



## Addendum

### A Guidance

This October 2009 version is a long awaited update for the much earlier initial version. Whilst it introduces many acceptable changes and improvements, I consider that it is not ready for application. I will not try and summarise all the acceptable changes and improvements in this commentary rather I will focus on the issues that I think still need to be clarified and resolved. Consistent with the Deficiency system used in GMP audits, I have divided my comments to deal with Critical, Major and Other issues in this version.

#### 1 Critical issues:

1.1 Rotational testing: There are a number of references to “rotational” testing of batches of the finished product throughout the document. **Note 5 on page 6 defines Rotational testing as “the performance of specified tests on pre-selected batches and/or at pre-determined 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.”** It is noted that this approach should be supported by written justification which may be reviewed at a TGA GMP audit of the manufacturer or by the OCM. Such a definition will allow manufacturers to fully test only say every 10<sup>th</sup> batch or one batch per year. Such an extended approach is regarded by TGA OMQ auditors as not being rotational rather a version of reduced testing and consequently they issue a Major Deficiency when such an approach is identified during a GMP audit. The auditors state that **rotational testing involves undertaking critical tests on every batch and one of more other tests on a regular rotational basis for every batch subject to the rotation process being completed within a defined time.** Hence, there is an inconsistency in the way two different parts of TGA are dealing with the same matter. Until this inconsistency is resolved, the QBI guidance cannot be implemented.

Note that rotational testing is further qualified by the statement on page 4, paragraph 3, “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.”

The Questions and Answers on the Use of QBI adds further clarification at question 10 “A predetermined rotational testing program for all relevant actives should be applied.”

So the justification for the implementation of any rotational testing would still need to meet the criteria that “quality and safety of the medicine is assured through other testing”.

1.2 Note 3 page 5 re legislative instrument reference/mention:

1.2.1 As there is no separate definition of “legislative instruments”, it is taken to mean a document underpinned by the *Therapeutic Goods Act 1989* or the Regulations. It may include RASML, SUSDP, a condition imposed under Section 28 of the Act, a standard under section 10 of the Act, TGO’s, Gazette Notices and so on..

As such, many ingredients or components of an ingredient for which a QBI procedure is needed, cannot have the QBI procedure applied if this note is followed. This will ensure that this document then becomes superfluous and of little use as guidance document.

1.2.2 This note appears to be inconsistent with the flow chart with a YES answer to the question relating to reference in a Schedule of SUSDP or otherwise restricted.

1.2.3 This note appears to be inconsistent with Note 3 on page 5 as referenced by the second paragraph in the Scope on page 2 with regard to restricted ingredients.

1.2.4 This note appears to have been inserted in this latest version of the guidance without any consultation with industry or OICG. Until this issue is resolved, it is recommended that the QBI guidance not be implemented.

## **2 Major issues:**

2.1 Page 2, Scope, paragraph 2, line 4 with reference to restricted ingredient “excipients”: This is a new requirement although I can see why it has been included. The inclusion here is not addressed on page 3 where the requirements for “active” ingredients are the only type of ingredient discussed.

2.2 Page 3, Assessing the suitability ...dot 3: The “performance” etc is inconsistent with the wording and consequences of that on page 4 paragraph 2 line 4 and paragraph 3 line 5 where the word “established” is used. These two words are also inconsistent with the consequences of the use of the word “tested” in the relevant box in the flow chart on page All are now inconsistent with the words, intent and consequences of the original version of the guidance in which it was the suppliers competency to provide a valid assay result that was being verified.

2.3 Page 3, Assessing the suitability ... dot 3: The new use of the term “by a TGA licenced or approved manufacturer” significantly alters the intent and consequences of the term used in the earlier version of the guidance which did not specify who was going to do this task. This change is reflected in the new flowchart. The Code 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.’* This indicates that the Code allows raw material CoA results from a supplier who has passed vendor assurance/validation, and raises the question of having to use a TGA licenced or approved manufacturer.

2.4 Page 6 paragraph 1 dot 2: The example suggests that the assay MUST be performed and this infers that the assay is to always to be done. This outcome is inconsistent with the equivalent statement in the flow chart that says that rotational testing may be acceptable where supported by documentation.

2.5 Page 7, flowchart: The box that asks the question “has the potency of the active ingredient (or a component in the ingredient?) been tested etc” refers to the ingredient or the component in a starting material and NOT in a finished product.

2.5 Page 7, flow chart: The box that asks the question “has the potency of the active ingredient (or a component in the ingredient?) been tested etc (given that it is for starting materials)” has two answers.

a) If the answer is YES, there should be another immediate question box ie “Is a valid assay available for the ingredient or component in the finished product?” and there are then two answers to that question.

i) if the answer is YES: The active ingredient or component can either be assayed or entered into a rotational testing program with a “Rotational” type QBI statement.

ii) if the answer is NO: The active ingredient or component is recorded as not being assayed and QBI’d (or words to that effect).

b) if the answer is NO, the subsidiary question ““Is a valid assay available for the ingredient or component in the finished product?” still applies. There are still two answers to that subsidiary question.

i) if the answer is YES, the active ingredient should be assayed in each batch of the finished product with rotational testing for this active ingredient or component being considered.

ii) if the answer is NO, the box at the bottom right hand corner of the flow diagram still applies.

## **3 Other issues:**

3.1 Page 2, Scope, paragraph 1, last line: The words “or ingredient” need to be added.

3.2 Page 5, Note 2, line 2: is this presence “at a defined amount or concentration”. If so, then such words need to be added.

3.3 Page 6, Note 6, paragraphs 1 and 2: Need to insert “ingredient” or “in an ingredient” in lines 1 and 2 in paragraph 1 and in line 2 of paragraph 2 as relevant.

#### **B Explanatory note:**

1 This has been developed with the same general issues as recorded above for the guidance. Consequently, the above comments can be cross applied to this Explanatory note document.

2 The following additional comments are made:

2.1 Page 2, paragraph 8: The words “Raw materials” need to be replaced twice with “starting materials”.

2.2 Page 2, paragraph 8: The last sentence about not QBI’ing is inconsistent with the guidance in general and with the flowchart in particular.

2.3 Page 2, footnote a: The definition of “critical tests” needs to be in the final version of the referenced TWG guidance. It would help if the web address of this TWG guidance was given here (as it is on page 4)

2.4 Page 3, note 4: The manufacturer of the API (read starting material) and not the supplier is qualified not validated.

2.5 Page 3, note 5: Has the same issue about the definition of “Rotational testing” as in the QBI guidance.

2.6 Page 3, note 6: This note does not make sense.

2.7 Page 4, paragraph 2, line 4: This means that if an associated quantitative claim is made for the component (eg EPA and DHA in fish oils) they have to be assayed and cannot be QBI’d. Does this mean that a rotational testing program is not allowed?

#### **C Q & A document:**

1 Page 1, Question 1, last two lines: This part of the answer reverts back to the wording in the original version of the QBI guidance about verifying the supplier’s competency to provide a valid assay result.

2 Page 2, Question 2: It is to be noted that profiling may be important in stability testing programs.

3 Page 2, Question 4a, footnote 2: What is the progress of this joint activity given that it has been ongoing for at least two years?

4 Page 3, Question 6, footnote 4: What is the progress of this joint activity?

5 Page 4, Question 9, last line: This use of QBI reflects a “permanent QBI situation” and so could be said to be a QBI situation without reference to a rotational testing program.

6 Page 4, Question 10: This definition of rotational testing is in dispute (see above).

7 Page 4, Question 11, paragraph 2, sentence 2: If the batch is OOS but acceptable with the ARTG record, this means that the specification being used to drive the testing is tighter than the requirements of ARTG (or other relevant legislative instruments?). Manufacturers and Sponsors need to address such an inconsistency between specification and ARTG rather than opening up accepting OOS results.