MOH/S/IMR/92.23(GU)-e

GUIDELINE FOR

HERBAL MEDICINE RESEARCH

NATIONAL COMMITTEE FOR RESEARCH AND DEVELOPMENT OF HERBAL MEDICINE
(NRDHM)
MINISTRY OF HEALTH MALAYSIA

FIRST EDITION

MINISTRY OF HEALTH MALAYSIA

NATIONAL COMMITTEE FOR RESEARCH AND DEVELOPMENT OF HERBAL MEDICINE (NRDHM)

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Foreword

Herbal medicine is widely used in Traditional and Complementary Medicine (T&CM) practices. With its increasing use within the Malaysian community, there needs to be more specific guidance on the requirements for herbal medicine research to produce evidence-based herbal medicine products with therapeutic claims. Therefore, the pathway of herbal product development involving preclinical and clinical research must be well outlined in tandem with the 'Guideline on Natural Products with Therapeutic Claim' from the regulators.

The primary purpose of this guideline is to provide structured guidance to be utilised by researchers, academicians, clinicians, T&CM practitioners, and relevant stakeholders of the herbal industry. This guideline outlines a concise yet informative description of the prerequisites and processes involved in planning and conducting herbal medicine-related research in the Malaysian context.

This guideline will bridge the gap often associated with the population's demand for other treatment options besides conventional medicine. This effort will also help accommodate the growing interest in herbal medicine research and spur the discovery of herbal products with therapeutic claims in Malaysia.

Finally, I congratulate the working group involved in documenting this guideline. My sincere gratitude goes to the National Committee for Research and Development of Herbal Medicine members for their invaluable contribution to this collective endeavour.

Tan Sri Dato' Seri Dr. Noor Hisham bin Abdullah
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The successful completion of this document well within the specified timeline would not be possible without the endorsement of the National Committee for Research and Development of Herbal Medicine (NRDHM) Main Committee members. Special gratitude to the NRDHM Technical Committee members for their expertise, knowledge-sharing and commitment during the multiple sessions of drafting and reviewing the draft guideline. We would also like to thank the Head of Units of Herbal Medicine Research Centre, Institute for Medical Research for their immeasurable technical contribution.

Last but not least, appreciation is also due to the relevant institutes/divisions under the Ministry of Health, public universities and local T&CM and herbal industry stakeholders for contributing their insightful comments and suggestions.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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ABBREVIATIONS

CA	Competent Authority
CTIL/CTX	Clinical Trial Import Licence/ Clinical Trial Exemption
DRGD	Drug Registration Guidance Document
EMA	European Medicines Agency
FDI	Food-Drug Interphase
FIH	First-In-Human
FSQD	Food Safety and Quality Division
GACP	Good Agricultural and Collection Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IP	Investigational Product
MOH	Ministry of Health Malaysia
MREC	Medical Research Ethics Committee
MyGAP	Malaysian Good Agricultural Practices Scheme
NIH	National Institutes of Health
NOAEL	'No-observed-adverse-effect' level
NPRA	National Pharmaceutical Regulatory Agency
NRDHM	National Committee for Research and Development of Herbal Medicine
OECD	Organisation for Economic Co-operation and Development
PI	Principle Investigator
TG	Test Guideline
WHO	World Health Organisation

GLOSSARY

Active ingredient

Active ingredients refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardised to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient (World Health Organisation (WHO), 2000).

Biological activity

Biological activity refers to a change in the baseline function of an animal or part of an animal brought about by the administration of a test substance (WHO, 1993).

Characterising compound

A natural constituent of a plant part that may be used to assure the identity or quality of a plant preparation, but is not necessarily responsible for the plant's biological or therapeutic activity. In herbal medicines where the active ingredients or characterising compounds have been identified, the preparation of these medicines should be standardised to contain a defined amount of the active ingredients/ characterising compounds, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine can be considered as one active ingredient (WHO, 1993).

Excipient component/substance

An excipient is a component of a medicine other than the active substance, added in the formulation for a specific purpose. Excipients may be added to extracts in order to adjust the concentration; enhance stability; limit microbial growth; and to improve drying, flow, or other manufacturing characteristics. Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances etc., as well as the component of the outer covering of the medicinal products, e.g. gelatine capsules (EMA, 2007).

Extract

The complex, multi-component mixture obtained after extraction using a solvent to select for, or remove, components of the herbal material. Extracts may be in dry, liquid or semi-solid form. Extracts are not the same as expressed juices, pure chemicals isolated from a herb or synthetically modified plant constituents (Therapeutic Goods Administration (TGA), 2011)

Finished herbal products or herbal medicinal products

Medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations. They may consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixed herbal product can also be used. They may contain excipients in addition to the active ingredients. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin (e.g. animal materials and mineral materials). Generally, finished products or mixed 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 (WHO, 2000).

Herbal materials

Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include 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 (WHO, 2000).

Herbal medicine

A plant-derived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants. In some traditions, materials of inorganic or animal origin may also be present. These include herbs, herbal materials, herbal preparations and finished herbal products. Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities (WHO, 2000).

Herbal monograph

Documentation which provides a basic description of the herb used for therapeutic purpose, and it includes nomenclature, part used, constituents, range of application, contraindications, and side effects, incompatibilities with other medications, dosage, use, and action of the herb. The herbal monograph represents the most comprehensive and critically reviewed body of information on herbal medicine as it elaborates on the scientific information on the safety, efficacy, and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use (Alamgir, 2017).

Herbal pharmacopoeia

Documentation which represents qualitative and therapeutic monographs on botanicals. The pharmacopoeia contains specific monographs governing the quality of specific herbal products (Alamgir, 2017).

Herbal preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials. They are produced with the aid of extraction, distillation, expression, fractionation, purification, concentration, fermentation 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 (WHO, 2000).

Investigational Product (IP)

A pharmaceutical form of an active ingredient including plant/animal-derived medicinal products or placebo or any standardised herbal formulation that is being tested in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use (NPRA, 2021).

Markers

Chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control

purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation (EMA, 2008).

Natural products

Products consist solely of one or more naturally occurring substances of a plant, animal or mineral, or parts thereof. The Malaysian regulation defines natural products to include traditional medicines, finished herbal products, herbal remedy, homeopathic medicines and natural products with therapeutic claim (NPRA, 2022b).

Therapeutic activity/effects

Therapeutic activity refers to the successful prevention, diagnosis, and treatment of physical and mental illnesses. Treatment includes beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being, as well as improvement of symptoms (WHO, 2017).

Therapeutic claims

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 (NPRA, 2022c).

Traditional medicine

Traditional medicine refers to any product used in the practice of indigenous medicine in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and homeopathic medicine. It shall not include any sterile preparation, vaccine, any substance derived from human parts, any isolated and characterized chemical substances ("Control Of Drugs And Cosmetics Regulations", 1984).

Traditional and Complementary Medicine (T&CM)

A form of health-related practice designed to prevent or treat or manage ailments or illnesses or preserve the mental and physical well-being of an individual which includes traditional Malay medicine, traditional Chinese Medicine, traditional Indian medicine, homeopathy, Islamic medical practice and complementary therapies and excludes medical or dental practices used by a medical or dental practitioner respectively ("Traditional and Complementary Medicine Act 2016 (Act 775)," 2016).

INTRODUCTION

1. INTRODUCTION

1.1. OBJECTIVE

In view of the growing interest for clinical research involving herbal medicine in Malaysia, this guideline has been developed following the implementation of the 'Guideline on Natural Products with Therapeutic Claim: Appendix 7B of the Drug Registration Guidance Document (DRGD), 2022' issued by the National Pharmaceutical Regulatory Agency (NPRA) (NPRA, 2022c). The main objective of this guideline is to provide a concise yet informative description on the prerequisites and processes involved in planning and conducting herbal medicine related research in Malaysia. This encompasses the procurement of scientific data, starting from the initial herbal medicine discovery prior to entering the preclinical research stage, followed by the clinical stage of the drug development pathway.

1.2. SCOPE OF THE GUIDELINE

This guideline is intended for research involving formulated natural products utilising or containing herbs. All requirements stated in this guideline have taken into consideration the local and international guidelines and regulations for the conduct of research, specifically pertaining to herbal and natural products. This guideline is tailored to the herbal research environment in Malaysia. Nonetheless, the outlined essential data can be adapted for use in other countries as well, in accordance with their respective regulatory requirements.

It is important to note that these guidelines may not be fully applicable to "traditional preparation of herbs within a particular Traditional & Complementary Medicine (T&CM) practice". It should be clear that T&CM encompasses the entirety of a practice, which includes the practitioners of traditional medicine and/or complementary medicine. These practices may involve the use of herbal therapies, procedure-based treatment (e.g. acupuncture), or both. The overall research on T&CM practice and modalities, especially the procedure-based therapy, is addressed in the 'Framework on Traditional and Complementary Medicine Research in Malaysia' guideline.

1.3. FINISHED HERBAL PRODUCT CATEGORIES

Herbs include plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered (WHO, 2013). Finished herbal products can contain multiple phytoconstituents which may or may not contribute to its desired therapeutic effect. In order to develop products containing herbs as an ingredient, it is important to distinguish between the different product categories, with different regulatory specifications (Figure 1). This is to ensure that the relevant data are produced to enable the product to be marketed in accordance to the respective regulatory requirements.

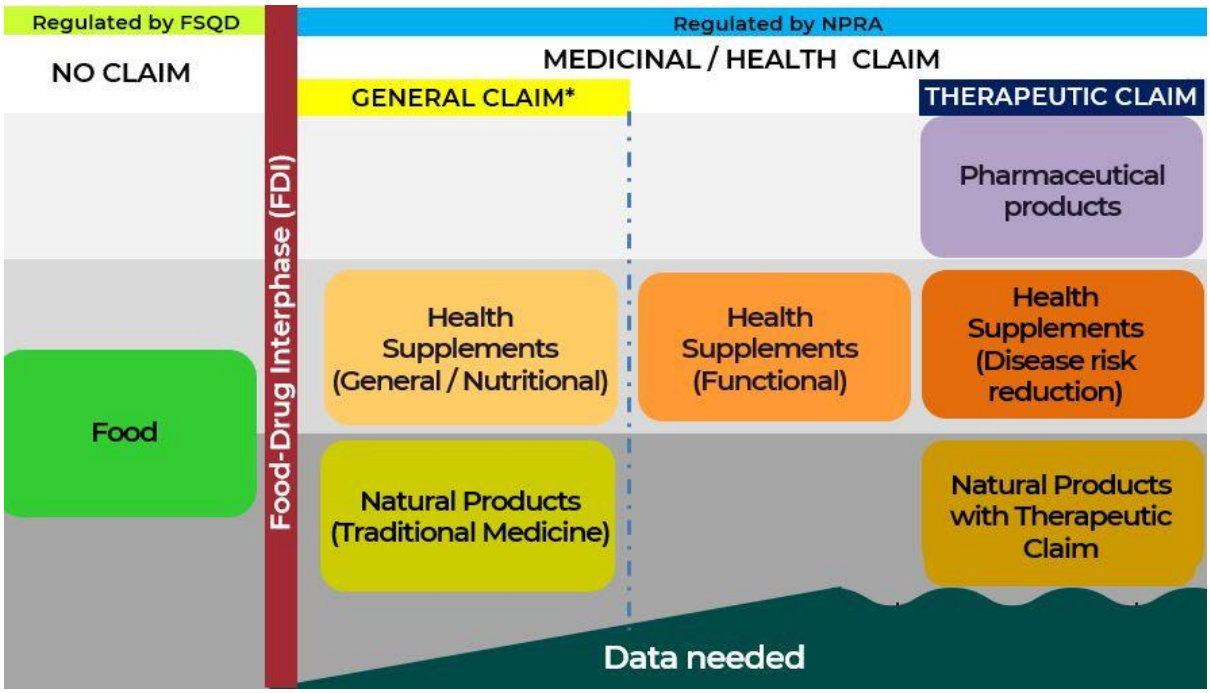

Figure 1: Product categories utilising herbs/herbal materials/herbal ingredients
*General claim: refers to beneficial effects for general health maintenance/wellness, enhancing bodily structure/ function and physical wellbeing, as well as relief of any physiological discomfort.
If the product category lies more to the right of the figure with stronger medicinal claim, more experimental data is required to approve its registration and use.
FSQD: Food Safety and Quality Division. NPRA: National Pharmaceutical Regulatory Agency

As depicted in Figure 1, the regulatory body governing the regulation of different product categories depends on whether there is a medicinal/health claim pertaining to the product in question. It should be clear that "food" should not have any medicinal/health claim, whereby in Malaysia it is regulated under the Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia (MOH). Products with a combination of food ingredients and active ingredients (not

traditionally consumed as food) for oral consumption are termed as Food-Drug interphase (FDI) products (NPRA, 2022a). Examples of food ingredients are fruit, vegetables, meat, poultry, milk, cocoa, and cereal. Examples of active ingredients are vitamins, minerals, herbs, enzymes, probiotics, prebiotics, and other ingredients that are not traditionally consumed as food. FDI itself is not a product category, but an interphase to determine whether the products concerned will be regulated as food (under the FSQD's purview), or a drug (under the NPRA's purview).

