Ministry of Health Malaysia

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

GUIDELINES FOR STANDARDISATION OF HERBAL MEDICINAL PRODUCTS

GUIDELINES FOR

STANDARDISATION, SAFETY AND CLINICAL EVALUATION OF HERBAL MEDICINAL PRODUCTS

Message by

The Honourable Dato Chua Jui Meng,
Minister of Health of Malaysia

Traditional medicine has formed the basis of health care throughout the world since the earliest days of mankind and is still widely used. It has been estimated that nearly 80% of the world's population use some form of traditional and complementary medicine (T/CM). The use of herbal medicines is growing steadily worldwide, increasing at a rate of 10-20% annually.

Of the approximately 250,000 known plant species in the world today, it is estimated that only about 5% have been examined for their medicinal properties and 25% of all prescription drugs are based on plants belonging to only 40 species. There are at least 150,000 species of flowering plants in the tropics and in South East Asia alone, there are 35,000 species of which 8,000 are found in Malaysia. In the tropics, a total of 6,000 floral species have been reported to possess medicinal values. Of these, a total of 1,230 local species have been recorded as plants used in traditional medicines. Malaysia is one of the 12 mega biodiversity countries in the world and is nestled in the oldest rainforest in the world. It is also a melting pot of 3 important T/CM systems, namely the Malays, Chinese and the Indian traditional medicine systems and It is hardly surprising therefore to note the growing interest of T/CM amongst policy makers, researchers, clinicians, entrepreneurs and the community at large in this country.

This growing popularity and appeal of T/CM the world over, have created both an opportunity and the obligation for the Government to conduct proper scientific studies and evaluation in T/CM. It has been reported that an estimated USD 500 million is spent annually on T/CM compared to USD 300 million on modern medicine in Malaysia. There is now greater demand for evidence on the safety, efficacy and quality of T/CM products and practices.

I would like to therefore congratulate the **National Committee for Research & Development in Herbal Medicine (NRDHM),** the brainchild of the Ministry of Health, for producing several guidelines pertaining to herbal medicine research to ensure that good research practices, as well as authenticity, safety, efficacy of therapies involving herbal medicinal products are assured. These guidelines are indeed very timely and will serve to enhance consumer confidence in T/CM.

Dato Chua Jui Meng,
Minister of Health of Malaysia

Message by

Y Bhg Tan Sri Datu Dr. Mohamad Taha bin Arif
Director General of Health
Ministry of Health

The Ministry of Health (MOH) is responsible for ensuring the availability of appropriate, safe, effective health care services in the country. While much of the healthcare currently provided by the MOH is driven by modern medicine which is based on scientific evidence, there is a growing interest in the use of traditional and complementary medicine (T/CM) as either an alternative or an adjunct to modern medicine. The MOH launched the policy on T/CM in 2001 in recognition and anticipation of the increasing popularity of T/CM not only in this country but also worldwide.

The WHO encourages the integration of safe and efficacious T/CM into mainstream healthcare system. Before considering the integration of T/CM into our mainstream health care system, the MOH has the responsibility of ensuring that only appropriate, safe and effective herbal medicines of consistent quality are developed and available to those in need. It is also our responsibility to ensure that the herbal medicinal products not only meet the required product quality standards (GMP), but have also in place, the necessary evidence to support its safe and appropriate use in specific disease states (evidence-based therapeutic use). The development of such medicinal products needs to be carried out in a coordinated, systematic and scientific manner, similar to that of pharmaceutical drug development.

It is therefore gratifying to note that the Ministry of Health, through the **National Committee for Research & Development in Herbal Medicine (NRDHM)**, has produced four guidelines for researchers in T/CM to use as guidance documents to strengthen research and development in herbal medicine and thus bring the practice of T/CM to a higher level of quality for greater acceptance by providers of modern medicine and the public. The stage will then be set for the integration of modern and T/CM into mainstream healthcare system.

Tan Sri Datu Dr. Mohamad Taha bin Arif
Director General of Health
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Message by

Dato Dr. Hj Mohd Ismail Merican
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There are generically three groups of traditional/herbal preparations in Malaysia: the Malay traditional preparations, the Chinese preparations, and the Indian traditional preparations. Within each of these groups are different remedies that are being compounded and sold for the same disease indication. It is very clear that there is a great deal of variation and secrecy as to the composition of these "local" remedies. Absence of standardisation is a common feature. The lack of collaboration and co-operation within the group and between groups make it difficult to develop a truly Malaysian traditional/herbal formulary for treatment of the different illnesses found in this country.

Some of the reasons delaying the development of a national formulary specific for herbal products include the lack of co-ordination between the traditional herbalists and feeble attempts to systematically evaluate locally available flora to identify active ingredients that will be viable commercially, especially in the context of the emergence of new chemical entities.

In order to facilitate the future development of traditional/herbal medicines in this country, one has to understand the processes and activities that need to be in-place to ensure that commercially viable herbal products can be systemically developed and internationally marketed. Acknowledging that herbal medicines can contribute to the economy of the country, the development of such medicinal products need to be carried out with some urgency.

The timely approval by the Malaysian Cabinet of the establishment of the **National Committee for Research & Development in Herbal Medicine (NRDHM)** in April 2002 under the auspices of the Ministry of Health and chaired by the Deputy-Director General of Health (Research and Technical Support) has given herbal medicine research the much needed catalyst to steer it in the right direction and in accordance with international standards.

