



**RESEARCH
GUIDELINES
FOR EVALUATING
THE SAFETY
AND EFFICACY
OF HERBAL
MEDICINES**



**World Health Organization
Regional Office for the Western Pacific
Manila**

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 180 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of human resources for health, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; coordinating the global strategy for the prevention and control of AIDS; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Statistical Classification of Diseases and Related Health Problems; and collecting and disseminating health statistical information.

Reflecting the concerns and priorities of the Organization and its Member States, WHO publications provide authoritative information and guidance aimed at promoting and protecting health and preventing and controlling disease.

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FOREWORD

Herbal medicines have been used for thousands of years. The practice continues today because of its biomedical benefits and place in cultural beliefs in many parts of the world. The economic reality of the inaccessibility of modern medication for many societies has also played a major role in the broad use of herbal medicines.

The World Health Organization has recognized the contribution and value of the herbal medicines used by a large segment of the world's population. A growing interest in usage has created the need for greater precision in preparation and evaluation and has stimulated research into herbal medicines' various uses and applications.

The Western Pacific Region has a rich tradition of preparation and use of herbal medicines. In 1992, the WHO Regional Office for the Western Pacific invited a group of experts to develop criteria and general principles to guide research work on evaluating herbal medicines. These guidelines have been prepared for research on different forms of herbal medicines, including those in traditional use. Basic scientific principles as well as any special requirements related to the use of herbal medicines in traditional practice have been incorporated in these guidelines.

These guidelines are published to support the application of evaluation principles by modern science to a tradition of herbal medicine that is still extremely vibrant and of growing interest throughout the world.

A handwritten signature in black ink, reading "S. T. Han". The signature is written in a cursive, flowing style.

S.T. Han, MD, Ph.D.
Regional Director

1. INTRODUCTION

Background

Herbal medicines, as the major remedy in traditional medical systems, have been used in medical practice for thousands of years and have made a great contribution to maintaining human health. A majority of the world's population in developing countries still relies on herbal medicines to meet its health needs. The use of these medicines has a particularly rich tradition among the peoples of the Western Pacific Region. In recent years, this has extended far beyond its original ethnic setting. The attention paid by health authorities to the use of herbal medicines has increased considerably, both because they are often the only medicine available in less developed areas and because they are becoming a popular alternative medicine in more developed areas.

The World Health Organization is fully aware of the importance of herbal medicines to the health of many people throughout the world, as stated in a number of resolutions adopted by the World Health Assembly and the Regional Committee for the Western Pacific. Thus herbal medicines have been recognized as a valuable and readily available resource for primary health care, and WHO has endorsed their safe and effective use. A comprehensive programme for the identification, cultivation, preparation, evaluation, utilization and conservation of herbal medicines has been developed. Meanwhile, it has been realized that medicinal plants are a valuable resource for new pharmaceutical products and thus a potential source of new drugs as well as for economic development.

WHO supports the appropriate use of herbal medicines and encourages the use of remedies that have been proven to be safe and effective. A few herbal medicines have withstood scientific testing, but others are used simply for traditional reasons to protect, restore or improve health. Most herbal medicines still need to be studied scientifically, although the experience obtained from their traditional use over the years should not be ignored. Member States have been seeking the cooperation of WHO in identifying safe and effective herbal medicines for use in their national health care systems. As there is not enough evidence produced by common scientific approaches to answer questions of safety and efficacy about most of the herbal medicines now in use, the rational use and further development of herbal medicines will be supported by further appropriate scientific studies of these products, and thus the development of criteria for such studies.

Goals

- To strengthen research in the evaluation of the safety and efficacy of herbal medicines.
- To strengthen and promote the rational use of herbal medicines.

Objectives

- To ensure the safety and efficacy of herbal medicines used in the health care systems of countries within the Region and elsewhere in the world.
- To provide research criteria for evaluating the safety and efficacy of herbal medicines and to propose a basis for the Member States to develop their own research guidelines for the study of herbal medicines.

Introduction

- **To facilitate the exchange of research experience and other information so that a body of reliable data for the validation of herbal medicines can be accumulated.**

Definition of terms

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.
Characterizing 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.
Biological activity	A change in the base-line function of an animal or part of an animal brought about by the administration of a test substance.
Therapeutic activity	An intervention that results in the amelioration of the manifestations of human disease.
Processed plant materials	Plant materials treated according to traditional procedures to improve their safety and/or efficacy, to facilitate their clinical use, or to make medicinal preparations.
Medicinal preparations of plant materials	Medicinal preparations that contain one or more of the following: powdered plant materials, extracts, purified extracts, or partially purified active substances isolated from plant materials. In certain cases, materials of animal or mineral origin may also be included in such preparations.