The allowable claim for traditional herbal medicines includes general health maintenance and relieving/alleviating mild symptoms. The complete list of these indications acceptable to be applied for traditional herbal medicine is as detailed in 'Appendix 7: Guideline on Registration of Natural Products (DRGD)' (NPRA, 2022b). Therapeutic claim is defined as 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 (NPRA, 2022c).

A health supplement means any product that is used to supplement a diet and to maintain, enhance and improve the health function of the human body. These products may contain substances derived from botanical materials, in the form of extracts or concentrates. The data requirements for registration differ according to the claim proposed. For health supplement products making 'Disease Risk Reduction' claim, it must be substantiated by the evidence from human intervention studies on ingredient and/or product to which it has been supported (NPRA, 2022c). Products that are developed from isolated compounds derived from natural resources or botanicals will not fall under the scope of this guideline.

When herbal medicine in a pharmaceutical dosage form (e.g. capsule, tablet, syrup etc.) is investigated, it should follow the research pathway to meet the product-related data requirements laid out by the NPRA, with reference to the DRGD and the Malaysian Guideline on Clinical Trial Import Licence (CTIL)/ Clinical Trial Exemption (CTX). Herbal medicine products are regulated under the Poisons Act 1952, Sale of Drugs Act 1952, and Control of Drugs and Cosmetics Regulation 1984.

INITIAL RESEARCH AND DISCOVERIES

2. INITIAL RESEARCH AND DISCOVERIES

2.1. OVERVIEW

New herbs or herbal products can be discovered through various approaches. The initial process typically starts with the identification of the plant species of interest, especially those with documented traditional use. The candidate herbs may also be selected through comprehensive literature search based on prospective therapeutic effect from previous studies (Katiyar et al., 2012). This may involve investigating hundreds of potential therapeutic plants or phytochemicals, which are subsequently screened for biological activity. Once the candidate herb(s) is finalised, therapeutic claim validation is through the conduct of preclinical and clinical studies for evidence substantiation prior to its approval for marketed use. The herbal drug discovery pathway is summarised in Figure 2.

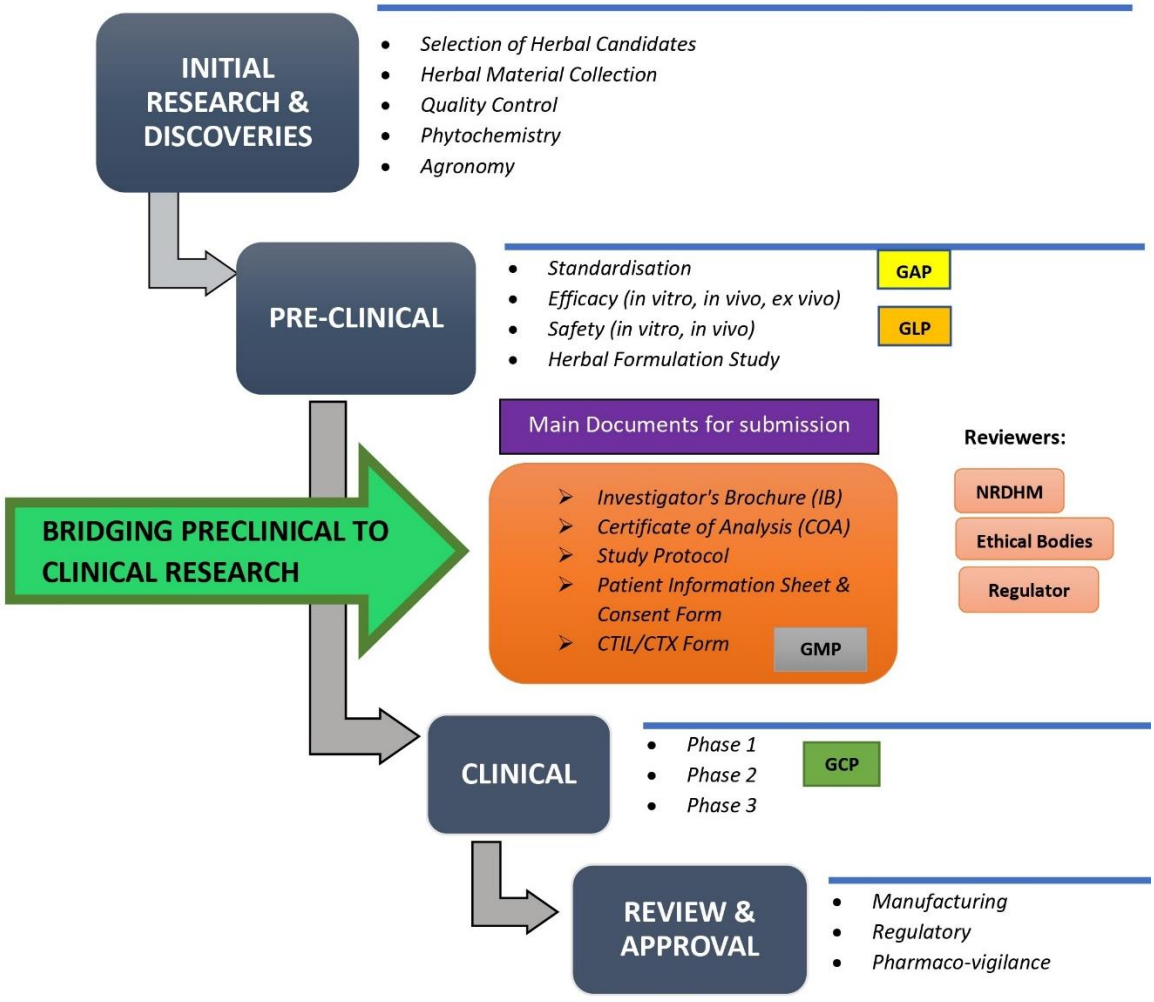

Figure 2: A summary of the pathway for herbal drug discovery
GAP: Good Agricultural Practice; GLP: Good Laboratory Practice; GMP: Good Manufacturing Practice; GCP: Good Clinical Practice; NRDHM: National Committee for Research and Development of Herbal Medicine

2.2. SELECTION OF HERBAL CANDIDATES

Traditional Knowledge

The selection of herbal material for research can be accomplished by screening through literature of traditional knowledge on plants known to have therapeutic uses and by getting records from traditional practitioners who employ these herbs in their practice. The literature can be found in historical published sources including books of medical practice in Ayurveda (e.g., *Charaka Samhita* (Samhita, 1949)), Traditional Chinese medicine (e.g., *Ben Cao Gang Mu: Compendium of Materia Medica* (李時珍, 1826)), Unani (e.g., *Firdaus al-Hikmah* (al-Tabari, 1981)), Siddha (e.g., *Thiruvalluvar's Thirukkural*), and traditional Malay medicine (e.g., *Kitab Tib* (Piah, 2006)), as well as peer-reviewed scientific journal publications about the prior use of the herbs in traditional foods and remedies.

Recent research undertaken by the Forest Research Institute Malaysia (FRIM) has recorded the usage of medicinal herbs by the various groups of *Orang Asli* and practitioners of traditional Malay medicine in Peninsular Malaysia. The research data and knowledge has been published as well as kept by the Intellectual Property Corporation of Malaysia (MyIPO) in an effort to protect intellectual property. For the indigenous group of Sarawak, extensive documentation has been conducted by Sarawak Biodiversity Centre, while in Sabah, the effort is led by Sabah Biodiversity Centre. The documentation work has generated a number of publications that can serve as references for future research activities. A list of approved reference books on traditional knowledge and herbal medicinal plants in Malaysia, used and cited by the Malaysia Traditional Knowledge Digital Library (MyTKDL), is available via the MyIPO Portal (MyIPO, 2013).

Published Literature

Various sources of credible published literature from peer-reviewed scientific journals with strong research methodology and data collection can also provide data and information on promising herbs with therapeutic effects.

Preliminary Screening

One of the initial steps in the drug development process is evaluating numerous extracts, fractions, or pure compounds to determine if they induce the desired chemical reaction such as anti-oxidation or biological activity at the level of the model organism, cell, pathway, or molecule. The in vitro experimentation offers early insights into the biological activity and potential use of the test materials as therapeutic agents. High-throughput screening, targeted screening, and physiological screening are just a few of the different screening techniques that could be applied.

In Silico Screening

Drug development has found in silico screening of isolated compounds as possible therapeutic targets to be highly beneficial. For example, molecular docking, molecular dynamics and quantitative structure–activity relationship (QSAR) modelling can be used to screen known phytochemicals for biological activity by predicting their binding mechanism and affinity, as well as analysing their binding capabilities within the 3D structure of proteins related to specific disease conditions (Patil et al., 2022). Consequently, herbal materials containing biologically active phytochemicals may be chosen as the subject of a study for the therapeutic target.

2.3. HERBAL MATERIAL COLLECTION

Herbal material collection is crucial to systematic herbal medicine research. The materials could be collected from either wild or cultivated sites. Adulteration of different species, varieties or different plant parts during the collection process must be avoided (EMA, 2006). The harvesting method must not have detrimental effects on the plant growth and surrounding environment in order to ensure the optimum conditions for herbal materials to regenerate.

Wild Plant Collection

Medicinal plants/herbal substances from species that are listed as endangered (CITES, Convention on International Trade in Endangered Species of Wild Fauna and Flora) must not be collected unless the relevant Competent Authority (CA) has

given its authorisation. Collectors of medicinal plants/herbal substances should be informed and made aware of all issues relevant to the protection of the environment and conservation of plant species. This will include information on regulations related to protected species.

Cultivated Plant Collection

Collection of authentic herbal materials from the cultivated sites is preferred over collection from the wild in order to ensure sustainable raw materials supply and uniform quality. According to the 'Guideline on Natural Products with Therapeutic Claim' (NPRA, 2022c), medicinal plants collected from cultivated sites should adhere to relevant good agricultural and collection practice (GACP) guidelines, such as the WHO GACP guidelines (WHO, 2003) and the Malaysian Good Agricultural Practice Scheme (MyGAP). MyGAP is a comprehensive certification scheme for the agricultural, aquaculture, and livestock sectors based on Malaysian Standard MS 1784: 2016, Good Agricultural Practice (GAP) - Crop Commodities (Ministry of Agriculture and Food Security (MAFS), 2022). The scheme is intended to be utilised by farm owners in order to produce fresh quality products which are safe to be consumed. It is recommended that the studied herbal raw materials originate from farmers/farming companies with MyGAP accreditation or its equivalent.

Access to Biological Resources and Benefit Sharing (ABS) Act 2017 (Act 795)

Being the 12th biodiverse country, Malaysia has to safeguard its resources from biopiracy and has internationally ratified the Convention of Biological Diversity (CBD) in December 1993. The objectives of the CBD are:

i. Conservation of biological diversity,
ii. Sustainable use of its components and
iii. To ensure fair and equitable sharing of the benefits arising out of the utilization of genetic resources.

The Nagoya Protocol is a supplementary agreement to the CBD that supports the implementation of the third objective. In 2017, Malaysia has enacted the ABS Act to implement the CBD and Nagoya Protocol, dealing with access to biological resources and traditional knowledge associated with biological resources and the

sharing of benefits arising from their utilization. This Act has been enforced in Malaysia since 18 December 2020.

The ABS Act governs the access and use of biological resources, and the fair and equitable sharing of benefits that might arise from the utilisation of the biological resources between the users and providers ("Access to Biological Resources and Benefit Sharing Act 2017 (Act 795)," 2017). In Malaysia, “biological resource” includes:

i. The genetic resources, organisms, microorganisms, derivatives, and parts of the genetic resources, organisms, microorganisms, or derivatives;
ii. The population and any other biotic component of an ecosystem with actual or potential use or value for humanity; and
iii. Any information relating to (i) and (ii).

Traditional knowledge associated with a biological resource is also recognised as a resource covered by the Act. The biological resource can be ‘in-situ’ or ‘ex-situ’ (Figure 3). In-situ refers to ecosystems or natural habitat and ex-situ is when the biological resource is found in botanical gardens, commercial, or universities’ collections. The users are researchers, universities, and industries while the providers can be the Federal Government or State Authority, indigenous and local community or an individual.

According to the Act, a person is said to have access to a biological resource if:

i. The taking of a biological resource from its natural habitat or place where it is kept, grown or found, including in the market for the purpose of research and development; or
ii. There is a reasonable prospect as determined by the CA that a biological resource taken by the person will be subject to research and development.

For all interested parties, especially researchers, the action of “taking” as interpreted in the Act involves acquisition:

i. In relation to an animal: to harvest, catch, capture, trap and kill or obtain in any other way;
ii. In relation to a plant specimen: to collect, harvest, pick, gather and cut or obtain in any other way;
iii. In relation to other biological resources including microorganisms: to collect, pick or obtain in any other way; or

iv. To obtain a biological resource in any other way.

