APPENDIX 7B

GUIDELINE ON NATURAL PRODUCTS WITH THERAPEUTIC CLAIM

Guidance documents are meant to provide assistance to industry and healthcare professionals on how to comply with governing statutes and regulations. They also serve to provide guidance to National Pharmaceutical Regulatory Agency (NPRA) officers, thereby ensuring transparency, fairness, and consistency in assessment of quality, safety and efficacy of a product.

Guidance documents are tools to assist stakeholders and do not have the force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document will be acceptable if they support an equivalent outcome resulting in high quality of natural products.

This document should be read in conjunction with the current laws and regulations, and with other relevant legislation as outlined in the current guidance document (Drug Registration Guidance Document, DRGD), which include ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR), Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption, Malaysian Guideline for Good Clinical Practice (GCP), Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products, as well as relevant sections of any other applicable guidance documents.

ACKNOWLEDGEMENTS

The National Pharmaceutical Regulatory Agency (NPRA), Pharmaceutical Services Programme, Ministry of Health Malaysia acknowledges its indebtedness to all stakeholders, who provided comments and advices during the preparation of this guideline.

1.0 INTRODUCTION

Natural products with therapeutic claims are required to be registered with the Drug Control Authority (DCA) before they can be marketed in Malaysia. This guideline aims to provide the requirements to support the quality, safety and efficacy of the natural product with therapeutic claims.

All therapeutic claims made for natural products should have adequate evidence to support all indications, and all claims made must be demonstrated to be true, valid and not misleading. The quality, safety and efficacy of the product should be proven, and the relevant data should be submitted to the DCA.

This guideline aims to provide guidance on making unbiased and truthful claims, supported by adequate evidence in order to protect the consumers from misleading claims.

2.0 SCOPE OF THIS GUIDELINE

This guideline encompasses the type of evidence to support the therapeutic claim for a natural product intended for human use. It also outlines what are the quality and safety data required and applicable to products containing herbal/ plant–medicinal ingredients in the form of standardized extract. The natural product with therapeutic claims shall not include any sterile preparation, any vaccines, any substance derived from human parts, any isolated and characterized chemical substances.

3.0 DEFINITION

3.1 THERAPEUTIC CLAIM:

A claim that is not documented in established pharmacopoeia or monographs, or a claim which is not the traditional use of the ingredient. It may include corroboration and verification of traditional use to relieve a symptom or help to treat a disease, disorder or medical condition, and it must be substantiated by scientific evidence.

The efficacy of a product and its ingredient(s) shall be based on the totality of the substantiation evidence provided including human study, non-clinical and empirical or historical data, as well as other documented evidence, where applicable on the end product. The study must show a consistent association between the active ingredient/herbal ingredient(s) and the therapeutic effect claimed.

The products with therapeutic claims must be manufactured in a Good Manufacturing Practice (GMP) compliant premises which follows the Pharmaceutical Inspection Co-Operation Scheme-Guide to Good Manufacturing Practice for Medicinal Products (PIC/S) guideline.

Non-clinical safety studies for therapeutic claims must be conducted in a facility which complies to Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP) requirement as mentioned in Directive No. 9, 2016, *Bil. (40) dlm.BPFK/PPP/07/25 Keperluan* Good Laboratory Practice (GLP) *bagi Kajian Keselamatan Bukan Klinikal Untuk Tujuan Pendaftaran Produk* New Chemical Entity (NCE)*, Biologik dan Produk Herba Dengan Tuntutan Terapeutik Tinggi.*

The Authority may request for further information or specify conditions not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product.

4.0 REGULATORY/ REGISTRATION REQUIREMENTS

The requirements for registration shall be in accordance with the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main Drug Registration Guidance Documents (DRGD), **Appendix 15, 1.1 General Requirements For Full Evaluation**. It covers:

- Part I - Administrative data and product information
- Part II - Data to support product quality (Quality Document)
- Part III - Data to support product safety (Nonclinical Document)
- Part IV - Data to support product safety and efficacy (Clinical Document)

4.1 ADMINISTRATIVE DATA AND PRODUCT INFORMATION (PART I)

Primary purpose: To provide a general introduction to the product. The Administrative Data is where required specific documentation in detail is put together such as application forms, label, package insert etc. Product Information contains necessary information which includes prescribed information, mode of action, side effects etc.