The terms of reference of NRDHM include the development and coordination of the strategic master plan for R&D in herbal medicine research, the production of relevant guidelines to ensure quality, safety and integrity of data in line with local regulations, creation of harmonization, understanding and collaboration between researchers, identification of training and infrastructure needs in herbal medicine R & D, the setting of targets and facilitation of new product discovery and development and addressing issues pertaining to Intellectual Property Rights management.

Members of NRDHM include senior representatives from the various ministries, universities and appropriate stakeholder agencies such as the Science University of Malaysia, Agriculture and Research Development Institute, Drug Control Authority, Ministry of Science ,Technology and Environment, Ministry of International Trade and Industry , Ministry of Education, Malaysian Industry Government Group for High Technology, Malaysian Herbal Cooperation and the Institute for Medical Research.

The guidelines that have been prepared by NRDHM pertain to clinical research, standardization, claims and intellectual property rights management. They will serve as guidance documents to ensure rigorous quality in herbal medicine research and safety of our herbal products. It is hoped that the quality of studies conducted will be of the highest standards and generating findings and products that are accepted not only in Malaysia, but also globally.

These guidelines have been prepared in consultation with various existing guidance documents from the Federal Drug Control Authority (FDA), USA the World Health Organisation (WHO), European Union and Therapuetics Good Administration (Australia)

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Terms of Reference

- To develop, coordinate and monitor the strategic master plan for Research & Development in Herbal Medicine Research.
- To produce relevant guidelines to ensure quality, safety and integrity of data in line with local and international regulations.
- To create harmonization, understanding and collaboration between researchers.
- To conduct dialogues and other related activities for promotion of Herbal Research & Development.
- To identify training and infrastructure needs in Herbal Medicine Research & Development.
- To set targets and facilitate new product discovery and development.
- To address issues pertaining to Intellectual Property Rights Management.

For this guidance document, the following individuals were invited to be part of the technical sub committee

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Guidelines for Standardisation, Safety and Clinical Evaluation of Herbal Medicinal Products

Introduction

Herbal (botanical) products are finished, labeled products that contain vegetable matter as ingredients. For a botanical product, the intended use may be as a food (including a dietary supplement), a drug (including a biological drug), or a cosmetic. The term *herbal (botanicals)* includes plant materials, algae, macroscopic fungi, and combinations thereof. It does not include fermentation products such as products fermented with yeast, bacteria, and other microscopic organisms,

Herbal drug products have certain unique characteristics that should be taken into account in the application of the guidance. Herbal drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, even the active constituent in an herbal drug is not identified, nor is its biological activity well characterized. Therefore, the documentation that should be provided for botanical drugs will be different from that for synthetic or highly purified drugs, whose active constituents can be more readily chemically identified and quantified. For example, active constituents in an herbal drug might not need to be identified during the pre-clinical development stage, if this is shown to be infeasible. In such circumstances, the NRDHM will rely instead on a combination of other tests (e.g., spectroscopic or chromatographic fingerprints, chemical assay of characteristic markers, and biological assay), controls (e.g., strict quality controls of the botanical raw materials and adequate in-process controls), and process validation (especially for the drug substance) to ensure the identity, purity, quality, strength, potency, and consistency of the herbal drug.

Herbal drug products that are derived from a single part of a plant (e.g., leaves, stems, roots, seeds), or from an alga or macroscopic fungus (e.g., a mushroom), are not considered to be fixed-combination drugs. Consequently, they would not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active ingredient makes a contribution to claimed effects.

Herbal drugs composed of multiple parts of a single plant species, or of parts from different plant species, currently are subject to the combination drug requirements.

Plant materials used in the production of herbal drug products often are not completely characterized and defined or are prone to contamination, deterioration, and variation in composition and properties. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, unlike synthetic or highly purified drug products, it may be difficult to ensure the quality of an herbal drug by controlling only the corresponding drug substance and drug product. To ensure that a herbal drug product is made consistently with good quality, the Investigator (sponsor) should have, in addition to final product testing, appropriate quality controls for the botanical raw materials and adequate in-process controls during manufacturing and final process validation, especially for the herbal drug substance.

Sponsors of early (P1 &P2) clinical trials on herbal products that have been legally marketed as dietary supplements and that do not have safety issues can submit less chemistry, manufacturing and control information than should be provided for later studies and for studies on products not previously marketed.

In the preclinical and early stage of clinical studies on an herbal drug, it is generally not necessary to identify the active constituents or other biological markers or to have a chemical identification and assay for a particular constituent or marker. Identification by chromatographic fingerprinting and strength by weight can be acceptable alternatives. Attributes for lot or batch release testing should be reported. Batch analyses on clinical lots should be submitted to demonstrate the batch-to-batch consistency and to help establish appropriate limits for fingerprinting. Efforts should also be made to identify active constituents prior to commencement of phase 3 studies.

A single formulation (i.e., one in which the components or ingredients and composition of the herbal drug substance and herbal drug product are kept constant) and a single-dosage form should be used throughout the different stages of the clinical trials. More important, the principal Investigator or product sponsor should, to the extent possible, obtain sufficient quantities of the herbal (botanical) drug product in a single batch from a single source of the herbal (botanical) drug substance and/or raw materials to sustain the preclinical and initial clinical trials. This is especially true if the sponsor does not have access to the manufacturing and controls information on the herbal (botanical) drug substance and finished product. Unless the sponsor is equipped to conduct quality assurance testing from batch to batch, using a single batch or source of product is the best way to eliminate any possible product differences or batch variations during the clinical trial. In addition, sufficient quantities of the herbal (botanical) raw material and herbal drug substance from the same batch should be retained for future chemical and/or pharmacological/toxicological testing. It is equally important to obtain the botanical drug product from a source willing to provide the NRDHM with detailed manufacturing and controls information when needed, or as clinical evaluation of the product progresses. These factors are crucial if the sponsor intends to pursue national and International approval for a drug claim for the botanical product.