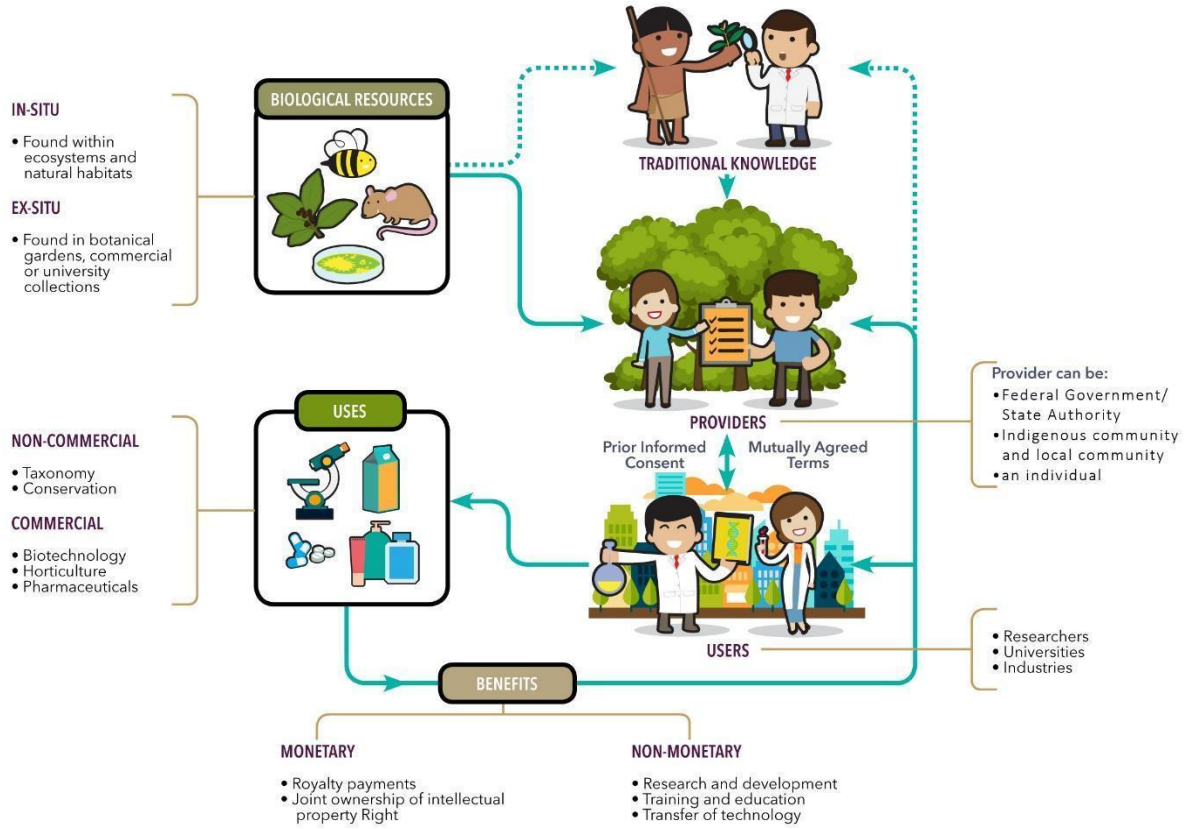

Figure 3: Illustration of the Concept of ABS Act (Act 795)
(Courtesy of the Ministry of Energy and Natural Resources, 2017)

The users are required to obtain a permit prior to the start of research, which can be categorised into:

i. Non-commercial research; and
ii. Potential commercial / Commercial research

The permit must be applied to the relevant CA where the biological resource is to be obtained from. The CA is in every state of Malaysia, with separate state regulations, requirements, and fees. For potential / commercial research, a "Prior Informed Consent with a Mutually Accepted Terms" document has to be signed between the user and provider. Templates of the mutual benefit agreement are available in the 'User's Guide to the Access to Biological Resources and Benefit Sharing Act 2017 [Act 795], 2021' guideline (Malaysia Biodiversity Centre (MBC), 2021). Failure to obtain a permit prior to conducting research may result in penalisation with a fine being imposed upon the researcher. Further details

regarding the Act and permit application processes can be reviewed at www.myabs.ketsa.gov.my.

Sarawak and Sabah have similar state laws, and permits can be applied from the Sarawak Biodiversity Centre (SBC) and Sabah Biodiversity Centre (SaBC) respectively. Access to biological resources for research and development, as defined under the Sarawak Biodiversity Centre Ordinance 1997, requires application via the Sarawak Online Research Application System (SORAS). The guidelines for research application through SORAS can be accessed at www.sbc.org.my. To access biological resources in Sabah, the researcher is required to have an access licence applied, which is to be submitted to the Sabah Biodiversity Council via www.sabcapps.sabah.gov.my.

Botanical Authentication

Once the herbal material has been collected, the botanical sample has to be authenticated. Plants typically have distinct morphological characteristics that define their species, as well as morphological discontinuities that serve as species boundaries. Therefore, botanical identification by morphology is an accurate and rigorous means of confirming the specimen's identity (Applequist & Miller, 2012). In addition, authentication may also be supplemented with data from DNA-based identification techniques such as DNA sequencing or DNA barcoding (British Pharmacopoeia Commission, 2018), which has also become an invaluable tool to detect adulteration in herbal raw materials (Ichim, 2019).

The candidate herbs for the study must be certified by a qualified botanist through voucher specimen authentication. A voucher specimen is defined as botanical reference material associated with a specific lot, or batch of biomass, and as such serves to document the identity and authenticity of the plant material for research purposes (Hildreth et al., 2007). Proper identification of the plant and plant parts, including organoleptic, macroscopic and microscopic examination should be provided. If more than one variety of a given species is used, each should be specified and retained for each batch. A certificate of authenticity signed by a trained botanist is mandatory, for each herbal raw material in the investigational product (IP). Researchers can approach Kepong Herbarium (KEP) FRIM or experts

from public universities with established herbaria (e.g. UKM, UM, UPM) for these services. Studies utilising misidentified or low-quality herbs will produce evidence with questionable reliability.

2.4. QUALITY CONTROL OF HERBAL MATERIALS, PREPARATIONS AND FINISHED PRODUCTS

For validation of herbal raw materials or candidates to be investigated, investigators should follow specifications outlined in certified herbal monographs detailing the quality parameters of the selected herb. Herbal monographs contained in national pharmacopoeias and other authoritative documents serve a crucial role in the quality control of herbal materials, preparations, and finished products (Jamal, 2006).

A monograph is a written specification that describes the principal characteristics of a herbal material/preparation/finished product and gives information and methods for determining these characteristics, allowing for its authentication and quality control for "fitness of use." A pharmacopoeia, on the other hand, consists of a collection of several monographs. These standard specifications are the key documents in a quality assurance procedure to produce herbal products with well-defined quality, safety, and efficacy. The Malaysian Herbal Monograph (Malaysian Herbal Monograph (MHM) Committee, 2015) is currently one of the main references used by pharmaceutical companies in the development of herbal products involving local Malaysian herbs. Other established regional/international pharmacopoeias indexed by WHO (WHO, 2021) may also be used.

In many parts of the world, the quality of herbal materials, preparations and finished products are required to follow the specifications published in the relevant monograph in national pharmacopoeias. For research involving new herbal materials not yet described in any official herbal monograph, new monograph specifications for the herbal raw material, herbal preparation, and finished herbal products must be developed. This document will then be referred to in the quality control procedure during the manufacturing of the product. Common quality control requirements in the development of herbal monographs are available in the 'Guidelines on Natural Products with Therapeutic Claim' (NPRA, 2022c),

'Manufacture of Herbal Medicinal Products (Annex 7) in the Guide to Good Manufacturing Practice for Medicinal Products: Annexes' (Pharmaceutical Inspection Co-Operation Scheme (PIC/S), 2022), 'Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products' (EMA, 2022), and 'Quality Control Methods for Herbal Materials' (WHO, 2011). Validation is required for the qualitative and quantitative methodologies developed for the quality control of herbal raw materials, preparations, and finished products (EMA, 2022).

2.5. PHYTOCHEMISTRY

Selection of herbal markers

The selection of herbal markers for a herbal material/preparation/finished product is determined by the nature and intended use of the herbal medicine's constituents. Generally, there are two categories of markers (EMA, 2008):

i. Analytical markers are constituents or groups of constituents that serve solely for analytical purposes.
ii. Active markers are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

WHO recommends following a selection criterion (WHO, 2017) to determine which marker substance is best used for identification and quantification of the herbal material as follows (in order):

i. If constituents with known therapeutic activity have been identified, they should be used as markers.
ii. If (i) is not the case, but constituent(s) with recognised biological activity are known, they should be used as markers.
iii. If the above cases are not applicable, the identity and quantity of herbal materials, preparations, and medicines may be established by the production process and by analysing marker substance(s) containing other characteristic constituent(s).

The herbal markers should be used as chemical references for qualitative and quantitative assessments during quality control of the specific herbal material, preparation, and finished product. Markers for quantification should be representative of the main therapeutic or pharmacological profiles of the herbal

materials and finished products. Markers for identification should be specific for one plant or for certain plant species and genera. If this is not the case, other marker(s) should be selected for specific identification (WHO, 2017).

Isolation and identification of herbal markers

The isolation of herbal constituent(s) as markers for the defined therapeutic effect must be guided by their biological activity utilising appropriate optimised extraction, various chromatographic and in vitro bioassay techniques. Markers should be detectable and quantifiable with available analytical methods such as thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), liquid chromatography-mass spectrometry (LC–MS), gas chromatography-mass spectrometry (GC-MS) or high-performance liquid chromatography (HPLC). The biologically active compounds may be isolated using a bioassay-guided approach or targeted bioactive compound approach through system biology and metabolomics studies (Mukherjee et al., 2021). The isolated herbal marker needs to be characterised using suitable spectroscopic techniques to elucidate its chemical structure.

Purity determination of herbal markers

Herbal markers isolated from plant sources should conform to international chemical or pharmacopeial standards for reference substances. They must be of high purity needed by national standards of respective countries, as determined by validated physical and chemical analytical procedures (WHO Expert Committee, 2006).

Quantification of herbal markers in herbal preparations and finished herbal products

The amount of herbal marker(s) present in the herbal material, preparation, and finished product, must be quantified using a validated method (e.g. HPLC, LC-MS, or GC-MS) based on the intended therapeutic dose (EMA, 2022). This is to ensure the herbal material actually contains sufficient amounts of the active marker proposed to exert the intended therapeutic effect, reflecting its quality and potential efficacy.

2.6. AGRONOMY

To maintain a regular supply of high-quality herbal raw materials, it is necessary to investigate the agronomic aspects of herb growing, including ecology, biology, chemistry, earth science, and genetics. Innovative agronomic methods and technology are required to increase crop yields and protect against unfavourable climate, weeds, pests, infection, and soil erosion. Standardised agronomic practices as outlined by established guidelines e.g. MyGAP/ WHO GACP should be followed by industries with intent in registering their products under the 'natural products with therapeutic claim' category.

PRECLINICAL RESEARCH

3. PRECLINICAL RESEARCH

3.1. INTRODUCTION

This section is intended to provide guidance on producing the required scientific evidence in herbal medicine research and product development, prior to entering clinical testing. For natural products with therapeutic claim, data requirement differs according to the type of IP intended to be used, intended therapeutic indication, as well as the availability of previous data on documented human use.

3.2. STANDARDISATION

Standardisation is defined as adjusting the herbal drug preparation to a defined content of a constituent or group of substances (Mosihuzzaman & Choudhary, 2008). It involves prescribing a set of standards or inherent characteristics, constant parameters, and definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety, and reproducibility (Sachan et al., 2016). This is achieved by adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts) (EMA, 2010).

For reliable clinical studies and consistent favourable therapeutic effects, standardised herbal medicines of uniform quality and containing well-defined ingredients are needed. The phytochemical components found in a herbal composition determine its pharmacological characteristics. A consistent pharmacological effect is not expected without consistent quality in a phytochemical mixture (Mosihuzzaman & Choudhary, 2008).

There are different declaration requirements for standardisation to be detailed in the monographs of herbal materials and herbal preparations contained in finished herbal products. For instance, to declare standardisation specifications for a herbal material/substance, the following characteristics have to be stated (EMA, 2010):

i. Name of the herbal material/substance.
ii. Quantity of the genuine herbal material/substance (without excipients)
iii. Name and quantity of the active or analytical marker(s) (standardised herbal materials/substances), if applicable.

For example:

Where a herbal medicinal product contains:

- Senna leaf, cut.
- Constituents with known therapeutic activity:
  2.55 % hydroxyanthracene glycosides, calculated as sennoside B.
- Quantity of the genuine herbal substance as a range:
  85 - 96 %. Excipients for adjustment: 4 - 15 %.
- Quantity of the standardised herbal substance (herbal substance and excipients for adjustment) in the herbal medicinal product:
  1.3 g/tea sachet.

The declaration of standardisation should be:
Each tea sachet contains 1.30 g *Cassia senna* L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf), corresponding to 33 mg hydroxyanthracene glycosides, calculated as sennoside B

In the case of standardised extracts, the following characteristics have to be stated in the declaration:

i. Name of the herbal substance used.
ii. Type/physical state of the herbal preparation.
iii. Quantity of the genuine herbal preparation (without excipients)
iv. Name and quantity of the active or analytical marker(s) (standardised herbal preparations), if applicable.
v. Name and composition of extraction solvent(s).

For example:

Where a herbal medicinal product contains:

- Dry extract from Horse chestnut seed
- Constituent(s) with known therapeutic activity: 19 % triterpene glycosides, calculated as anhydrous ßaescin.
- Quantity of the genuine extract (as a range): 70 - 95 % genuine extract.
- DER genuine: 5 – 8 : 1.
- Excipients for adjustment: 30 - 5 %.
- Other excipients: 0 %.
- Extraction solvent: Ethanol 80 % V/V.
- Quantity of the standardised extract (genuine herbal preparation and excipients for adjustment) in the herbal medicinal product:
  200 mg/capsule.

