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Guidance on the Acceptance Criteria of Quantification by Input (QBI) of Active Ingredients Claimed on Label of Traditional Medicine and Health Supplement (TMHS) Products

NATIONAL PHARMACEUTICAL REGULATORY AGENCY

MINISTRY OF HEALTH MALAYSIA

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1.0 Background:

According to the Malaysian Drug Registration Guidance Document (DRGD) Third Edition, Third Revision July 2022 (Appendix 6: Guideline on Registration of Health Supplements and Appendix 7: Guideline on Registration of Natural Products), it is a requirement to conduct quantitative assay test for all active ingredients claimed on product label. However, this may not be possible or practical to achieve in some cases.

Therefore, National Pharmaceutical Regulatory Agency (NPRA) proposes to consider allowing Quantification by Input (QBI) for TMHS products.

2.0 Principles:

Quantification by Input (QBI) means the content of an active ingredient is estimated from the amount dispensed during the manufacture of the product. This practice is done when the assay of active ingredient could not be achieved in the finished product.

The acceptance criteria of QBI to a particular active ingredient in a finished product only can be applied to the finished product that is manufactured in a facility that comply to the Malaysian Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements, 1st Edition, 2008 or any acceptable/ equivalent standard.

3.0 Scope:

This guidance document describes the criteria for QBI to be accepted at which quantitative assay can be excluded for active ingredient claimed on the label of TMHS finished product. Please note that this guidance does not override or replace the need to comply with DRGD requirements.

3.1 Active ingredient includes active components/ compounds claimed on product label.

3.1.1 Active ingredient **declared in QUEST system which is of biological origin WITHOUT components/ compounds claimed on product label** is not required to conduct assay test.

e.g. Curcuma longa extract 50mg does not require assay test.

e.g. Deer placenta extract 200mg does not require assay test.

3.1.2 Active ingredient **declared in QUEST system which is of biological origin WITH components/ compounds claimed on product label** is required to conduct assay test.

e.g. Marigold extract 50mg providing Lutein 10mg and Zeaxanthin 2mg.

Assay test for Lutein 10mg and Zeaxanthin 2mg are required.

e.g. Fish oil 1000mg providing DHA 180mg and EPA 120mg.

Assay test for DHA 180mg and EPA 120mg are required.

3.1.3 Active ingredient **declared in QUEST system which is in isolated form** is required to conduct assay test. (Applicable for Health Supplement products only)

e.g. Active ingredient as Lutein 10mg.

Assay test for Lutein 10mg is required.

3.2 Types of Product Claims (General Claim/ Functional Claim/ Medium Claim/ Disease Risk Reduction Claim/ Therapeutic Claim)

3.2.1 QBI is applicable for both health supplement product (general claim and functional claim) and natural product (general claim and medium claim) which require abridged evaluation.

3.2.2 QBI is not applicable for health supplement product (Disease Risk Reduction Claim) and Natural Product with Therapeutic Claim which require full evaluation.

4.0 Determination of Acceptance Criteria for QBI:

4.1 When determining whether the content of an active ingredient in TMHS product could be quantified by input, the following points need to be considered:-

4.1.1 Any quantitative claims* (amount) made for the active ingredient on product label.

4.1.2 The availability of an assay method in monograph/ compendial (pharmacopoeia) to quantify or achieve the assay results for the active ingredients in the finished product. Assay method is considered available if there is monograph/ compendial (pharmacopoeia) for one of the following:

i. Monograph/ compendial (pharmacopoeia) for active ingredient, OR
ii. Monograph/ compendial (pharmacopoeia) for finished product with different dosage form, OR
iii. Monograph/ compendial (pharmacopoeia) for finished product with different formulation

4.1.3 Assay method is available but assay results are difficult or unable to achieve due to trace/ undetectable amount/ interference between ingredients.

4.1.4 The capability to conduct assay test on the active ingredient raw material by a finished product manufacturer. Finished product manufacturer may use in-house method or method from supplier when assay method is not available in monograph/ compendial (pharmacopoeia).

4.2 If the finished product manufacturer is unable to conduct the testing of active ingredient raw material with proven justification (Example: no in-house lab facilities, lack of testing instruments/ equipment, etc.), they are allowed to outsource to other 3rd party/ external laboratories to conduct the testing.

* A 'quantitative claim' is a claim made for a product which states that a particular quantity of an active ingredient, or components/ compounds in an active ingredient, is present in the product. (Refer to 3.0 Scope)

4.3 Determination of QBI acceptance criteria are described in the flow chart below. Once acceptance criteria for QBI has been determined, the words `Not Assayed. Quantified by Input` or words with similar meaning may be used for the active ingredient on the certificate of analysis of the finished product and stability data. (Refer to the example of certificate of analysis of the finished product and stability data).