1 Herbal (Botanical) Products with previous reported Human Use

A. Description of Product and Documentation of Human Use

1. Description of Botanicals Used

The following information should be provided for ***each*** of the botanical raw materials used as ingredients in a botanical drug product:

- Common or usual names of the plant, alga, or macroscopic fungus
- Synonyms (e.g., Latin, Greek, English, Spanish, Chinese Malay Arabic Sanskrit)
- Name of variety, species, genus, and family, including the name of the botanist who first described the species or variety, if known

- Chemical class of the active constituent (the chemical constituent that is responsible for the claimed pharmacological activity or therapeutic effect) or characteristic marker (a chemical constituent used for identification and/or quality control purposes), if known

2. History of Use

The sponsor should include information found in historical sources (e.g., books of medical practice in Ayurveda, traditional Chinese medicine, Unani, Sida and traditional Malay medicine) and scientific literature about the prior human use of the herbal (botanical) product, and each of its ingredients, in traditional foods and drugs. The literature should be provided in English (and in its original language, if other than English).

3. Current Marketed Use

The sponsor should include information about the nature and extent of the current worldwide use of the herbal (botanical) product, and each of its ingredients, in foods and drugs, including evidence concerning its marketing experience worldwide. For a foreign-marketed herbal (botanical) product, the sponsor should provide data (wherever available) that verify its safe human use, including official proof of the annual sales volume, an estimate of the size of the exposure population, and the rate of adverse effects.

B. Chemistry, Manufacturing, and Controls (Chemical Standardisation)

Outlined below is the minimum Chemical, Manufacturing and Control (Chemical Standardisation) information that should be submitted, in an investigational approval document to support studies in humans (a phase 1 or phase 2 clinical trial) on a herbal (botanical) product that is currently lawfully marketed without any known safety issues in the international market. Literature references and relevant official compendia or published standards should be provided wherever possible.

1. Botanical Raw Material

A certificate of authenticity signed by a trained botanist should be provided, for each herbal (botanical) raw material in a product.

2. Herbal (Botanical) Drug Substance

The type of *manufacturing process* (e.g., pulverization, decoction, expression, aqueous extraction, or ethanolic extraction) should be provided. This is especially important where more than one process exists in the literature on which the safety of the herbal (botanical) drug substance is based.

3. Herbal (Botanical) Drug Product

An herbal (botanical) drug product is manufactured from an herbal (botanical) drug substance by adding one or more excipients, mixing, blending, granulating, tableting, encapsulating, or performing other dosage form-specific procedures, followed by packaging. When packaged without further processing, an herbal (botanical) drug substance is considered the drug product. The following information should be provided for an herbal (botanical) drug product:

a. A *qualitative description* of the finished product, including the dosage form, route of administration, names of all ingredients (i.e., herbal (botanical) drug substance and excipients), and a statement that the product is not adulterated with potent, toxic, or addictive botanical substances, synthetic or highly purified drugs, or biotechnology- or other naturally derived drugs.

b. The *composition or quantitative description* of the finished product (i.e., the quantity of the herbal (botanical) drug substance) expressed in terms of amount per dosage unit. This information should be provided in tabulated form.

Example for a single-herb botanical drug product:

Component	Amount per 1-g tablet
Senna leaf extract (1:8 powdered aqueous extract)	250 mg

Example for a multi-herb botanical drug product:

Component	Amount per 1-g tablet
A 1:5 powdered, aqueous extract from 1:1 mixture of *Forsythia suspensa* Vahl. flowers and *Lonicera japonica* Thunb. fruits	600 mg

c. If available, the *manufacturer's certificate of analysis* for the study product or *authorization to allow the NRDHM to cross-reference* its previous submission in Malaysia for the relevant information. If this information is unavailable for a foreign-marketed product, the sponsor should perform *quality testing* on the product according to the recommendation listed for herbal (botanical) products that have not been previously marketed, a heavy metal analysis, and an animal safety test, if applicable, and should provide the *test results* in the investigational approval document. The study product should be from a single source and, where feasible, from a single batch. A product sample from the batch to be used in the clinical study should be retained for possible future testing by NRDHM.

4. Placebo

The components of any placebo used should be described.

5. Labeling

The following labeling information should be provided:

a. A copy of the container label and the immediate outer carton label of the marketed product to be used in the clinical study.

b. A mock or printed representation of the proposed container label that will be provided to the investigators in the proposed clinical study. It should contain the following information: protocol number; patient number; sponsor(s) name; product name or code number; strength and/or potency; recommended storage conditions; lot number; and the statement, _Caution: New drug _ Limited to investigational use. In a placebo-controlled clinical trial, both the study drug and the placebo should be properly labeled to protect the integrity of the blinded study.

C. Safety Pharmacology/Toxicology (Preclinical Safety Assessment)

Since these products have well established histories of human use, to support initial clinical trials, previous human use experience and available animal toxicity data concerning the clinical formulation and the individual botanical ingredients within the formulation must be provided. If the product has already been used in the country as a dietary supplement, it would be adequate to provide a database search to identify information relevant to safety and effectiveness of a) the final formulation of the proposed herbal product; b) the individual botanical ingredients, and c) known chemical constituents of the herbal ingredients. The format for integrating and submitting the data for review is provided.

For herbal products **NOT** already in the Malaysian market, the type and nature of preclinical safety pharmacology/toxicology information needed, prior to commencement of initial clinical trials, will be determined on a case-by-case basis depending on the indications, proposed dosage, and available supporting safe human use information.

