Ministry of Health Malaysia

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

GUIDELINES FOR LEVELS AND KINDS OF EVIDENCE TO SUPPORT CLAIMS FOR THERAPEUTIC PRODUCTS

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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
Ministry of Health

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.

Guidelines for levels and kinds of evidence to support claim for therapeutic products

1. Claims based on evidence of traditional use

Traditional medicines are used by some 60% of the world's population and in some countries are extensively incorporated into the public health system. They are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation that underpins the use of these traditional medicines.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken as regard their mode of action and effect. Evidence of traditional use may be used to support claims for therapeutic products. The National National Committee For Research and Development in Herbal Medicine (NRDHM) has adopted the following definition of "traditional use" for regulatory purposes.

Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purposes.

In assessing traditional use, the text and context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances and certain behavioral rules promoting healthy diets and habits are likely to apply to them. In these cases Holistic principles are part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered.

In making a claim based on traditional use, products and substances that form part of traditional therapies should identify the therapy to which they belong as well as the product description/name and the symptom/indication/condition for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homeopathic medicine, aromatherapy and other indigenous medicines. Where there are multi-component products which comprise active ingredients from different traditional therapies, the therapy from which each ingredient is derived from needs to be described in the claim.

Adapted from the Guidelines for levels and kinds of evidence to support claims for therapeutic goods produced by the Therapeutic Goods Administration, PO Box 100, Woden ACT 2606, Australia, in April 2000.

'Where tradition of use has been recorded as an oral rather than written history, evidence of such claim should be obtained from the appropriate practitioner or indigenous groups, who maintain such history.

Modification of the classic formulations in traditional Chinese Medicine (TCM) and Ayurvedic medicine must be based on the classical theory associated with the therapy and on traditional methods of preparation, in order for these products to make a traditional claim. For example, to meet the criteria for a traditional claim using evidence of traditional use, the overall formulation of a TCM needs to reflect the classical methods of combination. Claims for combinations in Western Herbal formulations must be based on evidence linking the particular formulation (including methods of preparation) with traditional preparations, and must reflect the traditional knowledge about each individual herb in the product.

With respect to multigenerational use of homeopathic medicines, it is recognized that homeopathic medicine represents a special case where the manufacturing process of serial dilution is a major component of the tradition of use of the therapy. Providing that a new substance is prepared according to principles described in the appropriate approved homeopathic Pharmacopoeia, and satisfies safety requirements, claims may be assessed on an "evidence of traditional use" basis. Evidence of traditional use includes independent written histories of use in traditional or contemporary homeopathic literature, multigenerational use, homeopathic proving, records of clinical use and records of the set of symptoms provoked by a "crude" substance. Claims made in relation to homeopathic products must be consistent with the homeopathic picture of the remedy or remedies on which the claim is based.

Substances that have been altered significantly in their constituent profile from the classical traditional medicine, for which the claim is being made, require scientific evidence in order to substantiate their claimed action.

Combinations of substances, some of which have a history of traditional use, and others which do not but are supported by scientific evidence, may make claims based both on their traditional-use components and the scientific evidence, thus allowing a mixed claim. Should scientific evidence be contrary to the evidence based on traditional use, the claim used must reflect the truth, on balance of the evidence available.

For listable multi-component products, traditional claims can be based on the evidence of traditional use for the product itself, or on evidence for an individual component or components about which claims are made. However, the dose of the component or components mentioned in the claim must be consistent with the evidence, and the composition and preparation of the product must be consistent with the holistic principles of the tradition about which the claim is made.

2. What kinds of claims does the evidence support?

There are two types of evidence which can be used to support claims on therapeutic products. These are scientific evidence and evidence based on traditional use of a product or substance.

3. Claims based on scientific evidence

There are various types of claims based on scientific evidence that can be made; they are generally categorized according to the type of information they convey. Traditionally, claims can be ranked in relation to the relative strength of the claim and

their likely impact on consumers. These rankings provide a basis for the level of scientific evidence which may be required to support each type of claim.