The declaration of standardisation should be:
Each capsule contains 140mg of extract (as dry extract) from *Aesculus hippocastanum* L., semen (Horse chestnut seed) corresponding to 38 mg triterpene glycosides, calculated as anhydrous ß-aescin. Extraction solvent: Ethanol 80 % V/V.

For finished herbal products, a detailed qualitative description is required, including the dosage form, route of administration, and names of all ingredients (including excipients). This must include an added statement that the product is not adulterated with any potent, toxic, or addictive botanical substances, synthetic or highly purified drugs, or other naturally derived drugs. The information on composition or quantitative description of the finished product (i.e., the quantity of the herbal substance) expressed in terms of amount per dosage unit, must be presented in tabulated form as shown in Table 1. For products containing active ingredients, the amount in which they are present in the herbal IP should be declared. For a multi- herb preparation, its composition should be expressed in terms of relative ratio of the individually processed herbal substances or of the individual raw material, whichever is applicable.

For a structured guide in the declaration statement of herbal substances and herbal preparations, investigators can refer to The International Council for Harmonisation (ICH) guidelines 'Declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products' (EMA, 2010).

Type of product	Component	Amount per 1 g tablet
Single-herb product	Senna leaf extract	250 mg
Multi-herb product	1:1 mixture of *Forsythia suspensa* Vahl. flowers extract and *Lonicera japonica* Thunb fruits extract	300 mg of *F. suspensa* Vahl. extract 300 mg *L. japonica* Thunb extract

Table 1: Examples of composition declaration for single/multi-herb products

3.3. EFFICACY STUDIES

Efficacy is a relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. The efficacy of a product and its ingredient(s) must be based on the totality of the substantiation evidence presented, which includes human studies, non-clinical and empirical or historical data, as well as additional documented evidence on the end product, if relevant (NPRA, 2022c). The research must show a clear link between the active ingredient/herbal ingredient(s) and the claimed therapeutic effect. At the preclinical development stage, efficacy studies aim to demonstrate proof-of-principle, and define the pharmacological effects predictive of the human response (EMA, 2020). It is important for herbal medicines, and particularly for those made from mixture herbal products, that the requirements for proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications (WHO, 2000). This will later help in the design and interpretation of the planned toxicokinetic and clinical studies going forward.

For efficacy claims with traditional knowledge, supportive evidence can be presented from any of the following sources:

i. Standard reference (reference textbooks, pharmacopeia, monographs)
ii. Recommendations on usage from reference regulatory authorities or reference organisations
iii. Good quality scientific evidence from preclinical studies (in vitro and in vivo), and human observational studies (case report/studies/series)
iv. Report prepared by expert committees/ expert opinion (subject to authority approval)
v. Published scientific reviews and meta-analysis

The data from these documents can be used to justify and guide further efficacy studies to prove the therapeutic claim. With or without traditional knowledge, all IPs will require pharmacological efficacy data at preclinical level (in vitro and in vivo), ideally explicit to the formulated product intended to be used in future clinical trials. Preclinical efficacy data should include:

i. Primary pharmacodynamics (PD): studies on the therapeutic effects, and mode of action, of a substance in relation to its desired therapeutic target.

ii. Secondary pharmacodynamics: studies on the mode of action and/or effects of a substance not related to its desired therapeutic target.
iii. Bioavailability/pharmacokinetic (PK) studies encompassing:
    - metabolic and plasma protein binding data
    - absorption, distribution, metabolism, excretion (ADME)
    - biochemical drug interaction
    - characterisation of metabolite(s)

Efficacy claims for products with established pharmacological studies at clinical level (if any) should be presented covering safety profiling, and confirmatory study of efficacy in humans. Efficacy data on similar products of the same herb may be used as supportive evidence. The level of evidence and the grading of recommendations must correspond to the nature of the illness to be treated, or the nature of the physical or mental function to be influenced and regulated. In the case of herbal mixtures, it should be highlighted that each individual herb combined in the herbal mixtures must have a medicinal or scientific justification for its inclusion. This is taking into consideration the possibility that efficacy data may differ when the IP consists of multiple herbs due to herb-herb interaction (WHO, 2000).

3.4. SAFETY STUDIES

Herbal safety and toxicity have become an issue of concern due to the wide use and easy availability of herbal medicines. Although herbal medicinal products are widely considered to be of lower risk, they are not completely free from the possibility of toxicity or other adverse effects (De Smet, 2004). Safety pharmacology and toxicological studies are critical in determining the safety of herbal medicinal products where clinical evidence is limited. The data is critical for determining the risk-to-benefit ratio of these herbal materials, guiding preliminary studies, and predicting potential toxicity. In general, preclinical toxicity studies are conducted to determine the ultimate safety profile of herbal products before proceeding with clinical trials. These include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure and potential reversibility. The information obtained is used to estimate an initial safe starting dose and dose range applicable for the clinical trials (U.S. Food Drug Administration (FDA), 2010).

General Toxicity Studies

The objective of toxicity studies is to identify the target organs and/or systems for toxicity and the threshold doses for producing toxic effects. These studies provide information valuable for designing long-term clinical studies at safe doses with appropriate monitoring of adverse effects. Studies must comply with the Good Laboratory Practice (GLP) guidelines for proof of safety on experimental animals prior to its use in human subjects. They can be performed in rodents and/or non-rodents according to specified requirements. Examples of commonly conducted toxicity testing based on the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) for the testing of chemicals (OECD, 2001) include, but not limited to, the following:

i. Acute toxicity testing: single-dose (OECD TG No. 420, 423, 425) (OECD, 2002)
ii. Sub-acute toxicity testing: Repeated dose 28-days oral toxicity studies in rodents (OECD TG No. 407) (OECD, 2008).
iii. Sub-chronic toxicity testing: Repeated dose 90-days (OECD TG No. 408) (OECD, 2018a)
iv. Chronic toxicity testing: Repeated dose from 6 to 12 months (OECD TG No. 452) (OECD, 2018c).

Acute toxicity study is usually an initial screening step in the assessment and evaluation of the toxic characteristics of tested materials. The animals are treated with a single dose of the test material and kept under observation for any clinical signs of toxicity for a period of 14 days. The repeated dose toxicity studies are designed to characterise the toxicological profile of the test materials following repeated administration. This includes identification of toxicity potential on target organs and the relationship of exposure and response produced by the test materials. It also provides an estimate of the no-observed-adverse-effect level (NOAEL) which can be used for establishing safety criteria for human exposure.

The recommended duration of the repeated dose toxicity studies is usually related to the duration, therapeutic indication and scope of the proposed clinical trial. In principle, the duration of the animal toxicity studies conducted in two mammalian species (one rodent and one non-rodent) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the

repeated dose toxicity studies (EMA, 2009). Repeated dose toxicity studies in two mammalian species (one rodent and one non-rodent) for a minimum duration of 2 weeks would generally support any clinical development trial up to 2 weeks in duration. Clinical trials of longer duration should be supported by repeated dose toxicology studies of at least equivalent duration. Six-month rodent and 9-month non-rodent studies would generally support dosing for longer than 6 months in clinical trials (EMA, 2009).

Genotoxicity

Genetic toxicology is the study of adverse effects on a genetic material, deoxyribonucleic acid (DNA) caused by genotoxic materials which may affect the integrity of cells (Krishna & Hayashi, 2000). The mutagenic effects induced by materials can occur in the genome of either somatic or germinal cells. The detection of mutagenic effects in somatic cells is an important factor in the assessment of cancer, while in germ cells alterations can indicate risk of adverse heritable genetic changes (Engineering Biology Research Consortium (EBRC), 2007).

The objective of these studies is to identify any possible genetic toxicity on long-term use. Several methods (in vitro and in vivo) and guidelines for genotoxicity assays have been developed by researchers and regulatory authorities to screen for possible genotoxic materials. In general, every single drug in development will be tested through a battery of genetic toxicology assays. A complete assessment of genetic toxicity through a standard battery of tests is given in the 'ICH S2(R1) Genotoxicity testing guideline' (EMA, 2013), listing two options for testing:

<u>Option 1</u>

i. An in vitro test for gene mutation in bacteria (Bacterial reverse mutation assay).
ii. A cytogenetic test for chromosomal damage (the in vitro metaphase chromosome aberration test or in vitro micronucleus test), or an in vitro mouse lymphoma TK gene mutation assay.

iii. An in vivo test for genotoxicity, generally a test for chromosomal damage using rodent hematopoietic cells, either for micronuclei or for chromosomal aberrations in metaphase cells.

Option 2

i. An in vitro test for gene mutation in bacteria (Bacterial reverse mutation assay).
ii. An in vivo assessment of genotoxicity with two different tissues, usually an assay for micronuclei using rodent hematopoietic cells and a second in vivo assay. Typically, this would be a DNA strand breakage assay in the liver, unless otherwise justified.

Carcinogenicity

The objective of this study is to identify tumorigenic potential in animals and to assess the relevant risk in humans. These studies are conducted by observing test animals for a major portion of their life span for the development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration. They must be conducted if there is concern about the carcinogenic potential of the IP from previous observations of repeat dose toxicity studies. Carcinogenicity studies are also applicable if the expected clinical use is continuous for at least 6 months (OECD TG No 451) (OECD, 2018b).

Developmental and Reproductive Toxicity (DRT)

Reproductive toxicology refers to the study of the adverse effects of test materials on any aspect of the development and reproductive systems. These include any impairment of reproductive function, the induction of adverse effects in the embryo such as growth retardation, malformations and death, and the induction of adverse postnatal effects (Andrew and Michael, 2002). Various test guidelines have been prepared by international regulatory agencies (e.g. U.S. FDA, OECD, ICH, U.S. Environmental Protection Agency) to provide the appropriate methods to be carried out. Below are the standard OECD guidelines for DRT.

i. OECD TG 414: Prenatal developmental toxicity study
ii. OECD TG 415: One generation toxicity study
iii. OECD TG 416: Two-generation toxicity study
iv. OECD TG 426: Developmental neurotoxicity study

v. OECD TG 421 & 422: Reproductive /developmental toxicity screening

Specific Toxicity Studies

Specific toxicity tests should be conducted where relevant, which may include:

i. Local tolerance (skin, eyes, GIT, etc.): to evaluate local tolerance by the intended therapeutic route
ii. Hepatotoxicity, nephrotoxicity
iii. Phototoxicity
iv. Immunotoxicity
v. Juvenile animal toxicity
vi. Abuse toxicity: should be considered for drugs that are distributed into the brain and produce central nervous system activity, regardless of therapeutic indication.

The duration of each respective study should mirror the duration of the IP treatment intended for clinical trial. Any relevant documented safety assessment data in humans (if any) can be used to support safety claims, which may involve:

i. Estimation of initial safety and tolerability
ii. ADME study, PK/PD study
iii. Documentation: in the form of clinical study reports, published clinical papers, periodic safety update reports etc.

Estimation of Safe Human Dose

The calculation of the initial dosage in humans is a critical step in ensuring the safety of individuals in First-in-Human (FIH) clinical trials. When defining the recommended beginning dose in humans, all relevant non-clinical data, such as pharmacological dose response, pharmacological/toxicological profile, and pharmacokinetics, should be taken into account.

The NOAEL calculated in nonclinical safety studies conducted in the most sensitive and relevant animal species provides the most critical information. Various factors, including pharmacodynamics, specific characteristics of the drug, and clinical trial design, can then alter the appropriate dose. The amount of nonclinical supporting data that is appropriate will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration

of dosing. Detailed descriptions on different exploratory clinical approaches are described together with the non-clinical testing programs that would be recommended, which can be found in guidelines published by the European Medicines Agency (EMA) (EMA, 2009), as well as the U.S. FDA (U.S. FDA, 2005).

3.5. HERBAL FORMULATION STUDY

Research on the best dosage form of standardised herbal materials and preparations for the intended therapeutic application is required to guarantee optimal and effective delivery of the active constituents to the targeted body areas. The various dosage forms include tablets, capsules, creams, ointments, solutions, etc. The formulation may contain one or more herbal materials or preparations in a defined quantity to provide the specific therapeutic effect. The profiles of pharmacokinetics and stability of the dosage form must be investigated. It is also necessary to develop quality control specifications for the dosage form.

Good Manufacturing Practice (GMP PIC/S)

Good Manufacturing Practice (GMP) is a standard that should be followed by manufacturers of registered pharmaceuticals/veterinary products/health supplements/traditional products and/or notified cosmetics to ensure that the manufactured products are safe, efficacious and of quality. The manufacturing company must be certified with a GMP certificate, following the 'Pharmaceutical Inspection Cooperation Scheme (PIC/S) – Guide to Good Manufacturing Practice (GMP) for Medicinal Products' guideline (Secretariat of the Pharmaceutical Inspection Convention, 2022). GMP PIC/S certificate application and manufacturing plant inspection in Malaysia is currently handled by the GMP Section, Centre of Compliance and Quality Control, NPRA (GMP Section Centre of Compliance and Quality Control, 2022).