D. Bioavailability

Depending on the complexity of the herbal (botanical) drug product to be studied, pharmacokinetic and pharmacodynamic information may be helpful in the design and interpretation of clinical studies. Herbal (Botanical) products often consist of more than one chemical constituent. In some cases, a product(s) active moieties may not be known, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may not be feasible. However, when feasible a sponsor should attempt to monitor the blood levels of known active ingredients, representative markers, or major chemical constituents in a herbal (botanical) drug product.

2 Herbal (Botanical) Products with no previous Human Use Information

A. Description of Product and Documentation of Human Use

The following should be provided for each raw material contained in an Herbal (botanical) product not previously marketed.

1. Description of Botanicals Used

• Morphological and anatomical description (including gender, if applicable) and a photograph of the plant or plant part, alga, or macroscopic fungus used

• Natural habitat and geographical distribution of the plant, alga, or macroscopic fungus

• Current sources of the plant, alga, or macroscopic fungus, including its geographical location and whether it is cultivated or harvested from the wild

• A statement indicating whether the species is any of the following:

- Determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora;

- Entitled to special protection under any Malaysian Law or international treaty to which the Malaysia is a party;

- The critical habitat of fauna that have been determined to be endangered or threatened

2. History of Use (If Any)

• Method of preparation, processing, and formulation

• Routes, schedules, and doses of administration

• Medical claims

• Contraindications and adverse events that have been associated with use in humans and animals

• Traditional geographical areas and populations in which such use occurred

• A description of the similarities and/or differences between the traditional preparation and the proposed clinical formulation

3. Current Investigational Use (If Any)

• Proposed therapeutic claim and dose regimen (mg/kg/dose and dose/day)

• All available information in the literature both in support of and in opposition to the proposed therapeutic claim

B. Chemistry, Manufacturing, and Controls (Chemical Standardisation)

Outlined below is the Chemical, Manufacturing and Control (Chemical Standardisation) information that should be submitted, in an investigational approval document to support human studies (a phase 1 or phase 2 clinical trial) using a herbal (botanical) product that is not currently, or for which there are known safety issues.

1. Botanical Raw Material

A herbal (botanical) drug substance can be derived from one or more herbal (botanical) raw materials. The following apply to each individual botanical raw material used.

The herbal (botanical) raw material should be described as outlined below. If the botanical raw material has no documented history of use, the sponsor should so indicate. Proper identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination, should be provided. If more than one variety or source of a given species is used, each should be specified. A voucher specimen of the plant or plant parts should be retained for each batch.

In addition, the following items should be provided if available:

- Certificate of authenticity
- Name and address of the grower and/or supplier
- Harvest location and harvest time
- Collection, washing, drying, and preservation procedures
- Handling, transportation, and storage

2. Herbal (Botanical) Drug Substance

The following information should be provided for all botanical drug substances, regardless of whether they are prepared from one or more botanical raw materials:

a. A *qualitative description* of the herbal drug substance, including the name, appearance, physical and chemical properties, active constituent (if known), biological activity (if known), and clinical indication (if known) of each herbal (botanical) raw material. If the active constituent, biological activity, and/or clinical indication is unknown, the sponsor should clearly so state. In the case of a multi-herb substance, the sponsor should state whether the herbal drug substance is prepared by combining individually processed herbal (botanical) drug substances or by processing combined herbal (botanical) raw materials.

b. The *quantitative description* (*strength*) of the herbal drug substance. Historically, the strength of a herbal (botanical) drug substance is expressed simply as the absolute weight of the processed substance. The batch size and the yield of the process, relative to the herbal (botanical) raw material, should also be indicated. Furthermore, where the active constituents or other chemical markers are known and measurable, the amount in which they are present in the herbal (botanical) drug substance should be declared. For a multi-herb substance, its composition should be expressed in terms of the relative ratio of the individually processed herbal (botanical) drug substances or of the herbal (botanical) raw materials before processing, whichever is appropriate.

c. The name and address of the herbal drug substance *manufacturer* (processor)

d. The type of *manufacturing process.*

e. The *quality control tests* performed on each batch of the herbal drug substance and the available test results. These tests should include, but need not be limited to, the following attributes:

- Appearance
- Chemical identification by spectroscopic or chromatographic fingerprints. Examples of spectroscopic methods include ultraviolet, infrared, and Fourier transformed infrared. Examples of chromatographic methods include high performance liquid chromatography (HPLC), HPLC with diode array detection, thin layer chromatography (TLC), 2-dimensional-TLC, and gas chromatography.
- Chemical assay (or assay) for active constituents or characteristic markers, if available
- Assay for biological activity (or biological assay), if available
- Strength by weight (equivalent to herbal (botanical) raw material)
- Heavy metals
- Microbial limits
- Animal safety test, if applicable

A chemical assay and/or assay for biological activity should be performed if the herbal (botanical) drug substance is considered potent (i.e., highly active), toxic, addictive, or to have abuse potential (e.g., ephedra or marijuana).

f. A description of the *container* in which the herbal (botanical) drug substance is to be stored and/or shipped

g. Available *stability data* on the drug substance. The sponsor should develop stability-indicating analytical methods and conduct stability studies as the early human studies progresses.

h. The *container label*, which should reflect the qualitative and quantitativ description of the herbal (botanical) drug substance, as discussed above, an recommended storage conditions. Examples of labeling for single- and multi herb substances are shown below:

Single-herb substance:

• Expressed in terms of yield:
Senna, 10 kg, equivalent to 80 kg of dried leaves
or
Senna, 10 kg, 1:8 (w/w) powdered extract of dried leaves
• Expressed in terms of chemical markers or active constituents:
Senna, 10 kg, contains 2 kg of hydroxyanthracene glycoside (sennosides), calculated as sennoside B

Multi-herb substance:

• Prepared by combining individually processed herbal (botanical) dru substances:

Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, containin 3 kg of *Lonicera japonica* Thunb. 1:4 solid extract and 3 kg of *Forsythi suspensa* Vahl. 1:6 solid extract

• Prepared by processing combined herbal (botanical) raw materials:

Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, a 1:5 powdered extract prepared from 15 kg of *Lonicera japonica* Thunb. an 15 kg of *Forsythia suspensa* Vahl

3. Herbal (Botanical) Drug Product

The following information should be provided:

a. A *qualitative description* of the finished product

b. The *composition, or quantitative description*, of the finished product (i.e. the name and quantity of the herbal (botanical) drug substance and of eac excipient (if any), expressed in terms of amount per dosage unit and amoun per batch). This information should be provided in tabulated form. A quantitative description of the drug substance should be provided.

Example:

Component	Amount per tablet	Amount per batch
Senna	250 mg (equivalent to 2000 mg dried leaves)	10.0 kg (equivalent to 80.0 kg of dried leaves)
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

c. The name and address of the *manufacturer* of the finished drug product

d. A description of the *manufacturing process.* (If the herbal (botanical) drug substance is filled and packaged directly as the finished product without the addition of excipients and further processing, items b, c, and d will not apply.)

e. A list of the *quality control tests* performed on each batch of the herbal drug product and the available test results. These tests should include, but need not be limited to, the following attributes:

- Appearance
- Chemical identification by spectroscopic or chromatographic fingerprints
- Assay for active constituents or characteristic markers, if available
- Assay for biological activity (or biological assay), if available
- Strength by weight (of herbal drug substance)
- Microbial limits

- Other attributes specific to the dosage form of interest

A chemical assay and/or assay for biological activity should be performed if the herbal (botanical) drug substance is considered to be potent (i.e., highly active), toxic, addictive, or to have abuse potential.

f. A description of the *container/closure* in which the drug product is to be packaged

g. Available *stability data* on the drug product. The sponsor should develop stability-indicating analytical methods (using markers when feasible) and conduct stability studies as the initial clinical studies progresses.

4. Placebo (see previous section above on this subject)

5. Labeling (see previous section above on this subject)

Additionally, a quantitative description of the herbal drug substance per dosage unit should be provided. An example of a quantitative description for a multi-herb botanical drug product is shown below:

BRAND X. 100 tablets. Each 1-g tablet contains:
300 mg of *Lonicera japonica* Thunb. 1:4 solid extract and
300 mg of *Forsythia suspensa* Vahl. 1:6 solid extract

C. Safety Pharmacology/Toxicology (Preclinical Safety Assessment)

Safety pharmacology and toxicological studies are paramount in establishing the safety of herbal medicinal products where there has been no clinical experience. The information is essential for assessing risk-to-benefit ratio of the product, guiding initial clinical studies and predicting potential toxicity. These

herbal products, whilst not having any clinical human use, may have been used as part of traditional practice. Such traditional herbal products have evolved over time and have documented historical formula which defines the amount of each herbal ingredient falling within the range of traditional usage as well as the traditional processing methodologies. Further the traditional manner in terms of conditions of use, route, schedule of administration, and quantity of use are documented. For products that have such information and that are manufactured and proposed use is in accordance to documented traditional practices, may be considered for initial clinical studies without standard preclinical toxicological testing. Should the preliminary results show promising results, the prescribed safety pharmacology and toxicological studies must be conducted *prior* to further clinical testing.

Herbal products that are not prepared according to traditional formulation, preparation, or processing will be required to be subjected, fully, to the prescribed safety pharmacology and toxicological studies *prior* to conducting an initial clinical study. The nature of pre-clinical safety and toxicology information required prior to initiation will be determined on a case-by-case basis, depending on the indications, extent of traditional human use, preparation or processing methodology used and safety concerns about the new formulation.

D. Bioavailability

An herbal (botanical) product's active constituents may be unknown, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may not be feasible. However, when feasible a sponsor should attempt to monitor the blood levels of known active constituents, representative markers, or other major chemical constituents in an herbal drug product. Because there is less human use experience with botanical products that have never been lawfully marketed than with those that have been, a sponsor of a drug that has not been lawfully marketed should consult the NCRDHM on in-vitro and in-vivo procedures to assess potential drug-drug interaction when a clinical study includes co-administration with another drug.

For a herbal (botanical) product that is prepared according to traditional methodology, the nature of clinical pharmacology information needed should be determined on a case-by-case basis, depending on the indications, extent of human experience, target patient population, and projected length of clinical use.

E. Clinical Evaluation

Initial clinical studies of herbal products in this category are the same as those for products in the earlier category, except that due to the lack of previous clinical experience there are greater concerns regarding toxicity issues. Therefore greater assurance on the safety of the product will be required in the aspects of toxicology and chemical safety.

3 Herbal Products for expanded human use evaluation (prior to registration).

To support phase 3 clinical trials (pre-registration) using a herbal (botanical) product, regardless of its marketing experience, the following Chemical, Manufacturing and Control (Chemical Standardisation) information should be provided unless already submitted in the investigation approval document for phase 1/phase 2 studies on the product:

1. Expanded Clinical Studies

a. Herbal (Botanical) raw material

• A *description* of the botanical raw material as outlined in sections previously. If the herbal (botanical) has no documented history of use, this should be indicated. Proper identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination, should be provided. If more than one variety or source of a given species is used, they should be blended in a fixed proportion in a consistent manner. A voucher specimen of the plant or plant parts should be retained for every batch. In addition, a certificate of authenticity and information on the grower and/or supplier, growing conditions (including pesticides used), harvest location, harvest time, preservation procedures, handling, and shipping should be provided.