Claims that may be made about therapeutic products are categorized into three levels namely -high, medium and general. Different levels of evidence are required to support each level of claim. Within these three levels there are several different types of claims that may be made. For simplicity, this approach can be summarized as shown in Table 1.

There is a wide variety of references, research papers and texts which may be used as sources of evidence to support these claims. No list of acceptable references can be exhaustive, but some broad guidance for sponsors is offered. The absence of a reference from this list does not necessarily mean the reference is unsuitable for inclusion.

Sponsors should make sure that the research on which they rely on is relevant to the specific product being promoted and to the specific benefit being claimed. Further guidance for registration of herbal medicines is available from the Drug Control Authority (DCA).

Table 1. Levels and types of claims and the evidence required to support them- based on scientific evidence

Level of claim	Type of claim	Evidence required to support claim
HIGH	• Treats/cures/manages any disease/ disorder • Prevention of any disease or disorder • Treatment of vitamin or mineral deficiency diseases	High level Registration only considered on recommendation of National Committee For Research and Development in Herbal Medicine
MEDIUM	• Health enhancement • Reduction of risk of a disease/disorder • Reduction in frequency of a discrete event • Aids/assists in the management of a named symptom/disease/disorder • Relief of symptom of a named disease or disorder	Medium level Sponsor must hold the evidence for listable products
GENERAL	• Health maintenance, including nutritional support • Vitamin or mineral supplementation • Relief of symptoms (not related to a disease or disorder)	General level Sponsor must hold the evidence for listable products

Notes:

There are some specific exemptions to this table which are not considered to be high level claims.

2. *Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.*

3. *All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".*

4. *Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDL unless there is evidence to support a therapeutic effect below this level.*

4. Registrable diseases list

There is a list of diseases/disorders about which claims may be made only after evaluation of the product and the claim(s) through Registration of the product. The list refers to serious diseases/disorders and it applies to claims based on evidence of traditional use, as well as to those based on scientific evidence. The list is known as the "Registrable disease" list and it applies to medicines but not devices. Decisions made with respect to the Registration of medical devices are based on a different set of categorisations and guidelines.

The definition of a serious disease or disorder is one for which there is a substantial body of medical opinion that the disease cannot or should not be diagnosed or treated except under medical advice.

Claims for Registrable diseases may be made under certain circumstances, but only after the safety, quality and efficacy of the product and the claim(s), have been evaluated by the DCA or other relevant evaluation committee. Where a sponsor seeks to mention a Registrable disease in what would otherwise have been categorised as a medium or general level claim, that claim would become Registrable and the product would require Registration based on the recommendation of the National Committee for Research and Development in Herbal Medicine.

The "Registrable disease" list is shown in Table 2. DCA is in the process of developing a guideline to support the interpretation of the Registrable diseases list. The guideline identifies diseases/disorders that may be mentioned in claims on Listed goods, and therefore claims relating to these diseases/ disorders do not, in general, require Registration. DCA advice may be sought where sponsors are in doubt about diseases/disorders that are not included in either list.

Table 2. The registrable disease list (for medicines)

Disease/disorder/action-serious manifestation of	Disease/disorder/action-serious manifestation of (cont'd)
1) Abortifacient action.	2) Infectious diseases, including sexually transmitted diseases, but not: • symptomatic relief of upper respiratory tract infections; • management of cold sores; • the use of condoms to prevent transmission during sexual intercourse; or topical treatment for non genital warts.
3) Cardiovascular diseases but not • the use of devices to measure parameters or control circulation locally; or reference to assistance of peripheral circulation.	4) Insomnia -persistent
5) Dental and periodontal disease but not dental caries.	6) Mental diseases, ailments or defects including substance abuse.
7) Diseases of joint, bone, collagen, and rheumatic disease, but not • relief of symptoms; • osteoarthritis, or • calcium for the prevention of osteoporosis.	8) Metabolic disorders
9) Diseases of the eye or ear likely to lead to severe impairment, blindness or deafness.	10) Musculoskeletal diseases
11) Diseases of the liver, biliary system or pancreas, but not: • liver tonic or liver formula.	12) Neoplastic disease (as cancers)
13) Endocrine diseases and conditions, including diabetes and prostatic disease • pregnancy testing	14) Nervous system diseases, but not • foliate for neural tube defects
15) Gastrointestinal diseases or disorders but not • relief of symptoms	16) Renal diseases and diseases of the genito-urinary tract.
17) Hematological disorders and diseases	18) Respiratory diseases, but not: • symptomatic relief of upper respiratory tract infections.
19) Immune disorders and diseases	20) Skin diseases, other than relief of symptoms by topical treatment, with a warning not to use for long periods without medical advice. Sunscreens may however, carry claims relating to the prevention of skin cancer and skin damage.
21) Immunisation	22) Poisoning, venomous bites and stings treatment of.