BRIDGING PRECLINICAL TO CLINICAL RESEARCH

4. BRIDGING PRECLINICAL TO CLINICAL RESEARCH

4.1. INTRODUCTION

This section encompasses the process of compiling, presenting, processing and approval of the preclinical data to enter into clinical research. Investigators who have successfully conducted sufficient preclinical research involving a natural product with therapeutic claim will need to prepare a list of documents and obtain relevant certificates for submission to relevant committees as well as the regulatory bodies for the approval of conducting a clinical trial. All research conducted in MOH institutions and facilities should comply with the Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS), and Malaysian Guideline for Good Clinical Practice (GCP) (NPRA, 2018a). These researches must also be registered with the National Medical Research Register (NMRR) (nmrr.gov.my).

4.2. MAIN DOCUMENTS TO BE PREPARED

The documents, required for submission, must be suited to the intended phase of the planned clinical trial, and to the target population and disease to be studied.

i. Investigator's Brochure (IB)
ii. Clinical Trial Protocol
iii. Patient Information Sheet (PIS) & Informed Consent Form
iv. Clinical Trial Exemption (CTX)/Clinical Trial Import Licence (CTIL)

Investigator's Brochure

The IB is a compilation of the non-clinical and clinical data on the IP in human subjects. Its main aim is to give the investigators the knowledge they need to better comprehend, and adhere to several important aspects of the protocol, including the dose, dosing frequency/interval, administration methods, and safety monitoring measures. An example of the summary of contents in an IB for a herbal product following the Malaysian guideline for GCP format is outlined in Table 2.

1	TABLE OF CONTENTS	
2	SUMMARY	
3	INTRODUCTION	Background Rationale for Use History of traditional use Active ingredient Description <u>Herbal Raw Material</u> i. common names of the plant, algae or microscopic fungus, synonyms ii. plant morphology and anatomy iii. name of variety, species, genus, and family iv. natural habitat and geography description v. current sources of herbal materials vi. statement of endangered species <u>Herbal substance or extract</u> i. Ingredients – Plant (s) used in the study; singly or in combination ii. Plant part(s) used in the study e.g., leaves, stem, root, or in combination <u>Marketed product</u> i. Pharmaceutical presentation ii. Current marketed use
4	PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION	Physicochemical properties of herbal/drug substance Quality Control <u>Authentication of medicinal plant</u> i. Physical characterisation (colour, odour, taste) ii. Qualitative assay: Identification • Macroscopic/microscopic • Chemical identification by spectroscopic or chromatographic fingerprints. Spectroscopic methods include ultraviolet, infrared and Fourier transformed infrared. Chromatographic methods include high-performance liquid chromatography (HPLC), HPLC with diode array detection, thin layer chromatography (TLC) and gas chromatography. • Metabolites and phytoconstituents identified in the preparation iii. Quantitative assay: • Strength by weight (equivalent to herbal botanical raw material), test yield (%) • Chemical assay for active constituents or characteristic compound and concentration in herbal preparation • Loss on drying/Water content • Solubility, stability at room temperature • Heavy metals: Arsenic, Mercury, Lead, Cadmium etc. • Microbial limits: Total bacterial count, Yeast and mould, Bile tolerant gram-negative bacteria e.g. *Salmonella, E. coli, P. aeruginosa, S. aureus*

		• Adventitious toxins (e.g. aflatoxin), residual pesticides (if applicable) • Other attributes specific to the botanical raw materials or dosage form of interest for finished product <u>Preparation</u> i. Types of preparation – e.g., Fresh, Freeze-dried. Spray-dried etc. ii. Method of extraction – details of solvent used e.g. aqueous or organic solvent e.g. ethanol iii. Method of filtration, evaporation, drying (if applicable) <u>Formulation</u> i. Standardisation: • Active compound • Ingredients ii. Dosage form iii. Stability of Product • Storage condition • Proposed shelf life • Stability studies: results of at least one batch for a minimum duration of 3 months are required. iv. Containers/ Packaging: description on the types of packaging, materials used, packaging inclusions (desiccant, filler, etc.) if any v. Labelling vi. Storage and handling
5	NON-CLINICAL STUDIES	Non-clinical Test Item Non-clinical Pharmacology Pharmacokinetics and Product Metabolism in Animals Non-clinical Safety Assessment
6	CLINICAL STUDIES	Clinical data: Phase I, II, III Pharmacokinetics and Product Metabolism in Humans Safety and Efficacy Marketing Experience Distribution, Sales volume Phase IV: Post marketing surveillance
7	SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR	Posology and Method of Administration Special Precautions for Use Contraindications Use in Pregnancy and Lactation Drug Dependency/abuse Drug Interactions Overdose

Table 2: Example of content outline in an Investigator's Brochure of a finished herbal product

One section of the IB must be dedicated to provide an overall discussion of the non-clinical and clinical data, and should summarise the information from various sources on different aspects of the IP(s), wherever possible, as a guidance to the investigator(s) involved. It is important to provide the investigator(s) with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions, based on previous human experience and on the pharmacology of the IP. This information should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the IP (NPRA, 2018a).

Clinical Trial Protocol

Clinical trials should be scientifically sound, and described in a clear, detailed protocol. The protocol is a document outlining the design of a study, describing the objectives, methodology, the efficacy, and safety endpoints, statistical considerations and overall organisation of the research, to be carried out forming a template and guide to the research process as a whole. In addition, the protocol may also include the background and rationale for the trial. A summary of the required information is listed in Table 3 (NPRA, 2018a). Current ethical considerations require a qualified medical doctor (or dentist, where appropriate) with GCP training and certification to be named as the Principal Investigator (PI) of the clinical trial. This is owing to the fact that the PI must be fully responsible for all trial related medical (or dental) decisions, as the trial involves the health and safety of human subjects. This applies for all trial sites, in the case of multicentre clinical trials. Other professionals involved in the research can be named as co-investigators.

1. General Information 1.1 Protocol title, protocol identifying number, date, and amendment(s). 1.2 Name, title, address, and telephone number(s) of: • the sponsor and monitor • person(s) authorised to sign the protocol • sponsor's medical expert • investigator(s) who is (are) responsible for conducting the trial, and • trial site(s) • the qualified physician responsible for all trial-site related medical decisions (if other than investigator). • clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial. 2. Background Information 2.1 Name and description of the IP 2.2 Summary of findings from preclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial. 2.3 Summary of the known and potential risks and benefits, if any, to human subjects. 2.4 Description of and justification for the route of administration, dosage, regimen and treatment period(s)	3. Trial Objectives and Purpose 4. Description of the trial design: • description of the population to be studied • the primary endpoints and the secondary endpoints, if any • the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages. • measures taken to minimise/avoid bias, including: (a) Randomisation. (b) Blinding. • trial treatment(s), the dosage and dosage regimen including a description of the dosage form, packaging, and labelling of the investigational product(s). • expected duration of subject participation, the sequence, and duration of all trial periods, including follow-up, if any. • the "stopping rules" or "discontinuation criteria" for individual subjects, parts or entire trial. • accountability procedures for the IP, including the placebo(s) and comparator(s), if any. • maintenance of trial treatment randomisation codes and procedures for breaking code. • identification of any data to be recorded directly on the CRFs 5. Selection and Withdrawal of Subjects: • inclusion, exclusion & withdrawal criteria.	6. Treatment of Subjects • the treatment(s) to be administered, including the name(s) of all the product(s), dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each IP treatment/trial treatment group/arm • medication(s)/treatment(s) permitted (including rescue medication) • compliance monitoring. 7. Assessment of Efficacy 8. Assessment of Safety 9. Statistics • statistical methods for analysis with level of significance • sample size • missing, unused, and spurious data • reporting any deviation(s) from the original statistical plan 10. Direct Access to Source Data/Documents 11. Quality Control and Quality Assurance 12. Ethical considerations relating to the trial. 13. Data Handling and Record Keeping 14. Financing and Insurance 15. Publication Policy

Table 3: Summary of the information required in a clinical trial protocol

Patient Information Sheet (PIS) and Informed Consent Form

These documents are required for all human research subjects by which voluntary consent is obtained after the provision of information on all aspects of the trial that are relevant to the subject's decision to participate. In Malaysia, these documents are written in English and Malay to ensure that the potential subjects have maximum comprehension and understanding regarding the clinical trial. Translation into other languages, for example Chinese and Tamil, is encouraged. A written, signed, and dated form is used to document the informed consent of the subject.

Clinical Trial Exemption (CTX) / Clinical Trial Import Licence (CTIL)

Clinical Trial Exemption (CTX) is granted by the Director of Pharmaceutical Services under Regulation 15 (5) of the Control of Drugs and Cosmetics Regulations 1984 to a person who intends to manufacture product(s) only for the purpose of providing samples for clinical trials to avoid the provisions of Regulation 7 (1) or Regulation 18A of the Control of Drugs and Cosmetics Regulations 1984 (NPRA, 2021).

Clinical Trial Import Licence (CTIL) is a licence in Form 4 of the Schedule of the Control of Drugs and Cosmetics Regulations 1984, issued by the Director of Pharmaceutical Services under Regulation 12 (1) (c) of the same Regulations, allowing the licensee to import any product for clinical trials even if it is not a registered product (NPRA, 2021).

Products that require CTIL/CTX approval include (NPRA, 2021):

i. A product including placebo which is not registered with the DCA and is intended to be imported for clinical trial purposes.
ii. A product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form; AND when used for unapproved indication/ when used to gain further information about an approved use for clinical trial purposes.
iii. A traditional product with a marketing authorisation with an indication for “traditionally used” when used for unapproved indication/ therapeutic claims for clinical trial purposes.

iv. An unregistered product, including placebo, manufactured locally for the purpose of the clinical trial.

Further information regarding specific requirements for application of CTIL/CTX is available in 'Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption 7.1 Edition' at www.npra.gov.my.

4.3. APPROVAL PROCESS

All clinical trials involving use of herbal products or standardised herbal extracts in the form of finished product as the IP will need to go through an approval process prior to commencement of the clinical phase. This process is overseen by different committees and regulatory bodies with different requirements and approval criteria, namely the National Committee for Research and Development of Herbal Medicine (NRDHM), Medical Research and Ethics Committee (MREC) and NPRA as illustrated in Figure 4.

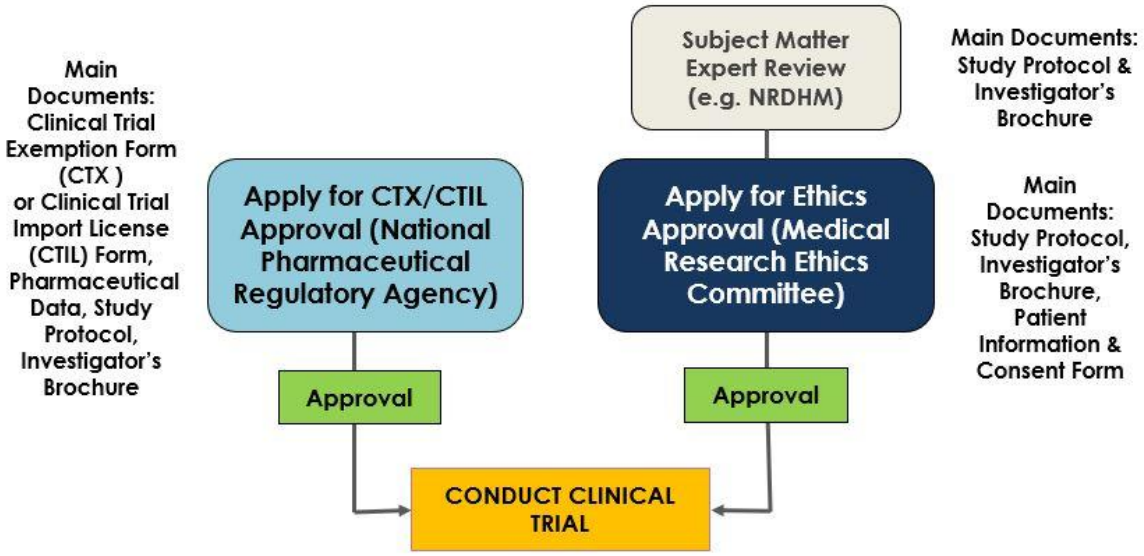

Figure 4: Flowchart of the approval process to conduct clinical trial

Role of National Committee for Research and Development of Herbal Medicine (NRDHM)

NRDHM aims to assist MREC as Subject-Matter Experts (SME) in reviewing the fitness and suitability of the herbal-based IPs intended to be used as an intervention in clinical trials. NRDHM acts to provide a separate and independent review of the scientific merits, quality, standardisation, efficacy, and safety data of

the herbal IPs, detailed in the IPs investigators brochure and clinical trial protocol. However, it is important to note that acknowledgement by the NRDHM does not automatically guarantee the approval by MREC, as NRDHM focuses mainly on the evaluation of preclinical data pertaining to the proposed herbal IP, and not the clinical trial as a whole. A detailed checklist of NRDHM requirements is available under Appendix 2: NRDHM Subject-Matter Expert Review.

Role of Independent Ethics Committee

Once the IP has passed the evaluation of NRDHM's committee, the investigator will subsequently need to acquire approval from MREC. MREC is an independent ethical review board which was established to review health research or other research protocols which involve human subjects and are conducted using facilities or resources from MOH. The investigators will need to submit all the relevant documents, supported by the acknowledgement certificate from NRDHM. Essential documents to be submitted for MREC's approval are as listed in Table 4 (National Institutes of Health (NIH), 2021).

