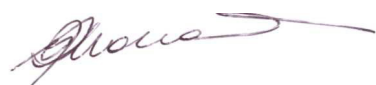
"When using rotational testing, can the testing laboratory (or the sponsor) always test the same active(s) from the list of all actives that are eligible for rotational testing?"

Addendum:

Please refer to the attached addendum for further comments.

If you would like to discuss any matters within this submission further, please do not hesitate in contacting me.

Yours sincerely



Dr Wendy Morrow

Executive Director
Complementary Healthcare Council

4 November 2009



Appendix 1 – Revised Flow Chart