• A chromatographic fingerprint of each herbal (botanical) raw material and the *chemical identity* of the active constituents or characteristic markers in the herbal (botanical) raw material

• The name and address of the herbal (botanical) raw material *manufacturer* (processor)

• A description of the *preparation* of the herbal (botanical) raw material, including collection, washing, drying, preservation, and/or detoxification and preservation procedures. Equipment and quantity used, temperature employed, processing time, in-process controls, and yield should be specified.

• The *quality control tests* applied by the botanical raw material supplier, including the following specifications:

- Botanical identification
- Chemical identification by spectroscopic or chromatographic fingerprint
- Chemical identification for active constituents or characteristic markers if active constituents are not known
- Assay for active constituents or characteristic markers if active constituents are not known
- Biological assay, if available
- Heavy metals
- Microbial limits

- Residual pesticides, including parent pesticides and their major toxic metabolites
- Adventitious toxins (e.g., aflatoxins)
- Foreign materials and adulterants

• A specimen of the herbal (botanical) raw material retained as the *reference standard* for use in identification, fingerprinting, and other comparative and non-comparative tests

• A *certificate of analysis* for a representative batch of the herbal (botanical) raw material

• A description of the *storage conditions,* including the container/closure system and temperature

b. Herbal (botanical) drug substance

• A *qualitative and quantitative description* of the herbal drug substance and the name and address of the *manufacturer.*

• A *chemical identification* for the active constituents or characteristic markers in the herbal drug substance, as an alternative. If the chemical identity is unknown, a representative chromatographic fingerprint may suffice.

• Appropriate *specifications* (tests, methods, and acceptance criteria) for the herbal (botanical) raw material, similar to the list of quality control specifications in the earlier section for herbal (botanical) raw materials as, established by the botanical drug substance manufacturer. Upon receipt of each batch of the raw material and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.

A description of the *manufacturing process* for the herbal (botanical) drug substance. The description should include the quantity of herbal (botanical) raw material, equipment, solvents, temperature/time for mixing, grinding, extraction and/or drying, yield, and in-process controls. The yield of the process, expressed as the amount of the extract relative to the amount of the original botanical raw material, should also be indicated. If more than one herbal (botanical) raw material is introduced to produce a multi-herb substance, the quantity of each raw material and the sequence of addition, mixing, grinding, and/or extraction should be provided. If a multi-herb substance is prepared by combining two or more individually processed herbal (botanical) drug substances, the process leading to each herbal (botanical) drug substance should be described separately.

• The *quality control tests*, including, but not limited to, the following specifications:

- Appearance
-Chemical identification by spectroscopic or chromatographic fingerprints
- Chemical identification for the active constituents or, if unknown, the characteristic markers
- Chemical assay for the active constituents, or the characteristic markers if the active constituents cannot be determined. If several herbal (botanical) raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be carried out for several active constituents or markers.
- Biological assay
- Strength by weight
- Residue on ignition
- Water content
- Residual solvents
- Heavy metals
- Microbial limits
- Animal safety test, if applicable
- Residual pesticides
- Radioisotope contaminants, if applicable
- Adventitious toxins (e.g., aflatoxins)
- Endogenous toxins (e.g., pyrrolizidine alkaloids)
- Other attributes specific to the botanical raw materials from which the drug substance is derived

• A description of all *test methods* and, where appropriate, their validation reports

• A description of the batch of herbal (botanical) drug substance designated as the *reference standard* for use in fingerprinting and other comparative tests

• Test results for a representative batch (i.e., *batch analysis*)

• A description of the *container and closure* used to package the botanical drug substance

• Sufficient *stability data* on the herbal drug substance to support its safe use during clinical studies.

• Stability-indicating analytical methods should be established.

• Information on the *container label* as described previously

c. Herbal (Botanical) drug product

• A *qualitative description and the composition* of the dosage form and the name and address of the *manufacturer*

• Appropriate *acceptance specifications* established by the herbal (botanical) drug product manufacturer for the herbal (botanical) drug substance, similar to the quality control tests described in the previous sections. Upon receipt of each batch of the drug substance and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.

• A description of the *manufacturing process*, without the actual batch record. The description should include weighing, mixing, blending, sieving, in-process controls, and other processes, as appropriate.

• The *quality control tests*, including, but not limited to, the following specifications:

- Appearance
- Chemical identification by spectroscopic or chromatographic fingerprints
- Chemical identification for the active constituents or, if unknown, the characteristic markers
- Chemical assay for active constituents or, if unknown, the characteristic markers
- Biological assay
- Strength by weight
- Residual solvents
- Microbial limits
- Adventitious toxins (e.g., aflatoxins)
- Other attributes specific to the dosage form of interest

• A description of all *test methods* and, where appropriate, their validation procedures

• Test results for a representative batch

• A description of the *container and closure* used to package the finished product

• Sufficient *stability data* on the drug product to support its safe use during clinical studies. Stability-indicating analytical methods should be established.

d. Placebo if applicable

e. Labeling (see sections for investigational labels and for quantitative description)

B. Safety Pharmacology/Toxicology (Pre-clinical Assessment)

To ensure safety prior to expanded clinical studies and to support registration of the herbal drug product safety and toxicity information needs to be provided. In this aspect, an herbal drug product when considered for registration will be evaluated in a similar manner to a new drug registration. Previous human use information would, normally, be considered insufficient, especially when it is indicated for chronic therapy. Systematic toxicological evaluation may be needed to supplement available knowledge on general toxicity, teratogenicity, mutagenicity and carcinogenicity of the final herbal drug product. Depending on the clinical indication (e.g. target patient population, disease state etc), route of use, and duration, the sequence of submission of these data may vary, hence in some instance may be carried out concurrently with Phase Three clinical trials. Details of studies are provided in the Annex.