4.2 QUALITY DOCUMENTS (PART II)

Primary purpose: The product and its ingredient(s) is determined by the quality of the starting material, development, in-process controls and process validation, and by specifications applied to them throughout development and manufacture.

4.2.1 Authentication of the medicinal plants/ ingredients

4.2.1.1 Collection/ cultivation and/or harvesting of medicinal plants/ ingredients should follow other relevant guidance such as the Malaysian Standard on Good Agricultural Practice (GAP) – Part 8: Herbs (MS: 1784-8:2009)

4.2.1.2 The botanical identity such as the scientific name (genus, species, sub-species/ variety, author and family) - of each medicinal plant should be verified by qualified experts from government agencies or other qualified agencies.

4.2.1.3 The authentication of the medicinal plant/ ingredient must be determined following the parameters in established monographs/ pharmacopeias.

4.2.1.4 The botanical source, plant part used and its state (e.g.: whole, reduced, powdered, fresh, dry) should be defined.

4.2.1.5 Requested tests are listed as below, while specifications should be supported by established monographs/ pharmacopeia:

Tests	Specifications	Results
Appearance/Organoleptic characteristics		
Qualitative Test: Identification/ Macroscopic/Microscopic/ Chemical fingerprint		
Loss on drying / Water content		
Purity tests • Foreign Matter • Total Ash Content • Acid insoluble ash*		
Extractive values* • Water Soluble • Ethanol Soluble		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mold Count (TYMC) • Bile tolerant gram-negative bacteria		

Tests	Specifications	Results
• *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Other Tests (any required testing)		

** These tests might not apply to all medicinal plant/ingredient and must be justified by the applicant.*

4.2.2 Information on the standardized extracts

4.2.2.1 To state the botanical source and type of preparation (e.g.: dry or liquid extract). Ratio of herbal substance to the genuine herbal preparation must be stated.

4.2.2.2 Information on the standardized extracts used in products shall be provided which include (but not limited to);

(i) chemical marker/ biomarker of the standardized extracts
(ii) information on the solvent system used to obtain the standardized extracts
(iii) method of identification of Active Ingredient(s) in the standardized extracts
(iv) method of quantification of Active Ingredients(s) in the standardized extracts

4.2.2.3 Methods used for both identification and quantitative analysis need to be validated

4.2.2.4 Applicants shall refer to Checklist for Protocol Analysis and Analytical Method Validation available in NPRA website for details of the test methods.

4.2.2.5 Quality Control of the Standardized Extracts

(i) Protocol of Analysis for the tests on standardized extracts must be provided.
(ii) Requested tests are listed as below, while specifications should be supported by established monographs/ pharmacopeia:

Tests	Specifications	Results
Appearance/ Organoleptic characteristics		
Qualitative Test: Identification		
Quantitative Assay		
Loss on drying / Water content		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mould Count (TYMC) • Bile tolerant gram-negative bacteria • *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Impurities • Related/ degraded substance • Pesticide residues • Solvent residues		
Adventitious Toxins • Aflatoxins		
Other Tests (any required testing)		

(iii) Certificate of Analysis (CoA) for the standardized extracts need to be attached (**minimum of 2 batches**).

4.2.3 Finished Product Formulation

4.2.3.1 Description/ Physical characteristics/ Appearance/ Organoleptic characteristic

4.2.3.2 Information on the complete formulation of the product which include:

(i) Scientific name of the ingredient and the part used
(ii) Name of active ingredient(s)/ Standardized extract(s)
(iii) Name of other ingredients(s) e.g. adjuncts, excipients, preservative, colour, flavours
(iv) Strength of each ingredient

4.2.3.3 Standardization of Extract

For example: The extract is standardized to contain:
-X% of compound A (assayed by HPLC/UV etc)
-Y% of compound B (assayed by HPLC/UV etc)

4.2.3.4 Quality Control of Finished Product

(i) Protocol of Analysis for the tests on finished product must be provided.
(ii) Methods used for both identification and quantitative analysis need to be validated
(iii) Tests and Specification Limits (Shelf-life and Release Specifications)

Tests	Specifications	Results
Appearance/Description of the dosage form		
Identification		
Quantitative Assay		
Microbial Contamination Test: - • Total Aerobic Microbial Count (TAMC) • Total Yeast and Mould Count (TYMC) • Bile tolerant gram-negative bacteria • *Salmonella* • *Escherichia coli* • *Staphylococcus aureus* • *Pseudomonas aeruginosa*		
Heavy metal limits: - • Arsenic • Mercury • Lead • Cadmium		
Uniformity of weight (for tablets & capsules)		
Disintegration (for pills, tablets & capsules)		

Tests	Specifications	Results
Impurities • Related / degraded substance • Pesticide residues • Solvent residues		
Adventitious Toxins • Aflatoxins		
Other Tests (any required testing)		

(iv) Certificate of Analysis (CoA) for the finished products need to be attached (**minimum of 2 batches**).

4.2.3.5 Validation of Analytical Method (Microbial Contamination Test, Heavy Metal Test and Quantitative Assay of the Finished Product)

Validation Reports must be submitted and their contents should include:

(i) Introduction
(ii) Specificity
(iii) Repeatability
(iv) Linearity
(v) Range
(vi) Accuracy
(vii) Precision
(viii) Precision (intermediate precision/ruggedness)
(ix) System suitability testing
(x) Detection Limit (if applicable)
(xi) Quantitation Limit (if applicable)
(xii) Conclusions

Applicant shall refer to Checklist for Protocol Analysis and Analytical Method Validation available in NPRA website for details of the data to be submitted.

4.2.3.6 Information on the laboratory/ies

If quality control tests are conducted by an external laboratory, the following information should be stated:

(i) Name and address of the laboratory
(ii) Type of tests conducted by the external laboratory
(iii) Reasons why the tests are not performed by the manufacturer

4.2.4 Stability of Product

a) Storage condition to be included on the label.

b) Proposed shelf life.
- Stability studies/ completed stability studies/ accelerated stability studies should include summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies.
- Stability studies results/data for 2 batches are required.

c) Outline of on-going or proposed stability studies
- Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

4.2.5 Containers/ Packaging

a) Immediate containers/ packaging
- Type
- Material
- Capacity, where applicable
- Closure and liner (type and material), where applicable

b) Other container(s)/ packaging(s)

c) Dose-measuring device/ applicators/ administration set/ etc. if any
- Description/ Type
- Material
- Capacity, where applicable

d) Packaging inclusions (desiccant, filler, etc.) if any
- Description and compositions

e) Any known interaction between the product and packaging material, if any.

4.3 NON-CLINICAL DOCUMENT (PART III)

Primary purpose: To provide a comprehensive, factual synopsis of the non-clinical data. The non-clinical studies should be conducted prior to the initiation of any clinical studies. Therefore, the interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the natural product should be addressed in the nonclinical overview.

In vitro studies as well as animal studies (*in vivo*) are intended to generate the non-clinical data. Data from animal study should be derived from animal model which can represent human condition related to claim. The methodology should be an acceptable and valid procedure to measure the parameter. Data from animal studies are important to give the preliminary efficacy and safety data prior to the conduct of human study. When data from animal (*in vivo*) and *in vitro* studies are submitted as substantiation of claims, an explanation on its relevance to humans should be included.

Requirements:

4.3.1 Should present an integrated and critical assessment of the pharmacologic, pharmacokinetic and toxicologic evaluation.

4.3.2 Relevant scientific literature of related active ingredient(s) of product can be considered as an additional supporting document.

4.3.3 Non-clinical studies must be conducted in OECD GLP compliance facility.

4.3.4 Content and Structural Format:
4.3.4.1 Overview of the Nonclinical Testing Strategy
4.3.4.2 Pharmacology
4.3.4.3 Pharmacokinetics
4.3.4.4 Toxicology
4.3.4.5 Integrated Overviews

4.3.5 Nonclinical Written Summaries Format:
4.3.5.1 Introduction
4.3.5.2 Pharmacology written summary
4.3.5.3 Pharmacology tabulated summary
4.3.5.4 Pharmacokinetics written summary
4.3.5.5 Pharmacokinetics tabulated summary
4.3.5.6 Toxicology written summary
4.3.5.7 Toxicology tabulated summary

4.4 CLINICAL DOCUMENT (PART IV)

Primary purpose: The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies.

Scientific data should be derived from intervention human studies, that are well designed in accordance with recognized scientific principles, with statistically and clinically significant outcomes addressing the specific traditional claim. The acceptable principles for human studies can be referred to internationally accepted guidelines, for example, ICH-GCP Guidelines.

Requirements:

4.4.1 Should describe and explain the overall approach to the clinical development of a product.

4.4.2 Assess the quality of the design and performance of the studies, and to include a statement regarding GCP compliance.

4.4.3 Scientific evidence from human studies on end-product.

4.4.4 Content and Structural Format of Clinical Overview:
4.4.4.1 Product Development Rationale
4.4.4.2 Overview of Natural Product Formulations
4.4.4.3 Overview of Clinical Pharmacology
4.4.4.4 Overview of Efficacy/Claim benefits
4.4.4.5 Overview of Safety
4.4.4.6 Benefits and Risks Conclusions

4.4.5 Clinical Written Summaries Format:
4.4.5.1 Product Development Rationale
4.4.5.2 Overview of Natural Product Formulations
4.4.5.3 Overview of Clinical Pharmacology
4.4.5.4 Overview of Efficacy
4.4.5.5 Overview of Safety
4.4.5.6 Benefits and Risks Conclusions

4.4.6 Relevant scientific literature of related active ingredient(s) of product can be considered as an additional supporting document. Any deviation should be discussed and justified.

Examples of scientific evidence:

- Evidence obtained from at least one properly designed randomized controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice.

- Evidence can be obtained from well-designed controlled trials with or without randomization.
- Systematic reviews of the clinical research relating to particular subject areas
- Peer reviewed scientific data or meta-analysis (these evidences must be product specific and published in reputable peer reviewed journals)

Where there are differences between the ingredient and reported therapeutic benefit, a justification will be required in your evidence package to address the discrepancy.

Non-clinical studies, cellular or pharmacological studies, these alone are not considered sufficient evidence to support a scientific indication. However, such studies can be used to provide secondary support to human data.

Internationally recognised monographs and pharmacopoeias can also provide additional support to specific indications referring to health enhancement claims, but such items will need further evidentiary support from primary research articles and/or systematic reviews. The more specific the indication, the more evidence you need to provide to support your indication.

5.0 GLOSSARY

Active ingredient - The therapeutically active component in a medicine's final formulation that is responsible for its physiological action

Clinical Trial/ Study - Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Efficacy – a relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Product - a drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose; or a drug to be used as an ingredient of a preparation for a medicinal purpose.

Scientific evidence – a quantifiable data and usually includes reports of clinical trials in humans, human epidemiological studies, animal studies and other cellular or pharmacological studies. Due to the quantifiable nature of scientific evidence, scientific indications can imply clinical efficacy where the indication is supported by such data.

6.0 REFERENCES

1. Final concept paper on the implementation of different levels of scientific evidence in core-data for herbal drugs. EMEA/CPMP/ HMPWP/1156/03
2. Guidelines on the evidence required to support indications for listed complementary medicines, Therapeutic Good Administration (TGA), Version 3.0, January 2019.
3. General guidelines for methodologies on research and evaluation of traditional medicine, WHO/EDM/TRM/2000.1
4. Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption (Appendix D5: Pharmaceutical Data Format for Herbal/ Natural Products in Clinical Trials),
5. Drug Registration Guidance Document (DRGD) – available at website *www.npra.gov.my*
6. ASEAN Common Technical Dossier/ Requirements (ACTD/ ACTR)
7. Malaysian Standard Guideline on Good Agricultural Practice (GAP) – Part 8: Herbs MS: 1784-8:2009
8. Annex VII ASEAN guidelines on claims and claims substantiation for traditional medicines (Version 2.0)
9. Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products. EMA/HMPC/162241/2005 Rev. 2