No.	Item
1.	Investigator's Brochure
2.	Signed protocol and amendments, if any, and sample Case Report Form (CRF)
3.	Informed Consent Form (including all application translation)
4.	Any other written information
5.	Advertisement for Subject Recruitment (if used)
6.	Financial aspects of the study (where applicable)
7.	Insurance statement (where required)
8.	Signed agreement between involved parties (where applicable)
9.	Dated, documented approval/ favourable opinion of Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) (where applicable)
10.	Regulatory authority(ies) authorisation/ approval/ notification of protocol (where required)
11.	Curriculum vitae and/ or other relevant documents evidencing qualifications of investigator(s) and subinvestigator(s)

Table 4: Essential documents for MREC submission

Role of the National Pharmaceutical Regulatory Agency (NPRA)

Sponsors need to apply for CTX/ CTIL approval from NPRA for the IP and placebo to be manufactured or imported for use in clinical trials. The submission of CTX/CTIL applications to MREC and NPRA can be done in parallel (Figure 4). The approval from both parties is independent and will not affect the decision made by the other. An investigator or an authorised person from a locally registered

pharmaceutical company/sponsor/Contract Research Organisation (CRO) with a permanent address in Malaysia are eligible to apply for the CTX/ CTIL (NPRA, 2021). Apart from the details in the CTX/ CTIL application form, there are other important supportive documents that are required to be attached and submitted together with the application (Table 5). The details of these additional documents including CTX/ CTIL forms can be downloaded from the NPRA webpage for 'Application Forms for Clinical Trial'.

The complete information on how to apply for CTX/ CTIL can be obtained from the 'Malaysian Guideline for Application of CTIL and CTX' (NPRA, 2021).

No.	Item
1.	Table of content (a content page)
2.	Cover letter
3.	CTIL/CTX application form
4.	Receipt for processing fee (if applicable)
5.	A copy of Company Registration Certificate (if applicable)
6.	A copy of the applicant's Poison Licence Type A for pharmacist in the private sector or Annual Retention Certificate (ARC) for a public pharmacist, whichever applicable
7.	Letter of Authorisation, if applicable
8.	A copy of the opinion(s) of the Ethics Committee (EC) which is/are registered with Drug Control Authority (DCA)
9.	Clinical trial protocol
10.	Declaration by investigator/ principal investigator (PI)
11.	GCP certificate and CV for investigator/ PI of each trial site
12.	Informed consent form (Initial version only for one of the trial sites)
13.	Pharmaceutical data for all products that require CTIL/CTX
14.	Label for all products that require CTIL/ CTX
15.	Good Manufacturing Practice (GMP) Requirement
16.	Investigator's Brochure
17.	Overall risk and benefit assessment
18.	A copy of scientific advice from other regulatory agencies, if available
19.	Evidence of Phase 1 Unit Accreditation by NPRA
20.	Proof of Insurance Cover
21.	Declaration by Sponsor for CTIL/CTX Application Involving First-in-Human (FIH) Clinical Trial
22.	Electronic format (one electronic copy of all documents to be submitted)
23.	Other or additional documents

Table 5: Documents for CTX/CTIL submission

CLINICAL TRIAL

5. CLINICAL TRIAL

5.1. INTRODUCTION

Clinical trials can be defined as research investigations that involve humans as participants where they voluntarily receive specific interventions, new treatments, or tests, in order to prevent, detect, treat or manage various medical conditions (U.S. FDA, 2020; WHO, 2015). The main objectives of the clinical phase are to measure the safety and efficacy of an IP in humans, and to compare the effectiveness of an IP with that of existing standard treatment for a specified condition or disease. A clinical trial can only be conducted once ethical approval has been obtained. The conduct of clinical trials for herbal medicine is similar to those conducted by pharmaceutical companies for conventional medicine or new-found drugs in terms of procedure, regulatory requirements, and execution.

Clinical trials can be sponsored, or funded, by pharmaceutical companies, academic medical centres, voluntary groups, and other organisations (U.S. NIH, 2019). There are two types of clinical trials that can be conducted; Investigator Initiated Research (IIR) and Industry-Sponsored Research (ISR). IIRs are clinical studies which are initiated and managed by an individual investigator, an institution, a collaborative study group or a cooperative group who is/are researcher(s) from non-pharmaceutical companies. Meanwhile, ISRs are clinical studies which are funded by an industry organisation that has contracted with the investigator(s) to conduct clinical trials that involve intervention with diseases or biomedical conditions. For most of the trials, the sponsor designs the study and owns the protocol (Institute of Translational Health Sciences, 2020).

5.2. INVESTIGATOR

An investigator is a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator (PI) (NPRA, 2018a). The PI oversees the overall conduct of the trial, and is often a qualified clinician.

All investigators should meet the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications

through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or the regulatory authority(ies) (NPRA, 2018a). All investigators must obtain GCP certification to be part of a clinical trial study team.

5.3. PHASES OF CLINICAL TRIALS

The conduct of clinical trials can be described in four phases. Each phase has different objectives and specifications.

Phase 1 clinical trials, which usually includes first-in-humans (FIH) studies, are conducted to identify the safety of the IP on healthy human subjects. The Phase 1 trials include studies on determining safe human doses, mode of administration, and how the IP affects the human body (pharmacokinetics). However, for herbal products that have an established history of human use, Phase 1 clinical trials are generally unnecessary. This exception is only applicable if the IP concerned has not been altered or modified in any way, differing from its original formulation as what was previously registered, marketed and used. This is also provided that the IP has sufficient animal toxicity and pharmacokinetics data concerning the clinical formulation and individual ingredients within the formulation (WHO, 2005).

Phase 2 clinical trials are more focused on exploring the therapeutics of the IP, in terms of its effectiveness for the disease or condition for which the drug is being developed. This phase usually involves a larger sample size of selected subjects with the target disease/condition, in contrast with the healthy subjects in Phase 1. This phase substantiates the effectiveness claim in treatment, as well as establishing risks of serious toxicities, if any. It is very crucial to verify product tolerance in Phase 2 trial subjects, even though previous experience from human use may demonstrate clinical safety of the IP (WHO, 2005). Pharmacodynamics of the IP will be explored during this phase. A range of doses will be investigated using a relatively small number of participants per dose group. The results for this phase will be the basis for the confirmatory study design in Phase 3.

Phase 3 clinical trials are conducted to establish the overall benefit-risk ratio of the intervention and to provide an adequate basis for general clinical use. These trials

are the extended trial of safety and efficacy. The participants involved are usually in a larger group (several hundreds to several thousands) of subjects, with broader inclusion characteristics than in phase 2, and recruited from more study sites. Statistical comparison of the intervention to standard and/or placebo interventions, as well as any dose-response relationship, will be evaluated in this phase (WHO, 2005). The results from this phase will be the basis for the confirmatory therapeutics of the IP, in obtaining subsequent approval for registration and marketing.

Phase 4 clinical trials are also known as post-marketing surveillance studies. They are conducted to study any side effects over time from using a new treatment/product which has obtained approval from regulatory authorities for marketing. This phase will provide additional information on the IPs long-term safety and effectiveness, as well as identify adverse effects that may not have been apparent in prior trials (U.S. FDA, 2018).

5.4. CLINICAL TRIAL CONDUCT IN MALAYSIA

As of now, Phase 1 Clinical Trial facilities in Malaysia are only available in Hospital Ampang and Hospital Umum Sarawak (Kuching). The MOH has endorsed two relevant guidelines, one covering the overall landscape and conduct of Phase 1 clinical trials in Malaysia (Clinical Research Malaysia (CRM), 2017), and one on the accreditation of clinical trial facilities for FIH studies (NPRA, 2018b). In Malaysia, sponsors and contract research organisations (CRO) can conduct FIH studies in the Accredited Phase 1 Clinical Trial facilities only. Other phases of clinical trials can be conducted at any clinical trial site subject to current regulatory requirements including ministry establishments, private hospitals, medical teaching hospitals, clinics or clinical trial centres nationwide. The conduct of these trials may be subject to GCP inspections carried out by NPRA inspectors to verify the conduct of trials in accordance with the Malaysian Guideline for Good Clinical Practice, ethical standards and other regulatory requirements (NPRA, 2020).

For any planned interventional clinical trial, studies involving herbal IPs must follow the same required protocol and standard operating procedures as that of conventional drug IPs. To assist researchers, The National Institutes of Health (NIH),

MOH published a guideline in 2021, entitled 'NIH Guidelines for Conducting Research in the Ministry of Health (MOH) Institutions & Facilities'. This guideline covers all aspects in terms of requirements from relevant committees that oversee the trial approval process, from registration, ethical review, funding and legal considerations when involving MOH institutions (NIH, 2021)

On completion or termination of a trial, the investigators, and sponsors are expected to submit a Clinical Study Report to document the results and interpretation of the trial findings. This, along with other essential documents required during and after the trial, are detailed in the Malaysian Guideline for Good Clinical Practice (NPRA, 2018a). For reporting safety information arising from clinical trials involving IPs requiring the Clinical Trial Import Licence (CTIL) and/or Clinical Trial Exemption (CTX) in Malaysia, investigators/sponsors can refer to the Malaysian Guideline for Safety Reporting of Investigational Products (NPRA, 2014).

Contract Research Organisation (CRO)

CRO is an outsourcing firm or vendor that is hired by sponsors or investigators to help with clinical trial management and responsibilities. A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control throughout the conduct of the study. They are required to conduct clinical trials in accordance with guidelines and regulations at all times

Clinical Trial Insurance

Clinical trial liability is a specific high-risk area that requires maximum insurance protection, as it involves the intricate subject of human health and wellbeing. Claims involving clinical trials are often complex and expensive. A well-designed clinical trial insurance covers the investigators, sponsors, pharmaceutical companies as well as study site coordinators that conduct clinical trials and investigations, against the prospect of litigation. Clinical trial insurance should be obtained by the study sponsor to provide compensation to the study subject(s) in the event of physical damage or trial-related injury, as well as in the events of health impairment and death.

CONCLUSION

All the data obtained in the clinical trial needs to be submitted to NPRA to enable the IP to be approved and marketed as a herbal product with therapeutic claim. Once the product is registered and marketed, it has to go through Phase IV of the clinical trial, which is pharmacovigilance and post-marketing surveillance.

APPENDIX

1. Supplementary References

This guideline should be read and interpreted in conjunction with the current laws and regulations, as well as other relevant guidelines, where applicable, including but not limited to the following:

Table 7: Supplementary references

Document name	Document source (Link)	Organisation
Malaysian Laws & Regulations		
Sale of Drugs Act 1952 and Regulations	https://www.pharmacy.gov.my/v2/en/documents/sale-drugs-act-1952-and-regulations.html	
Poisons Act 1952 and Regulations	https://www.pharmacy.gov.my/v2/en/documents/poisons-act-1952-and-regulations.html	
Control Drugs and Cosmetics Regulation, 1984	https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/control-drugs-and-cosmetics-regulation-1984.pdf	
Access to Biological Resources and Benefit Sharing Act 2017 (Act 795)	https://www.mybis.gov.my/pb/3567 User guide: https://www.mybis.gov.my/pb/4497	
Animals Act 1953 (Act 647)	https://lom.agc.gov.my/act-view.php?type=amendment&lang=BI&act=A1452	
Animal Welfare Act 2015 (Act 772)	https://lom.agc.gov.my/act-detail.php?type=principal&lang=BI&act=772	
Medicines (Advertisement & Sale) Act 1956	https://www.pharmacy.gov.my/v2/en/documents/medicines-advertisement-sale-act-1956-and-regulations.html	
Dangerous Drugs Act 1952	https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/dangerous-drugs-act-1952.pdf	
Wildlife Conservation Act 2010 (Laws of Malaysia Act 716)	https://www.mybis.gov.my/pd/107	
International Trade in Endangered Species Act 2008 (Act 686)	https://www.mybis.gov.my/pd/109	

Traditional and Complementary Medicine Act 2016 (Act 775)	http://tcm.moh.gov.my/en/upload/aktaBI2016.pdf	
Sarawak Biodiversity Ordinance, 1997 with Amendments 2014	https://www.sbc.org.my/research-regulations-permit/ordinance-and-regulations/4-the-sarawak-biodiversity-ordinance-1997 https://www.sbc.org.my/research-regulations-permit/declaration-of-protected-resources/319-declaration-of-aglaia-stellatopilosa-and-aglaia-foveolata-as-protected-resources https://www.sbc.org.my/research-regulations-permit/declaration-of-protected-resources/297-declaration-of-botryococcus-spp-as-protected-resources	SBC
Sarawak Biodiversity Regulations, 2016	https://www.sbc.org.my/research-regulations-permit/ordinance-and-regulations/409-sarawak-biodiversity-regulations-2016 https://www.sbc.org.my/sbc-news/downloads/sarawak-biodiversity-ordinance-and-regulations/410-sarawak-biodiversity-fees-notification-2017 https://www.sbc.org.my/research-regulations-permit/ordinance-and-regulations/668-sarawak-biodiversity-regulations-amendment-2018	SBC
Sabah Biodiversity Enactment 2000	https://sabc.sabah.gov.my/content/sabah-biodiversity-enactment-2000	SaBC
General Research and Registration Guidelines		
(i) National		
Medical Research and Ethics Committee (MREC) for human subjects	https://www.nih.gov.my/mrec/	MREC
National Institutes of Health (NIH) Guidelines for Conducting Research in MOH Institutions and Facilities	https://www.nih.gov.my/images/media/publication/guidelines/NIH_Guideline_2021.pdf	NIH Malaysia