C. Bioavailability and Drug interaction.

It is assumed that data would already have been submitted, prior to initiation of early clinical studies, based on properly designed in vivo bioavailability studies, and that these data available. Interactions with other commonly used medicines, either synthetic/highly purified or herbal may occur. It is recommended that these be investigated.

D. Clinical Evaluation

Phase Three studies that are required to be carried out are similar to those carried out for synthetic drugs. These would include refinement of dose and dosing regimens in relation to wanted and unwanted clinical effects, evaluation of long term effectiveness, multi-ethnic population cohorts, and effect on various stages/severity of disease as well as drug-drug interactions.

4. End-of-Phase 3 Clinical Studies and Pre-registration Considerations (*Requirements for Registration)*

By the end of the phase 3 clinical trial, as the sponsor prepares to submit for registration, the following objectives should be reached:

a. Adequate controls for *botanical raw materials* should be established.

b. The *manufacturing process* should be finalized and validated, and *in-process controls* should be established. An executed batch record should be available.

c. *Batch-to-batch consistency* should be demonstrated for the herbal (botanical) drug substance and drug product based on results from all chemical, physical, and biological tests on all relevant batches. All chemical constituents present in the herbal drug substance batches should be qualitatively and quantitatively comparable based on spectroscopic and/or chromatographic fingerprinting.

d. Appropriate *specifications* (i.e., a list of test attributes, analytical methods and test procedures, and acceptance criteria), including identification and assay for active constituents, identification and assay for characteristic markers, and/or biological assay, should be established to control the quality of the herbal drug substance and product. Both the active constituents and the biological assay should be clinically relevant. If the identity of the active constituents is not known or a suitable assay cannot be developed, the

characteristic markers should be demonstrated to be clinically relevant by direct or indirect correlation to the clinical outcome (i.e. .related to the bioactive constituents).

e. *Analytical methods and test procedures* should be properly validated. Analytical methods used for fingerprinting should be capable of detecting as many chemical constituents as possible. Multiple fingerprints, using a combination of analytical methods with different separation principles and test conditions, may be useful. Additionally, the analytical methods in combination should be able to demonstrate the mass balance of the test sample.

f. A suitable *reference standard* for each of the herbal (botanical) raw materials, herbal drug substances, and herbal drug product should be established and retained.

g. *Stability-indicating analytical methods* should be developed to monitor the stability of the herbal drug substance and herbal drug product. The stability of a herbal (botanical) drug substance or product generally should not be based entirely on the assay of the active constituents, assay of the characteristic markers, or biological assay, because degradants formed during storage from other chemical constituents in the herbal (botanical) drug substance or product should also be controlled. An analytical method capable of detecting these degradants (such as a chromatographic fingerprint) should be established through exploratory studies by subjecting the herbal drug substance and herbal drug product to stress conditions.

h. A comparison of the similarities and/or differences in Chemical, Manufacturing and Control (Chemical Standardisation) information submitted at the time of consideration for initiation of the preclinical, clinical, and intended commercial products applications should be made regarding herbal (botanical) raw materials, herbal drug substance, and herbal drug product.

Definitions

The following definitions are intended for use in this guidance only.

Active Constituent: The chemical constituent in a herbal (botanical) raw material, herbal drug substance, or herbal drug product that is responsible for the intended pharmacological activity or therapeutic effect

Herbal (Botanical) Product: A finished, labeled product that contains vegetable matter, which may include plant materials (see below), algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a herbal (botanical) product may be a food, drug, or cosmetic.

Herbal (Botanical) Drug Product: An herbal (botanical) product that is intended for use as a drug; an herbal drug product that is prepared from an herbal (botanical) drug substance. Herbal (Botanical) drug products are available in a variety of dosage forms, such as solutions (e.g., teas), powders, tablets, capsules, elixirs, and topicals.

Herbal (Botanical) Drug Substance: A drug substance derived from one or more plants, algae, or macroscopic fungi. It is prepared from botanical raw materials by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. It may be available in a variety of physical forms, such as powder, paste, concentrated liquid, juice, gum, syrup, or oil. A herbal (botanical) drug substance can be made from one or more herbal (botanical) raw materials (see Single-Herb and Multi-Herb (botanical) drug substance or product). A herbal (botanical) drug substance does not include a highly purified or chemically modified substance derived from natural sources.

Herbal (Botanical) Ingredient: A component of a herbal (botanical) drug substance or product that originates from a herbal (botanical) raw material

Herbal (Botanical) Raw Material: Fresh or processed (e.g., cleaned, frozen, dried, or sliced) part of a single species of plant or a fresh or processed alga or macroscopic fungus

Chromatographic Fingerprint: A chromatographic profile of a herbal (botanical) raw material or herbal drug substance that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a batch and consistency from batch to batch

Cosmetic: An article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, or an article intended for use as a component of any such article, except that such term does not include soaps

Dosage Form: A pharmaceutical product type, for example, tablet, capsule, solution, or cream that contains a drug ingredient (substance) generally, but not necessarily, in association with excipients

Drug: (A) articles recognized in the official Pharmacopoeia of the Malaysia; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animal.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body

Drug Product: The dosage form in the final immediate packaging intended for marketing

Formulation: A formula that lists the components (or ingredients) and composition of the dosage form. The components and composition of a multi-herb botanical drug substance should be part of the total formulation.

Marker: A chemical constituent of a herbal (botanical) raw material, drug substance, or drug product that is used for identification and/or quality control purposes, especially when the active constituents are not known or identified.

Multi-Herb (Botanical Drug) Substance or Product: A herbal (botanical) drug substance or drug product that is derived from more than one herbal (botanical) raw material, each of which is considered a botanical ingredient. A multi-herb botanical drug substance may be prepared by processing together two or more herbal (botanical) raw materials, or by combining two or more single-herb botanical drug substances that have been individually processed from their corresponding raw materials. In the latter case, the individual single-herb botanical drug substances may be introduced simultaneously or at different stages during the manufacturing process of the dosage form.

Plant Material: A plant or plant part (e.g., bark, wood, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof) as well as exudates

Single-Herb (Botanical Drug) Substance or Product: A botanical drug substance or drug product that is derived from one botanical raw material. Therefore, a single-herb substance or product generally contains only one herbal (botanical) ingredient.

ANNEX

Guidance for Preclinical Safety and Toxicity Assessment

The following are points to consider in preparing a preclinical pharmacology/toxicology development plan for a botanical drug product that is intended to be used in large-scale human trials or to support an NDA. If questions arise during any stage of the clinical development of an herbal drug, sponsors are encouraged to consult the NRDHM.

1. Repeat-Dose General Toxicity Studies

The primary objective of long-term, repeat-dose toxicity studies in animals is to identify the target organs and/or systems for toxicity and the threshold doses for producing toxic effects. The studies provide information valuable for designing long-term clinical studies at safe doses with appropriate monitoring for predicted adverse reactions. Existing literature on the animal toxicity of a botanical drug product is often limited to single-dose (acute) toxicity studies. These studies may be inadequate to support the conclusion that a botanical drug product is *nontoxic* for multiple administrations because they were not designed to monitor the usual parameters of toxicity (e.g., clinical pathology and histopathology) or take into consideration the effect of more frequent dosing.

To support Phase Three clinical trials, repeat-dose toxicity of a drug product should usually be evaluated in two mammalian species (one of which is a non-rodent) by employing sufficiently high doses to produce a toxic effect or by using a maximum feasible dose. If possible, the drug should be tested using the same formulation and route of administration as proposed for clinical use. Animal studies should be of duration at least equal to that of the clinical trial (usually a minimum of two weeks). General animal toxicity studies need not exceed 6 months of testing in a rodent species and 9 months testing in a non-rodent species.

2. Nonclinical Pharmacokinetic/Toxicokinetic Studies

In the development of a new drug that is a single molecular entity, pharmacokinetic studies are often carried out to demonstrate systemic exposure and to relate exposure levels to toxicities in both animals and humans. Because botanical products usually consist of more than one chemical constituent, standard pharmacokinetic measurements to substantiate the systemic exposure of a botanical drug product in animals may be technically infeasible. However, monitoring major or representative chemical constituents in a botanical drug product can provide valuable information regarding systemic exposure. Depending on the complexity of the botanical drug product to be studied, pharmacokinetics could be helpful in the design and interpretation of toxicity studies.

3. Reproductive Toxicology

Reproductive toxicology studies, such as those on fertility/reproductive performance, teratology, and prenatal/perinatal development in animals, provide information on the potential of a botanical drug product to produce toxicity during the different stages of reproductive and developmental processes. In the absence of documentation on reproductive toxicity in humans or animals, these tests should be conducted prior to expanded clinical trials.

4. Genotoxicity Studies

Information on the potential of a botanical drug product to produce genetic toxicity should be obtained as early as possible, preferably before the initiation of human clinical trials. A complete assessment of genetic toxicity may be needed prior to expanded clinical trials. A standard battery of tests is defined in the ICH guidance's needs to be followed. If the tests chosen indicate that a drug is devoid of genetic toxicity, additional studies may not be needed. If one or more test results are positive, the sponsor may need to carry out additional genotoxicity tests in consultation with the NCRDHM.

5. Carcinogenicity Studies

Carcinogenicity studies may be needed to support marketing approval of a botanical drug, depending on the duration of therapy or any specific cause for concern. The toxicity profile of the botanical drug product and the indication and duration of the intended use may influence the need for carcinogenicity studies and their timing relative to clinical development. Doses used should be chosen according to the principles outlined in the ICH guidance's

6. Special Pharmacology/Toxicology Studies

A general evaluation of pharmacological activity on organs and/or systems is often performed during new drug development. This evaluation can be accomplished using established in vitro and in vivo assays of broad specificity that screen for the modes and sites of action of the botanical drug. When significant and unique toxicities to certain organs and/or systems are evident, the sponsor should provide further explanation of the mechanism of toxic actions, if necessary by performing additional in vitro or in vivo studies.

7. Regulatory Considerations

Preclinical toxicity studies conducted as part of botanical drug development and intended to support safety must be in accordance with regulations governing good laboratory practices under ICH guidelines.

To the extent possible, a botanical drug substance tested in animals should be prepared and processed in the same manner, and the botanical drug product should have the same formulation, as the product intended for human use. Both the drug substance and the drug product should be made with batch-to-batch consistency. If changes occur in the drug substance or product during clinical development, bridging toxicity studies might be needed.

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