4.4 Appropriate documentation (such as batch records, standard operating procedure (SOP), specification, testing procedure, etc.) should be in place to support QBI approach as well as ensuring the targeted quantity of active ingredient as per claimed on label can be achieved.

5.0 Implementation:

The implementation of this guidance document became effective on January 2023.

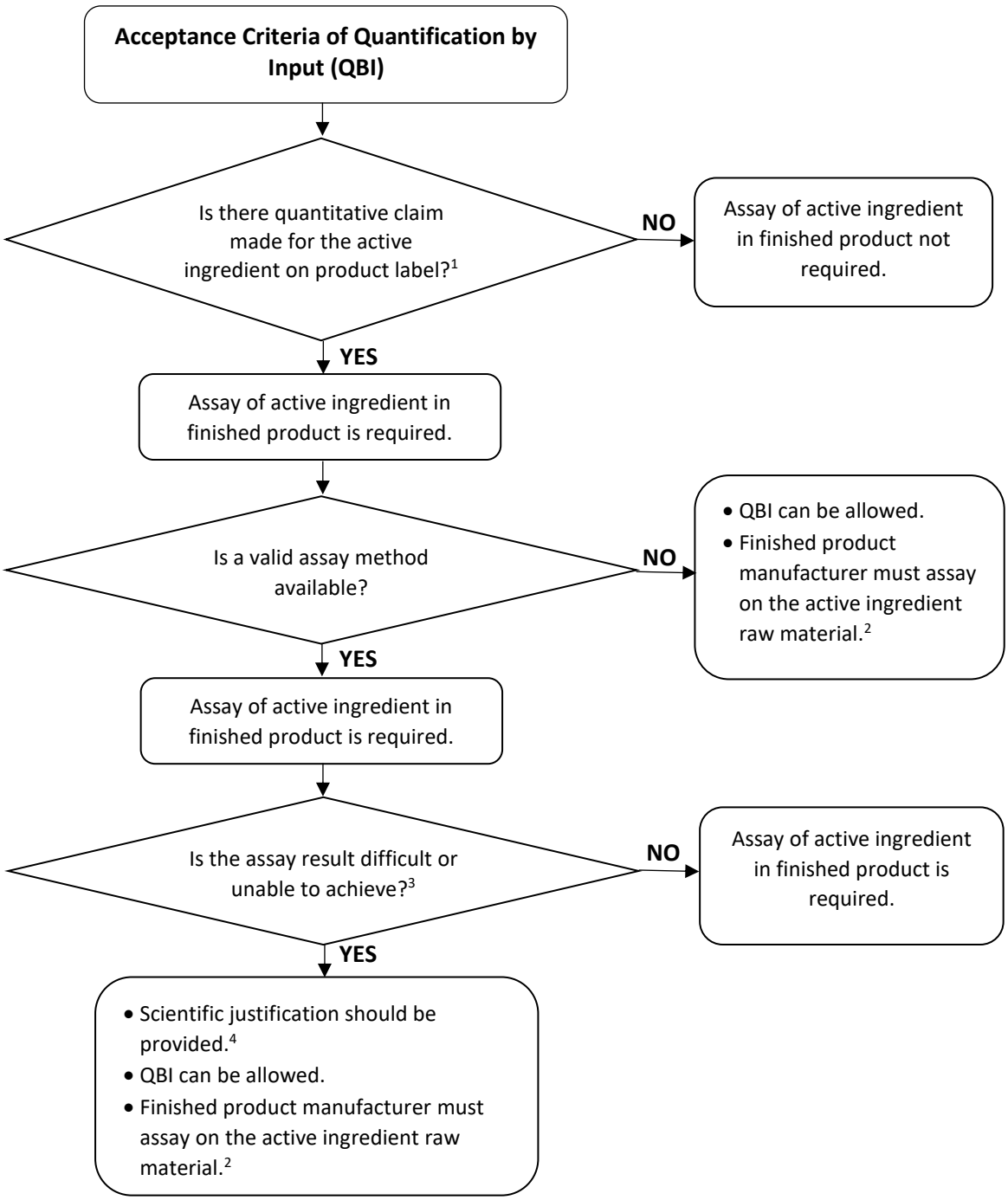
6.0 Abbreviations:

COA	Certificate of Analysis
DRGD	Drug Registration Guidance Document
GMP	Good Manufacturing Practice
QBI	Quantification by Input
SOP	Standard Operating Procedure
TMHS	Traditional Medicine and Health Supplement