Malaysian Guidelines for Good Clinical Practice (GCP) 4th Edition	http://www.nccr.gov.my/index.cfm?menuid=17	NCCR
Malaysian Guidelines for GCP Inspection, Edition 2.1	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA
Malaysian Guideline for Application of CTIL and CTX, 7th Edition	https://www.npra.gov.my/easyarticles/images/users/1140/Malaysian-Guideline-for-Application-of-CTIL-and-CTX-7.1-Edition-16.09.2021.pdf	
Application Forms for Clinical Trial	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-application-forms.html	NPRA
Good Laboratory Practice (GLP)	https://www.npra.gov.my/index.php/en/glp-main-page.html (Malaysia)	NPRA
	https://www.oecd.org/chemicalsafety/testing/good-laboratory-practiceglp.htm [International Organisation for Economic Co-operation and Development (OECD) Guidelines]	
Malaysian Good Agriculture Practices (MyGAP)	https://www.mafi.gov.my/documents/20182/361765/Garis+Panduan+MyGAP.pdf/1d3c05ea-dc45-4407-b068-8bd969cc62e0	MAFS
Malaysian Guideline for Phase I Unit Inspection and Accreditation Programme	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA
ASEAN Guideline for the Conduct of Bioequivalence (BE) Studies	https://www.npra.gov.my/images/reg-info/BE/BE_Guideline_FinalMarch2015_endorsed_22PPWG.pdf	NPRA
Malaysian Guideline for Safety Reporting of Investigational Products, 1st Edition	https://www.npra.gov.my/index.php/en/guideline-for-the-submission-of-product-samples-for-laboratory-testing/clinical-trial/clinical-trial-guidelines.html	NPRA
Drug Registration Guidance Document (DRGD) 3rd edition	https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document-drgd.html	NPRA
National Medical Research Register (NMRR)	http://www.nmrr.gov.my/	NIH/MREC

Malaysian Phase 1 Clinical Trial Guidelines	https://clinicalresearch.my/wp-content/uploads/2020/11/Malaysian-Phase-I-Clinical-Trial-Guidelines.pdf	CRM
Sarawak Online Research Application System (SORAS)	https://soras.sarawak.gov.my/soras/welcome	SBC
Sabah Biodiversity Access & Export Licence Online Application	https://sabcapps.sabah.gov.my/	SaBC
Procedures on Access & Export Licence Application – Non-Commercial Research 2022	https://tinyurl.com/4sbxaw7k.	
Application for Research in Perkampungan Orang Asli or Jabatan Kemajuan Orang Asli (JAKAO) facilities	https://www.jakoa.gov.my/umum/permohonan-penyelidikan/	JAKAO
(ii) International		
OECD Test Guidelines for Chemicals	https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm	OECD
OECD Genetic Toxicology Test Guidelines	https://www.oecd.org/chemicalsafety/testing/Genetic%20Toxicology%20Guidance%20Document%20Aug%2031%202015.pdf	OECD
European Medicines Agency (EMA) ICH Safety guidelines	https://www.ich.org/page/safety-guidelines	EMA
European Medicines Agency (EMA) ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m3r2-non-clinical-safety-studies-conduct-human-clinical-trials-marketing-authorisation_en.pdf	EMA
WHO Handbook for Good Clinical Research Practice	https://www.who.int/medicines/areas/quality_safety/safety_effectiveness /gcp1.pdf	WHO
International Ethical Guidelines for Biomedical Research Involving Human Subjects: Council for International Organizations of Medical Sciences (CIOMS)	https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf	CIOMS & WHO
WHO Operational Guidelines for Ethics Committees That Review Biomedical Research	http://www.nccr.gov.my/index.cfm?menuid=24&parentid=17	WHO
ICH Q1A (R2): Stability testing of new drug substances and drug products guideline	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-r2-stability-testing-new-drug-substances-products-step-5_en.pdf	EMA/ICH

T&CM based Research and Registration Guideline		
(i) National		
Guideline of Natural Products with Therapeutic Claim	https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document.html	NPRA
Guideline on Registration of Natural Products	https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document.html	NPRA
Checklist for National Committee for Research and Development of Herbal Medicine (NRDHM)	https://www.nih.gov.my/images/media/publication/guidelines/NIH_Guideline_2021.pdf	NRDHM
Good Manufacturing Practice (GMP) (in accordance with Pharmaceutical Inspection Co-Operation Scheme-Guide to GMP for Medicinal Products)	https://npra.gov.my/index.php/en/about/recognition-international-membership/pic-s.html https://picscheme.org/	NPRA
(ii) International		
WHO General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine	https://www.who.int/publications/i/item/9789241506090	WHO
Set of ASEAN Guiding Principles on Traditional Medicines and Health Supplements developed by the Traditional Medicines and Health Supplements Product Working Group (TMHSPWG)	https://www.hsa.gov.sg/international-collaboration-complementary-health-products/asean	TMHSPWG
WHO Research Guidelines for Evaluating the Safety and Effectiveness of Herbal Medicines, 1993	https://apps.who.int/iris/handle/10665/207008	WHO
WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems, 2004	https://apps.who.int/iris/handle/10665/43034	WHO
WHO Quality control methods for medicinal plant materials. World Health Organization, 1998	https://apps.who.int/iris/handle/10665/41986	WHO
WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines	https://www.who.int/publications/m/item/who-guidelines-for-selecting-marker-substances-of-herbal-origin-for-quality-control-of-	WHO

	herbal-medicines---trs-1003---annex-1	
European Medicines Agency (EMA) Guideline: Assessment of Clinical Safety and Effectiveness in the Preparation of EU Herbal Monographs for Well-established and Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/assessment-clinical-safety-effectiveness -preparation-eu-herbal-monographs-well-established-traditional	EMA
EMA Guideline: Clinical Assessment of Fixed Combinations of Herbal Substances/Herbal Preparations	https://www.ema.europa.eu/en/assessment-clinical-safety-effectiveness -preparation-eu-herbal-monographs-well-established-traditional	EMA
EMA Guideline: Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/specifications-test-procedures-acceptance-criteria-herbal-substances-herbal-preparations-herbal	EMA
EMA Guideline: Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products	https://www.ema.europa.eu/en/quality-herbal-medicinal-productstraditional-herbal-medicinal-products	EMA
EMA Guideline: Declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products	https://www.ema.europa.eu/en/declaration-herbal-substances-herbal-preparations-herbal-medicinal-productstraditional-herbal	EMA

2. NRDHM Subject-Matter Expert Review Form

	NATIONAL COMMITTEE FOR RESEARCH AND DEVELOPMENT IN HERBAL MEDICINE (NRDHM) ***JAWATANKUASA KEBANGSAAN PENYELIDIKAN DAN PEMBANGUNAN PERUBATAN HERBA (JKPPH)***

SUBJECT-MATTER EXPERT REVIEW FORM

Please find below the details of the information that are required to be included in the study protocol and Investigator's Brochure for studies that involve herb/s as the Investigational product.

A. BACKGROUND INFORMATION

1	Study protocol title	
2	Principal investigator	Name Contact details (Address, phone number/s, email)
3	Clinical Research Organization	Name Contact details (Address, phone number/s, email)
4	Sponsor	Name Contact details (Address, phone number/s, email)

B. STUDY DESIGN

5	Objective(s) of the study	
6	Endpoint(s) of the study	
7	Type of study	• eg Cohort, Cross over trial, RCT etc • Sampling size calculation
8	Control group	Details on the comparison group (Placebo or standard treatment)
9	Target group of treatment	• Intended group: Adult, Adolescent / Teenager, Children, Women of Childbearing age • Intended Disease /condition
10	Duration of treatment	Please state specifically how long the treatment is planned for:

		1. Not more or equal to 14 days 2. More than 14 days till 3 months 3. Long term (More than 3 months)
11	Mode of delivery	How will the Investigational product be taken by the patients? Oral, Topical application, Intravenous, Subcutaneous and others
12	Dosing	Amount and frequency New dose?
13	Concomitant treatment(s)	List the concomitant treatment(s)

C. DETAILS OF INVESTIGATIONAL PRODUCT

14	Details of Investigational product	• Type of product (refer Attachment A) • Ingredient(s) ○ Single plant ○ Combinations: name all ingredients ○ Part(s) of plant(s) used ○ Use of protected/ endangered species • All reported claim(s) • Intended use(s) for this study • Type of preparation (Eg Fresh, Freeze dried, Spray dried etc) • Method of extraction (To name the method used) • Standardized extract (To name marker(s))
15	Data of Investigational product	*## Below are the minimal data required for all Investigational products including fresh product* • Summary of Product Characteristic ○ (Invented) Name of medicinal product, strength, pharmaceutical form. Eg: xx 10mg tablet. ○ Description of pharmaceutical form • Standardization of extract • Analytical Method Validation • Quality data: In-Process Quality Control (IPQC), Finished Product Quality Control (FPQC) • Stability data (Container closure system, storage condition, proposed shelf-life) *## Below are the additional data for manufactured Investigational product* • Certificate of GMP

		• Certificate of Analysis • Description of Pharmaceutical Development • Protocol of Analysis • Standard labelling requirements • Bioavailability/ bioequivalent study

D.EFFICACY CLAIMS SUBSTANTIATION

16	Efficacy Claim with Traditional Knowledge	**Sources of information** (refer Attachment B) ## The references could be any of the following: 1. Standard reference (Reference textbooks, pharmacopoeia, monographs) 2. Recommendations on usage from reference regulatory authorities or reference organizations 3. Good quality scientific evidence from human observational studies: Case report / studies / series 4. Report prepared by expert committees/expert opinion (subject to Authority approval) 5. Published scientific reviews and meta-analysis 6. Documented/reported negative marker (e.g. Traditionally used for abortion) or adverse events
17	Efficacy claim with Pharmacological studies (Preclinical studies) **(OECD-GLP Compliance)** (Note**:** All non-clinical should be conducted in OECD/GLP compliance laboratory. This requirement will be mandatory in the very near future)	**Primary pharmacodynamics**. Study primary mode of action related to therapeutic activity – *In vitro* and *in vivo* **Secondary pharmacodynamics**. Study the additional mode of action of compounds. **Toxicokinetic and pharmacokinetic study:** ○ Metabolic and plasma protein binding data ○ ADME ○ Biochemical drug interaction

		○ Nonclinical characterization of human metabolite(s) **Safety pharmacology.** Assessment on core battery (Central Nervous System, Respiratory system, Cardiovascular System)

E. SAFETY DATA

18	Safety Data Based on Toxicology Study (OECD-GLP Compliance) (Note**:** All non-clinical should be conducted in OECD/GLP compliance laboratories. This requirement will be mandatory in the very near future)	**Genotoxicity** i. *In vitro* test ○ Ames test / Bacteria reverse mutation assay ○ Metaphase chromosome aberration assay ○ Mouse lymphoma L5178Y cell thymidine kinase gene mutation assay (MLA) ○ Comet assay ii. *In vivo* studies ○ Micronuclei in erythrocytes (in blood and bone marrow) ○ Chromosome aberrations in metaphase cells in bone marrow **Single-acute toxicity** i. Rodent ii. Non-rodent **Repeated dose (28 days)** i. Rodent ii. Non-rodent **Repeated dose (90 days)** i. Rodent ii. Non-rodent **Repeated dose (6 months/1 year)** i. Rodent ii. Non-rodent **Carcinogenicity** (Expected clinical use is continuous for at least 6 months) **Reproductive toxicity** (Depending on study population: Male, female, embryo-fetal (prior to Phase III))

19	Specialized Toxicity Studies	• Local tolerance (e.g skin/eyes/GIT etc) • Hepatotoxicity • Phototoxicity • Immunotoxicity • Juvenile animal toxicity • Abuse toxicity
20	Assessment in Human (Clinical)	• Estimation of initial safety and tolerability • ADME study • PK/PD study • Efficacy and safety profiling • Confirmatory study of efficacy • Primary endpoints identification (Please state) • Documentation: i. Clinical study reports ii. Published clinical papers iii. Latest periodic safety update report (PSUR)

F. INVESTIGATOR'S BROCHURE (IB)

21	Investigator's Brochure *(The IB is a requirement for herbal Investigational product(s) going for **clinical trials**)*	The content/format of IB should follow section 7.4 (Appendix 1) page 62 and section 7.5 (Appendix 2) page 63 Malaysian Guideline for GCP 4th edition **TITLE PAGE** *(Example)* Sponsor's Name: Product: Research Number: Name(s) Chemical, Generic *(if approved)* Trade Name(s) *(if legally permissible and desired by the sponsor)* INVESTIGATOR'S BROCHURE Edition Number: Release Date: Replaces Previous Edition Number: Date: **Table of Contents Of Investigator's Brochure** (Example) CONFIDENTIALITY STATEMENT (optional) SIGNATURE PAGE (optional) SUMMARY (preferably not exceeding 2 pages) **1. INTRODUCTION** **2. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION** 2.1 Introduction 2.2 Product description *(eg: (invented) name of medicinal product, strength, pharmaceutical form)* 2.3 Manufacturing of Product *(eg: GMP certificate)* 2.4 Quality Control Tests *(eg: In-Process Quality Control (IPQC), Finished Product Quality Control (FPQC))* 2.5 Quality Assurance 2.6 Stability *(eg: Container closure system, storage condition, proposed shelf-life)* 2.7 Attachments (may include certificate of analysis) 2.8 References

		3. NON-CLINICAL STUDIES 3.1 Introduction 3.2 Nonclinical Pharmacology 3.3 Pharmacokinetics and Product Metabolism in Animals 3.4 Toxicology study 3.5 Non-clinical study Report, tabulated overview 3.6 Conclusion 3.7 References **4. CLINICAL STUDIES (if any)** 4.1 Introduction 4.2 Types of Studies 4.3 Clinical study synopsis, tabulated overview 4.4 Conclusion 4.5 References **5 EFFECTS IN HUMANS** 5.1 Pharmacokinetics and Product Metabolism in Humans 5.2 Safety and Efficacy 5.3 Marketing Experience 5.4 References **6. SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATOR** 6.1 Mechanism of Action, administration 6.2 Use in treatment, duration of action 6.3 Precautions 6.5 Warnings 6.6 Potential Adverse Effects 6.7 Overdose 6.8 Directions for Storage, maintenance **7. APPENDICES (if any)** References on publications and reports should be found at the end of each chapter Appendices (if any).

REFERENCES

Access to Biological Resources and Benefit Sharing Act 2017 (Act 795), (2017). https://www.mybis.gov.my/pb/3567

al-Tabari, A. i. S. R. (1981). Firdaus al-Hikmah. *Urdu translation by Ashraf R). Karachi: Hamdard Foundation*, 294-297.

Alamgir, A. (2017). Pharmacopoeia and herbal monograph, the aim and use of WHO's herbal monograph, WHO's guidelines for herbal monograph, pharmacognostical research and monographs of organized, unorganized drugs and drugs from animal sources. In *Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1* (pp. 295-353). Springer.

Applequist, W., & Miller, J. (2012). Selection and authentication of botanical materials for the development of analytical methods. *Analytical and bioanalytical chemistry*, *405*.

British Pharmacopoeia Commission. (2018). DNA barcoding as a tool for botanical identification of herbal drugs in British Pharmacopoeia supplementary chapter SC VII D. TSO. In.

Control Of Drugs And Cosmetics Regulations (1984). https://www.pharmacy.gov.my/v2/sites/default/files/document-upload/control-drugs-and-cosmetics-regulation-1984.pdf

De Smet, P. A. (2004). Health risks of herbal remedies: an update. *Clinical Pharmacology & Therapeutics*, *76*(1), 1-17.

Engineering Biology Research Consortium (EBRC). (2007). *Health Risk Assessment Guidance for Metals (HERAG) Fact Sheet 05: Mutagenicity*. https://www.ebrc.de/downloads/HERAG_FS_05_August_07.pdf

European Medicine Agency (EMA). (2007). Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-excipients-dossier-application-marketing-authorisation-medicinal-product-revision-2_en.pdf

European Medicine Agency (EMA). (2008). Markers used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products.

European Medicine Agency (EMA). (2009). Guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. *International Conference On Harmonization Of Technical Requirements For The Registration Of Pharmaceuticals For Human Use. ICH Steering Committee*.

European Medicine Agency (EMA). (2010). Declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products - Scientific guideline.

European Medicine Agency (EMA). (2013). ICH S2 (R1) Genotoxicity testing and data interpretation for pharmaceuticals intended for human use.

European Medicine Agency (EMA). (2020). Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells.

European Medicine Agency (EMA). (2022). ICH Q2 (R2) Validation of Analytical Procedures *International conference of harmonization. Geneva, Switzerland*.

European Medicines Agency. (2006). Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin. *Emea,(February)*, 1-11.

European Medicines Agency (EMA). (2022). Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products.

GMP Section Centre of Compliance and Quality Control. (2022). *Frequently Asked Questions (FAQs) About GMP Inspection By National Pharmaceutical Regulatory Agency (NPRA)*. National Pharmaceutical Regulatory Agency (NPRA). Retrieved 5 September from https://www.npra.gov.my/images/2022/apb/FAQ-eng-apb2.pdf

Hildreth, J., Hrabeta-Robinson, E., Applequist, W., Betz, J., & Miller, J. (2007). Standard operating procedure for the collection and preparation of voucher plant specimens for use in the nutraceutical industry. *Analytical and bioanalytical chemistry*, *389*(1), 13-17.

Ichim, M. C. (2019). The DNA-based authentication of commercial herbal products reveals their globally widespread adulteration. *Frontiers in pharmacology*, *10*, 1227.

Institute of Translational Health Sciences. (2020). *Industry-Sponsored Clinical Trials. Clinical Research Handbook*. University of Washington. https://www.iths.org/investigators/handbook/set-up-the-study/industry-sponsored-clinical-trials/

Intellectual Property Corporation of Malaysia (MyIPO). (2013). *List Of Books Used As A Source Of Data In Malaysia Traditional Knowledge Digital Library (MyTDKL)*. MyIPO. Retrieved 5 September from https://www.myipo.gov.my/wp-content/uploads/2022/01/LIST-OF-BOOKS-MALAYSIA-TRADITIONAL-KNOWLEDGE-DIGITAL-LIBRARY.pdf

Jamal, J. A. (2006). Malay traditional medicine. *Tech Monitor (Special Feature: traditional Medicine: S & T Advancement)*, *1*, 37-49.

Katiyar, C., Gupta, A., Kanjilal, S., & Katiyar, S. (2012). Drug discovery from plant sources: An integrated approach. *Ayu*, *33*(1), 10.

Krishna, G., & Hayashi, M. (2000). In vivo rodent micronucleus assay: protocol, conduct and data interpretation. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *455*(1-2), 155-166.

Malaysia Biodiversity Centre (MBC). (2021). User's Guide to the Access to Biological Resources and Benefit Sharing Act 2017 [Act 795]. https://www.mybis.gov.my/pb/4497

Malaysian Herbal Monograph (MHM) Committee. (2015). *Malaysian Herbal Monograph 2015*. Institute for Medical Research.

Ministry of Agriculture and Food Security (MAFS). (2022). *Malaysian Good Agriculture Practice Scheme (MyGAP)*. Official Portal of Department of Agriculture, Ministry Of Agriculture And Food Industries. http://www.doa.gov.my/index.php/pages/view/373

Mosihuzzaman, M., & Choudhary, M. I. (2008). Protocols on safety, efficacy, standardization, and documentation of herbal medicine (IUPAC Technical Report). *Pure and Applied Chemistry*, *80*(10), 2195-2230.

Mukherjee, P. K., Banerjee, S., & Kar, A. (2021). Molecular combination networks in medicinal plants: understanding synergy by network pharmacology in Indian traditional medicine. *Phytochemistry Reviews*, *20*(4), 693-703.

National Institutes of Health (NIH). (2021). National Institutes Of Health (NIH) Guidelines For Conducting Research in Ministry Of Health (MOH) Institutions & Facilities, 3rd edition.

National Pharmaceutical Regulatory Agency (NPRA). (2014). Malaysian Guideline for Safety Reporting Of Investigational Products, First Edition.

National Pharmaceutical Regulatory Agency (NPRA). (2018a). *Malaysian Guideline for Good Clinical Practice* (4th ed.). National Committee for Clinical Research (NCCR), Ministry Of Health Malaysia.

National Pharmaceutical Regulatory Agency (NPRA). (2018b). Malaysian Guideline for Phase I Unit Inspection and Accreditation Programme. (First edition).

National Pharmaceutical Regulatory Agency (NPRA). (2020). Malaysian Guideline for Good Clinical Practice (GCP) Inspection. *Edition 2.1*.

National Pharmaceutical Regulatory Agency (NPRA). (2021). Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption Edition 7.1.

National Pharmaceutical Regulatory Agency (NPRA). (2022a). Appendix 1: Food-Drug Interphase (FDI) Products, Drug Registration Guidance Document (DRGD) Third Edition, Third Revision July 2022.

National Pharmaceutical Regulatory Agency (NPRA). (2022b). Appendix 7 Guideline On Registration Of Natural Products. Drug Registration Guidance Document (DRGD) (Second Revision January 2022).

National Pharmaceutical Regulatory Agency (NPRA). (2022c). Appendix 7B: Guideline On Natural Products With Therapeutic Claim. Drug Registration Guidance Document (DRGD)

Organisation for Economic Co-operation and Development (OECD). (2001). *OECD guideline for the testing of chemicals, Performance-Based Test* (Vol. 601). The Hershberger.

Organisation for Economic Co-operation and Development (OECD). (2002). *Test No. 420: Acute Oral Toxicity - Fixed Dose Procedure. OECD Test Guidelines for Chemicals*. https://www.oecd-ilibrary.org/content/publication/9789264070943-en

Organisation for Economic Co-operation and Development (OECD). (2008). *Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents. OECD Test Guidelines for Chemicals*. https://doi.org/doi:https://doi.org/10.1787/9789264070684-en

Organisation for Economic Co-operation and Development (OECD). (2018a). *Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents*.

Organisation for Economic Co-operation and Development (OECD). (2018b). *Test No. 451: Carcinogenicity Studies. OECD Test Guidelines for Chemicals*. https://doi.org/doi:https://doi.org/10.1787/9789264071186-en

Organisation for Economic Co-operation and Development (OECD). (2018c). *Test No. 452: Chronic Toxicity Studies. OECD Test Guidelines for Chemicals*. https://doi.org/doi:https://doi.org/10.1787/9789264071209-en

Patil, M., Patil, S., Maheshwari, V. L., Zawar, L., & Patil, R. H. (2022). Recent Updates on In Silico Screening of Natural Products as Potential Inhibitors of Enzymes of Biomedical and Pharmaceutical Importance. In *Natural Products as Enzyme Inhibitors* (pp. 105-123). Springer.

Piah, H. M. (2006). *Kitab Tib : Ilmu Perubatan Melayu*. Perpustakaan Negara Malaysia : Kementerian Kebudayaan, Kesenian, dan Warisan Malaysia.

Sachan, A. K., Vishnoi, G., & Kumar, R. (2016). Need of standardization of herbal medicines in modern era. *International Journal of Phytomedicine*, *8*(3), 300-307.

Samhita, C. (1949). Charaka Samhita. *Vols I-- VI, Jamnagar, India: Shree Gulab Kunverba Ayurvedic Society*.

Secretariat of the Pharmaceutical Inspection Convention. (2022). Guide To Good Manufacturing Practice For Medicinal Products (PE 009-16).

Therapeutic Goods Administration (TGA). (2011). Guidance on equivalence of herbal extracts in Complementary Medicines. *Department of Health and Aged Care, Australian Government*.

Traditional and Complementary Medicine Act 2016 (Act 775), (2016). http://tcm.moh.gov.my/en/upload/aktaBI2016.pdf

U.S. Food and Drug Administration. (2018). *Step 3: Clinical Research, The Drug Development Process*. U.S Food and Drug Administration. Retrieved 18 August 2022 from https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

U.S. Food and Drug Administration. (2020). *Conducting Clinical Trials*. U.S. Food and Drug Administration. Retrieved 18 August 2022 from https://www.fda.gov/drugs/development-approval-process-drugs/conducting-clinical-trials

U.S. Food Drug Administration (FDA). (2005). Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. *Center for Drug Evaluation and Research (CDER)*, *7*(0.001). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers

U.S. Food Drug Administration (FDA). (2010). ICH M3 Guidance for industry: nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. 1-30.

U.S. National Institutes of Health. (2019). *Learn About Clinical Studies. Clinicaltrial.gov*. NIH U.S. National Library of Medicine. Retrieved 18 August 2022 from https://clinicaltrials.gov/ct2/about-studies/learn

WHO Expert Committee. (2006). *Annex 3: General Guidelines for The Establishment, Maintenance And Distribution Of Chemical Reference Substances*. World Health Organisation.

World Health Organisation (WHO). (1993). Research guidelines for evaluating the safety and efficacy of herbal medicines. https://www.who.int/publications/i/item/9290611103

World Health Organisation (WHO). (2000). General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine.

World Health Organisation (WHO). (2003). WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants.*

World Health Organisation (WHO). (2005). Operational Guidance : Information Needed To Support Clinical Trials Of Herbal Products. (TDR/GEN/Guidance/05.1). https://apps.who.int/iris/handle/10665/69174

World Health Organisation (WHO). (2011). *Quality Control Methods for Herbal Materials*. World Health Organization.

World Health Organisation (WHO). (2013). Guidelines for the Appropriate Use of Herbal Medicines.

World Health Organisation (WHO). (2015). *Clinical Trials*. World Health Organisation. Retrieved 18 August 2022 from https://www.who.int/health-topics/clinical-trials#tab=tab_1

World Health Organisation (WHO). (2017). *Annex 1 WHO Guidelines for Selecting Marker Substances of Herbal Origin for Quality Control of Herbal Medicines*. World Health Organization.

World Health Organisation (WHO). (2021). Index of World Pharmacopoeias and Pharmacopoeial Authorities. *Review of World Pharmacopoeias. Working Document QAS/11.453/Rev*, *13*.

李時珍. (1826). *Ben Cao Gang Mu: 52 ch., fu : Tu juan 3 ch*. Ying De Tang. https://books.google.com.my/books?id=9_JlAAAAcAAJ


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