5. Claims based on evidence of traditional use

Claims which may be made about therapeutic goods using evidence of traditional use are categorised into two levels-medium and general according to the relative strengths of the claim. Medium level claims are stronger claims but their wording is required to be qualified and more evidence is required to support them. This general approach is summarised in Tables 3, 4, and 5.

Table 3. Levels and types of claims and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim[2]	Evidence required to support
MEDIUM	• Health enhancement[1] Reduction of risk of a disease / disorder • Reduction in frequency of a discrete event • Aids/assists in the management of a named symptom/disease/ disorder • Relief of symptoms of a named disease or disorder[5,6]	This (tradition) medicine has been used for indication) [5]. This claim is based on traditional use[3]	Primary evidence: Two of the following four sources that demonstrate adequate support for the indications claimed: 1. DCA-approved Pharmacopoeia. 2. DCA -approved Monograph. 3. Three independent written histories of use in the classical or traditional medical literature[4]. 4. Availability through any other country's government public dispensaries for the indication claimed.

Notes:

1. *Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.*
2. *Or words to this effect*
3. *Where scientific evidence is available to support the entire claim, the words, "This claim is based on traditional use" is optional.*
4. *In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts that accurately report the classical or traditional literature may be used to support claims.*
5. *Terms must be in the original language of the traditional medical culture, for example "Shen" not "Kidney" in TCM.*
6. *All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".*

Table 4. Levels and types of claims and the evidence required to support them based on evidence of traditional use

Level of claim	Type of claim	Wording of Claims	Evidence required to support
GENERAL	• Health maintenance, including for example claims relating to nutritional support. • Relief of symptoms (not referring to a disease or disorder)[2]. Claims for traditional syndromes and actions[3]	This (tradition) medicine has been traditionally used for (indication)[3]	Primary evidence: One of the following four sources that demonstrate adequate support for the indications claimed: 1. DCA-approved Pharmacopoeia. 2. DCA-approved Monograph. 3. Three independent written histories of use in the classical or traditional medical literature[4]. 4. Availability through any other country's government public dispensaries for the indication claimed.

Notes:

1. *Or words to this effect*
2. *All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".*
3. *Terms must be in the original language of the traditional medical culture, for example "Shen" not "Kidney" in TCM.*
4. *In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts that accurately report the classical or traditional literature may be used to support claims.*

Table 5. Levels and types of claims and the evidence required to support them - based on evidence of traditional use - non-primary evidence

Supporting evidence	Commonly referred to in appropriate prescribed teaching text books used in tertiary-level training of healthcare professionals. This evidence does not stand alone and may only be used in conjunction with primary evidence.

References

1) Regulatory Situation of. Herbal Medicines-Worldwide. Review World Health Organisation 1998

2) Guidelines for the assessment of Herbal Medicines-World Health Organisation 1991

3) Research Guidelines for evaluating Safety and Efficacy of Herbal Medicines. WPRO 1994

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5) Quality of Herbal Remedies-Assessment European Commision 1989

6) Quality Assessment of Natural Remedies. NLN Publication Nordic Council of Medicine 1996

7) Herbal Medicines Medicines Control Agency 1995

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9) Therapeutics Good Administrations-various directives on herbal Products TGA Australia

10) Draft Guidance to Industry-Botaical Products. FDA./CDER 2000