References

1. Therapeutic Goods Administration – Guidance on the use of the term `Quantified by Input` for listed complementary Medicines – Revised October 2009
2. Therapeutic Goods Administration - Quality for Listed Medicines Australian Regulatory Guidance Version 1.0, May 2020
3. Health Canada – Quality of Natural Health Products Guide

Flow Chart: Acceptance Criteria of Quantification by Input (QBI) of Active Ingredients Claimed on Label of Traditional Medicine and Health Supplement (TMHS) Products



Notes:

1. Some active ingredients of biological origin (e.g. Sacha Inchi oil, shark cartilage, Curcuma Longa extract) used in TMHS product may contain active components/ compounds. When there is associated quantitative claims made for the components/ compounds of an active ingredient on the label, assay test is required. However, if there is no quantitative claims made for the compounds of an active ingredient on the label, assay test is not required.
2. To be able to apply the principles of QBI in the finished product, the assay on the active ingredient raw material must be conducted by the finished product manufacturer before inclusion into the formulation. Finished product manufacturer may use in-house method, method from supplier or outsource to other 3rd party/ external laboratories to conduct the testing.
3. Assay method is available but assay results are difficult or unable to achieve due to trace/ undetectable amount/ interference between ingredients.
4. To provide scientific justifications and raw data based on the actual test attempted on the finished product and/ or literature reviews to show interference between ingredients in the finished product.

Examples of QBI Calculation

Example 1

Active Ingredient - Lutein	
Active Ingredient minimum potency in raw material COA	5%
Active Ingredient assay test result in raw material COA	5.1%

Finished Product (capsule)	
Amount of Lutein raw material per capsule	20mg
Target fill weight of product	500mg
Actual fill weight of product (during production)	510mg

QBI Value Calculation

Amount of Lutein raw material per capsule x active ingredient assay test result in raw material COA = 20 mg x 5.1% = 1.02 mg Lutein (Amount A)

Amount A x Actual fill weight of product (during production)/ Target fill weight of product
= 1.02 mg x (510 mg/500 mg) = 1.04 mg Lutein

Based on this calculation, the QBI value of lutein per capsule would be 1.04mg.

Example 2

Active Ingredient – Vitamin C	
Active Ingredient minimum potency in raw material COA	100%
Active Ingredient assay test result in raw material COA	100%

Finished Product (capsule)	
Amount of Vitamin C raw material per capsule	50mg
Target fill weight of product	100mg
Actual fill weight of product (during production)	101.2mg
Overage of Vitamin C	5%

QBI Value Calculation

Amount of Vitamin C raw material per capsule x Actual fill weight of product (during production)/ Target fill weight of product X Overage of active ingredient
= 50 x 101.2/100 x 1.05 = 53.1mg Vitamin C

Based on this calculation, the QBI value of Vitamin C per capsule would be 53.1mg.

Example of Certificate of Analysis

Company name/ Address:

Product Name:

Batch no. :

Dosage form:

Packaging:

Date of manufacture:

Date of expiry:

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: - All active ingredients/ compounds claim on label - **Active ingredients/compounds assayed by QBI**	To specify **To specify**	**Example: Results and statement `Not Assayed. Quantified by Input` or words with similar meaning**	**QBI**
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature:

Name:

Designation: (At least by Quality Control Manager or equivalent)

Date of signature:

Note: The above parameter are only as an example, other tests may be required for specific product.

Example of Stability Data

PRODUCT NAME : TABLET ABC 500MG **BATCH NO.** : **MANUFACTURING**

DATE: dd/mm/yy **TEMPERATURE:**30 °C ± 2 °C

EXPIRY DATE : dd/mm/yy **RELATIVE HUMIDITY**: 75 % ± 5%

Tests	**Specification**	**Frequency of Testing**							
		0	3	6	9	12	18	24	36
Product description	Film-coated tablet, brownish in colour								
Disintegration test	NMT 30 minutes								
Assays - All active ingredients/ compounds claim on label	eg: 90% -120% (ref….)								
Active ingredients/ compounds assayed by QBI	**To specify**	**`Not Assayed. Quantified by Input` or words with similar meaning**							
Microbial Contamination test: Total Aerobic Microbial Count Total Yeasts & Moulds Count Test for Specified Microorganisms	 NMT 2×10^4 NMT 2×10^2 ➢ NMT 1×10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1ml or MPN ➢ Absence of Salmonella in 10g or 10ml ➢ Absence of Escherichia coli in 1g or 1ml ➢ Absence of Staphylococcus in 1g or 1 ml								
Heavy metal test: Lead Arsenic Mercury Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)		NA						

Conclusion ----------

Analyst name: (signature) Verified by: (signature)
Name: Name:
Designation: Designation:
Date: Date: