GUIDELINE ON NATURAL PRODUCTS WITH THERAPEUTIC CLAIM

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National Pharmaceutical Regulatory Agency

Ministry of Health Malaysia

Foreword

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) employees, 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.

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Government agencies:

i) Institute Penyelidikan dan Perubatan (IMR)
ii) Bahagian Perubatan Tradisional & Komplementari, KKM (BPTK)
iii) Institute Penyelidikan Perhutanan Malaysia (FRIM)
iv) Clinical Research Centre (CRC), Hospital Serdang
v) Bahagian Pembangunan Kesihatan Keluarga, KKM
vi) Bahagian Kawalan Penyakit, KKM
vii) Bahagian Perkembangan Perubatan, KKM
viii) Bahagian Amalan Perubatan, KKM
ix) Bahagian Amalan dan Perkembangan Farmasi, KKM
x) Bahagian Penguatkuasaan Farmasi, KKM

1.0 INTRODUCTION

This guideline aims to provide information on the type of evidence required to support a therapeutic claim for natural product for human use. Natural products shall not include any sterile preparation, vaccines, any substance derived from human parts and any isolated substances.

Natural products are required to be registered with the Drug Control Authority (DCA) before they can be marketed in Malaysia. Consumers have the right to know what scientific evidence or traditional knowledge that exists to support any claim made on the product label. Public must have confidence when purchasing these products.

All claims made for natural products should have adequate evidence to support all indications and demonstrate all claims made for the medicine are true, valid and not misleading.

2.0 SCOPE OF THIS GUIDELINE

This guideline encompasses the type of evidence to support natural products with therapeutic claim for human consumption and it is applicable to products containing plant/herbal medicinal ingredients.

3.0 PRINCIPLES OF NATURAL THERAPEUTIC CLAIMS

Herbal products with therapeutic claim must be supported by scientific evidence in order to substantiate their claimed action.

Claims should primarily be based on evidence provided by well-designed human intervention studies on the end-product. The study must show a consistent association between the active ingredient/herbal ingredient(s) and the health effect.

4.0 REGULATORY/REGISTRATION REQUIREMENTS FOR NATURAL PRODUCTS WITH THERAPEUTIC CLAIMS

The requirements for registration of natural product with therapeutic claims shall be in accordance to 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) 2.1.1 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); and
- Part IV - Data to support product safety and efficacy (Clinical Document).

IMPORTANT NOTES:

Natural product with therapeutic claims must be manufactured in a Good Manufacturing Practice (GMP) Compliance premise which follows Pharmaceutical Inspection Co-Operation Scheme-Guide to Good Manufacturing Practice for Medicinal Products (PIC/S) guideline.

Non-clinical safety study for therapeutic claims must be conducted in a facility which comply to Organisation for Economic Coorperation and Development (OECD) *Good Laboratory Practice* (GLP) requirement as mentioned in *(40) dlm.BPFK/PPP/07/25 Bil. 9 Tahun 2016 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 timeline for evaluation is within 245 working days.

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

4.1 QUALITY DOCUMENTS (PART II)

Primary purpose: The quality of herbal ingredient, herbal preparations and herbal medicinal products is determined by the quality of the starting plant material, development, in-process controls and process validation, and by specifications applied to them throughout development and manufacture.

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

Required information:

4.1.1 Finished product

- Description/Physical characteristics/Appearance/Organoleptic Characteristic
- Composition (Complete formula) which include:

  -Scientific name of the herbal ingredient and the part of plant used

  -Name of active ingredient(s) / Standardized extract (s)

  -Name of other ingredients(s) e.g. adjuncts, excipients, preservative, colour, flavours

4.1.2 Standardisation of Extract

- For example: The extract is standardised to contain:

  -X% of compound A (assayed by HPLC/UV etc)

  -Y% of compound B (assayed by HPLC/UV etc)

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

4.1.3 Information on the laboratory/ies

If quality control tests are done by an external laboratory, state:

- Name and address of the laboratory
- Tests done by the external laboratory
- Reasons why the tests are not done by the manufacturer

4.1.4 Specifications of the Standardised Extracts

Tests	**Specifications**	**Results**
Appearance		
Qualitative Assay:		

Identification / Chemical fingerprint		
Quantitative Assay		
Loss on drying/Moisture		
Solubility		
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		
Other Tests (any required testing)		

*Certificate of Analysis for The Standardised Extracts need to be attached (**minimum of 2 batches**).

4.1.5 Method of Identification of Active Ingredient(s) in the Standardised Extracts

4.1.6 Method of Analysis of Active Ingredients(s) in the Standardised Extracts

- Both methods used for identification and quantitative analysis need to be explained
- Applicant shall refer to Checklist for Protocol Analysis and Analytical Method Validation available in NPRA website for details of the test methods.

4.1.7 Finished Product Quality Control

- Protocol of Analysis for finish product tests.

- Tests and Specification Limits (Check and Release Specifications)

Tests	Specifications	Results
Appearance		
Quantitative Assay		
Loss on drying/Moisture		
Solubility		
Microbial Contamination Test o Total Aerobic Microbial Count (TAMC) o Total Yeast And Mould Count (TYMC) o Bile tolerant gram negative bacteria o *Salmonella* o *Escherichia coli* o *Staphylococcus aureus* o *Pseudomonas aeruginosa*		
Heavy metal limits o Arsenic o Mercury o Lead o Cadmium		
Uniformity of weight		
Disintegration		

*Certificate of Analysis (CoA) must be certified by Quality Assurance Manager. CoA of 2 recent batches should be submitted.

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

Validation Reports need to be submitted & the contents of Validation Reports should include:

- Introduction
- Specificity
- Repeatability
- Linearity
- Range
- Accuracy
- Precision
- Precision (intermediate precision/ruggedness)
- System suitability testing
- Detection Limit (if applicable)
- Quantitation Limit (if applicable)
- 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.

4.1.9 Stability of Product

- Storage condition to be included on the label.
- Proposed Shelf life.
    - In the events if the extension of shelf life for clinical trial materials is required, industry will provide supportive data in the form of retest results will be considered.
    - Stability Studies*Completed stability studies/ accelerated stability studies (summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies).
    - Stability studies results of at least one batch is required.
    - On-going/ Proposed Stability Studies

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

4.1.10 Containers/ Packaging

- Immediate containers/ packaging
  - Type
  - Material
  - Capacity, where applicable
  - Closure and liner (type and material), where applicable
- Other container(s)/ packaging(s)
- Dose-measuring device/ applicators/ administration set/ etc., if any
  - Description/ Type
  - Material
  - Capacity, where applicable
- Packaging inclusions (desiccant, filler, etc), if any
  - Description and compositions
- Any known interaction between the product and packaging material, if any.

4.2 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

Requirements:

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

- GLP status for non-clinical studies

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

- Content and Structural Format:
  1. Overview of the Nonclinical Testing Strategy
  2. Pharmacology
  3. Pharmacokinetics
  4. Toxicology
  5. Integrated Overviews

- Nonclinical Written Summaries Format:
  1. Introduction
  2. Pharmacology written summary
  3. Pharmacology tabulated summary
  4. Pharmacokinetics written summary
  5. Pharmacokinetics tabulated summary
  6. Toxicology written summary
  7. Toxicology tabulated summary

4.3 CLINICAL DOCUMENT (PART IV)

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

Requirements:

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

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

- Scientific evidence from human studies on end-product.

- Content and Structural Format of Clinical Overview:
  1. Product Development Rationale
  2. Overview of Herbal Formulations
  3. Overview of Clinical Pharmacology
  4. Overview of Efficacy/Claim benefits
  5. Overview of Safety
  6. Benefits and Risks Conclusions

- Clinical Written Summaries Format:
  1. Product Development Rationale
  2. Overview of Herbal Formulations
  3. Overview of Clinical Pharmacology
  4. Overview of Efficacy
  5. Overview of Safety
  6. Benefits and Risks Conclusions

POINTS TO NOTE:

- Relevant scientific literature and related active ingredient(s)/ herbal 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.
  - Evidence obtained from well-designed studies such as epidemiological cohort and case-control studies.
  - Evidence obtained from multiple time series with or without intervention.
  - 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 support your indication.

5.0 Extension of Alphabets for Natural Products With Therapeutic Claim

The registration number of Natural products with therapeutic claims starts with 'MAL', followed by eight numbers, and ending with the letter B.

6.0 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.

Herbal medicine – Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products.

- **Herbal ingredient:** crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.
- **Herbal materials:** in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.
- **Herbal preparations:** the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include

preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

- **Finished herbal products:** herbal preparations made from one or more herbs. If more than one herb is used, the term mixture herbal product can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

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.

Systematic reviews - reports of the outcome of analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. In a systematic analysis only those trials that meet a number of pre-set conditions in relation to research design (for example: sample size, randomisation) are included in the final meta-analysis. Cochrane Reviews are examples of such systematic reviews.

7.0 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