2. GENERAL CONSIDERATIONS IN HERBAL MEDICINE RESEARCH

Legal considerations

Governments should actively promote the rational use of herbal medicines that have been scientifically validated. To do so, they need a national policy for approving those that are safe and effective for specified clinical indications. The adoption of such policy will help to overcome some of the legal barriers against the use of herbal medicines which in some countries may still be inadequately standardized.

Legislation concerning procedures for the registration of herbal medicine can play a very important role in ensuring that medicinal plant preparations are of acceptable quality, safety and efficacy. Research on herbal medicines, which is necessary to ensure their improved utilization by the public, would benefit from strong governmental endorsement.

Ethical considerations

Research on herbal medicines must be carried out in accordance with all relevant ethical guidelines.

Research on human subjects

When human subjects are involved, research must be conducted in accordance with four basic principles: justice, respect for persons, beneficence and non-maleficence.

Research on animals

Research on animals must be carried out with respect for their welfare and consideration must be given to using *in vitro* laboratory methods that may reduce experimentation on intact animals.

Respect for the environment

Proper consideration must be given to protection of the environment which supports the natural products that are the basis for herbal medicines and which may yield valuable medicinal products in the future.

Traditional knowledge on herbal medicine

Herbal medicines have been used by the traditional system of medicine for a long time. Prolonged and apparently uneventful use of an herbal medicine may offer testimony of its safety and efficacy. The research approaches should differentiate between herbal medicines which have had documented experience from a long period of use with those whose traditional use has not been established.

Traditional use of herbal medicine is usually an integral part of culture, which was developed within an ethnic group before the development and spread of modern science. Respect for the principle of the traditional system of medicine under study must be an important priority. Traditional knowledge and experience of the

use of herbal medicines should be considered when the research is proposed, prepared and conducted. Consultation with traditional medical practitioners is encouraged. In conducting research on herbal medicines which are based on traditional principles and techniques, such principles and techniques should be considered.

Regulatory requirements

Regulatory requirements may be different in different countries. As a general rule, traditional experience which means that long-term use as well as the medical, historical and ethnological background are well recorded, should be taken into account. *WHO Guidelines for the Assessment of Herbal Medicine** should be consulted for the registration of herbal medicine products.

In the design and conduct of researches on herbal medicine, the country's regulatory requirements must already be considered, particularly those required for registration of herbal medicine products.

Purposes of research

There are many reasons for carrying out research. An evaluation may be carried out to prove scientifically the traditional experience on the safety and efficacy of herbal medicines. It may also be conducted to validate a new-found plant material or a new combination of herbal medicines, or even a new indication, a new dosage form or a new administrative route for an existing herbal medicine. Purified or semi-purified compounds derived from herbal medicine may also be presented for research.

* *Guidelines for the assessment of herbal medicine programme on traditional medicine.*
Geneva: World Health Organization, document, 1991 (WHO/TRM/91.4).

The requirement of evidence as to the safety and efficacy of herbal medicines and the method of research chosen should be adjusted to the original purpose of the research.

Selection of research projects

Research projects should be selected with due consideration for several factors in addition to scientific interest. Three of these are:

- (1) potential value of the research results for improving the health of the community with due regard to the prevalence of disease and the feasibility of using alternative treatments;
- (2) the medical value of indigenous plants;
- (3) technical and financial considerations.

Research approaches

Research on herbal medicines in the past has generally been carried out by individual researchers working independently. One researcher may find an active principle whose pharmacological and toxicological properties are then further studied elsewhere. Finally, yet another group may decide to go directly to human studies.

A single multidisciplinary group may enable more rapid progress. In such a group the first step might be to collect information on folkloric experience whose scientific validity is then investigated. If appropriate pharmacodynamic studies seem to verify the traditional use, the group can begin to conduct more general pharmacological and toxicological tests to assure the safety of the medicinal product, which can then be tested in an initial clinical trial. Additional confirmatory clinical trials may be conducted if warranted.

General considerations in herbal medicine research

In certain instances, the isolation of an active substance may be useful in order to provide an exact dosage. In many cases, however, the plant preparation as a whole is therapeutically effective even though the active principle is not known. The clinical investigation of the therapeutic activity of such crude preparations may be useful, because that activity may depend not only on a single substance but may be influenced by a large number of other components in the herbal medicine.

Assuring access to relevant databases

Databases devoted to herbal medicines and natural products have been established in several countries and areas including China, Hong Kong, Japan and the United States. Easy access to such databases greatly facilitates the efforts of those interested in herbal medicines. Since the maintenance of such databases and access to them are costly, a government financial subsidy may be necessary in order to assure access of researchers and health planners to the information needed to hasten the rational use of herbal medicines in their countries.

Education

Dissemination of knowledge about herbal medicines in the form both of courses for professional health workers and of information for the public can greatly aid the overall effort to promote the rational use of herbal medicines.

3. RESEARCH STUDIES

Literature background

As the various traditions of herbal medicine have their roots in many different cultures and have only recently been investigated scientifically, it must be recognized that knowledge about herbal remedies is apt to be still perpetuated by oral tradition and found in anecdotal observations rather than in systematic laboratory and clinical studies that have been published in the scientific literature. Furthermore, it must also be recognized that while some publications on herbal medicines may not meet the stringent requirements of international peer-reviewed journals, they may still provide potentially useful observations and ideas for further study. Therefore, a thorough literature survey should be the starting point for every serious effort in herbal medicine research.

Protocol preparation

A carefully planned protocol is a prerequisite for preparing any successful research project. A survey of the literature should help to put the objective of the project into sharp focus. A working hypothesis is then formulated and the experimental approach to test this hypothesis is designed. The methods necessary to gather the relevant data must, however, be executed with due consideration for the ethical aspects that govern experiments on both animals and human subjects.

Quality specifications of plant materials and preparation

All research on herbal medicines must specify the quality of the plant material or the preparation being investigated, in order that studies conducted by one investigator may be corroborated by other investigators (see Guidelines A, page 27).

Non-clinical studies

The primary objectives of non-clinical studies are:

- to determine whether such studies support the clinical use of a herbal medicine;
- to characterize the range of pharmacological actions of herbal medicines; and
- to define the chemical characteristics of pharmacologically active natural products and to elucidate their mechanisms or actions.

Pharmacodynamic investigations

Pharmacodynamic investigations are conducted in the light of the expected therapeutic effect of a herbal medicine using appropriate non-human systems.

General pharmacological investigations

General pharmacological investigations are conducted to elucidate various pharmacological activities other than the main pharmacodynamic action. Such investigations usually cover the tests on nervous, cardiovascular and respiratory systems, and if necessary others, and should be performed on conscious or

Research studies

anaesthetized animals using adequate doses and proper routes of administration.

Toxicological investigations

Toxicological investigations are required to supplement human experience in defining possible toxicity from short-term use, but are particularly important in detecting toxicity that may occur either after prolonged exposure or years after the exposure has been discontinued. Generally, the longer the anticipated human use, the longer the test substance is administered to test animals.

Methods

In the conduct of non-clinical research on herbal medicines, standard methods are usually employed. However, the use of novel technologies and methods resulting from scientific progress should be encouraged.

1. Pharmacodynamic and general pharmacological methods should utilize animal models or bioassays that closely relate to human disease as described by either traditional or modern medicine (see Guidelines B, page 31).
2. Toxicological methods

Animal and other toxicity studies are conducted according to generally accepted principles, referred to collectively as Good Laboratory Practice (GLP), which should be consulted in order to design appropriate studies (see Guidelines C, page 35).

a. Systemic toxicity tests

Systemic toxicity tests refer to alteration of either physiology, anatomy (gross or microscopic) or clinical chemistry (including haematology) that result from pathological changes in any organ distant from the site at which a herbal medicine is administered.

- i. Acute toxicity tests aim to determine toxic manifestations of the test substance that occur when animals are exposed to one or more doses of the test substance within a single 24-hour period.
- ii. Long-term toxicity tests aim to determine toxic reactions when animals are exposed to the test drug for periods as long as their lifetime. In such tests, the animals are observed for behavioural changes as well as anatomical, physiological and biochemical manifestations of tissue damage. If pathological changes are detected during the period of drug administration, and the changes are not serious, it may be advisable to determine whether such changes are reversible after the drug is withdrawn. Thus, observations are made at intervals during continuous administration of the drug and then, at intervals after the drug has been withdrawn to determine whether such pathology is reversible.

- b. Local toxicity tests are done to determine the local irritation and/or systemic absorption of a herbal medicine used for local**

applications (such as respiratory inhalants, drugs applied to skin or mucosa).

- c. **Special toxicity test** - regulatory requirements for special toxicity tests vary among Member States. For herbal medicines containing commonly used herbs which have been used clinically for a long period of time, some countries may not require special tests. Mutagenicity tests, however, are commonly required. If any deviation from traditional use is contemplated (such as new use, new preparation, new route of administration or more prolonged administration), additional toxicity tests such as carcinogenicity, teratogenicity and reproduction studies may be recommended.

Clinical trials using herbal medicines

These guidelines for the clinical evaluation of herbal medicines attempt to recognize the long and diverse history of traditional medicine in the Region and the differences between the diagnostic systems of modern medicine and the various traditional medicines of the Member States. Although special considerations may be required, the general principles of the clinical trials of herbal medicines are similar to those applied to synthetic drugs if clinical trial is regarded to be necessary.

Clinical trials of herbal medicines may have two types of objectives. One is to validate the safety and efficacy that is claimed for a traditional herbal medicine. The other is to develop new herbal medicines or examine a new indication for an existing herbal medicine or a change of dose formulation, or route of administration. In some cases, trials may be designed to test the clinical activity of a purified or semi-purified compound derived from herbal medicines.

Clinical trial protocol development

The development of a protocol should be the joint effort of representatives from several disciplines such as clinical pharmacologists, pharmacists, biostatisticians, physicians and other relevant health care workers, as well as experts in traditional medicine. Ordinarily, the protocol group is chaired by the chief investigator, who is a physician. The protocol should include the following:

1. The title of the trial.
2. A clear statement on the objectives of the study.
3. The justification of the proposed trial based on the available information on safety and efficacy, including a consideration of the non-clinical data as well as the drug utilization pattern and the disease spectrum for the country concerned.
4. The rationale for the composition of the formula being studied and its relation to the principles of both herbal medicine and pharmacodynamic data.
5. The type of trial (such as controlled, open) and trial design (parallel groups, cross-over techniques), blind technique (double blind, single blind), randomization (methods and procedures).
6. Entry and exclusion criteria for study subjects (which may be based on diagnostic criteria of either modern or traditional medicine).
7. Number of trial subjects needed to achieve the trial objective, based on statistical considerations.
8. The therapeutic or clinical end points that are to be analysed at the conclusion of the trial (the unique nature of traditional medicine, which can relate to subjective wellness or quality of life, should also be

Research studies

considered when selecting the end points of the trial).

9. Control groups to be used (whether a therapeutic control group or a placebo group is used will depend on the disease being studied and the availability of alternative modern drugs or herbal medicines of proven efficacy).
10. The subjective and objective clinical observations and laboratory tests which will be recorded during the course of the trial.
11. The treatment schedule for the duration of the trial, including dosage form and route of administration and the details of the product being used as a therapeutic control.
12. Criteria for other treatments that may or may not be given to subjects during the trial.
13. Procedures for the maintenance of subject identification code lists, treatment record, randomization list and/or Case Report Form (CRF).
14. Information on establishment of the trial code, where it will be kept and when, how and by whom it can be broken in the event of an emergency.
15. The qualifications and experience of the investigators.
16. The facilities and the sites where studies will be undertaken.
17. Methodology for the evaluation of results (such as statistical methods and reports on patients or participants who withdrew from the trial).
18. Information to be given to trial subjects.

19. Relevant communications with appropriate regulatory authorities.
20. Information given to the staff involved in the trial.
21. Medical care to be made available to patients after the trial.
22. List of literature referred to in the protocol.

When considering the above items, special attention must be given to designing a protocol that eliminates bias and reduces variance.

Phases of a clinical trial

A step-by-step approach is usually followed in the development of new herbal medicines, but may ordinarily be less necessary for a study to validate the safety and efficacy of a traditional herbal medicine.

The point of entry to the trial phases will be determined by the nature and history of the herbal medicines being studied.

Clinical trials are generally designated in terms of a "phase", although study designs appropriate for the clinical evaluation of a herbal medicine may, strictly speaking, fall on the borderline between two of the following classical definitions of the usual phases.

Phase I: First trials for a new compound or a new formulation that are generally carried out with a small number of healthy volunteers or patients suffering from the disease for which the herbal medicine is intended. The main purpose of a phase I trial is to observe tolerance to the herbal medicine and therefore to get an indication of the dose that might be used safely in subsequent studies.

Research studies

Phase II: Studies on a limited number of patients to determine clinical efficacy and to further confirm safety. Such trials are preferably designed as randomized, double-blind, controlled studies, using for control groups either an existing alternative treatment or a placebo. The dosage schedules established in such studies are then used for a more extensive clinical study.

Phase III: A larger patient group is usually studied at several centres using a randomized double-blind design to validate preliminary evidence of efficacy obtained in earlier studies. Ordinarily, such trials are conducted under conditions which are as close as possible to the anticipated conditions of normal use.

Phase IV: Studies performed after the dosage form is available for general use. The main purpose of such studies is to detect toxic events that may occur so rarely that they are not detected earlier.

Individual countries may design clinical trials that follow the general principles embodied in the four phases mentioned above; namely, first to ensure general safety, then to determine efficacy and finally to use post-marketing surveillance to be certain that rare but serious adverse reactions are not occurring and to confirm the long-term efficacy.

Ethics review board

The trial protocol should be considered by an ethics review board. The board will generally be established at an institutional level but boards existing at a regional or national level can also be used. The board will be an independent body constituted of both medical and non-medical members who are not involved in the experimental activity of the trial under review. The board will verify that the rights of the patients participating in the trial are protected and that the trial is justified in medical and social terms. The board will also consider the suitability of the trial protocol, patient selection and

patient protection, and issues of informed consent of patients. The work of the board should be guided by the World Medical Association's Declaration of Helsinki (Annex 2).

The board will work under standard operating procedures which will be developed by each institution taking into consideration all necessary requirements of local regulatory authorities and related governmental agencies including such rules as those for Good Clinical Practice (GCP).

Responsibilities of investigators

The investigators who participate in the design of the protocol will also be responsible for preparing all necessary material for review by the ethics review board.

The investigators must be aware of such responsibilities as the following:

- the appropriate medical care of patients in the study;
- the ethical requirements for the trial (such as selection of patients, advice to patients);
- a knowledge of the product used in the trial;
- an appreciation of research methodology and the conduct of clinical trials (such as the recording and evaluation of results);
- an appreciation of the importance of careful monitoring of the trial and the need to take necessary action, to alter or terminate the trial if patients appear to be harmed by some aspect of the trial.

Responsibilities of the sponsor

If the product under investigation is supplied by a manufacturer, or if the trial is undertaken at the request of a manufacturer, the manufacturer (sponsor) has obligations to maintain the integrity of the investigators, the protocol group and the ethics review board, and to prevent harm to a patient. The sponsor of a study can be an institution or an individual investigator as well as a manufacturer.

The material supplied for the trial will be prepared according to Good Manufacturing Practices (GMP) to ensure the quality of the material used in the investigation. All data on the product will be made available to the investigator before the trial design is completed.

The sponsor must meet all of the local requirements set by regulatory authorities and government agencies and should be aware of standards of good clinical practice.

Data management

The aim of record keeping and the handling of data is to gather information from the trial without error in a form that can later be analysed and reported. A Case Report Form (CRF) for each patient in the trial must be completed and signed by the investigator and the patient's files, CRFs and other sources of primary data must be kept for future reference. Patient data must be handled in a way that maintains confidentiality and yet ensures accuracy. All efforts should be made to maintain error-free records.

When subjects are randomized to different groups, the randomization procedure used must be documented. In the case of a blinded trial, a code for the medicine actually administered must be kept under appropriate conditions.

Statistical analysis

Biostatistical expertise is required when the trial is designed, and must continue to be available as data are collected, analysed and prepared for the final report on the trial. Statistical considerations will govern the number of patients needed to obtain a significant result from the trial, the number of patients needed depending on the anticipated difference in the result between the treatment groups of the trial. The plan for the statistical analyses to be used at the conclusion of the trial must be determined in advance and specified within the protocol. When results are finally analysed, they should be presented in a form that facilitates clinical interpretation.

Reporting

The Chief Investigator will be responsible for preparing a final report of the trial which should be provided to the sponsor, the ethics review board, and any other authorities determined by local legislation. The results of the trials conducted on a herbal medicine should be published in a timely fashion and must include all significant positive and negative results. Even studies which fail to demonstrate efficacy should be published, as selective publication, showing only results that are favourable, will only lead to a form of misconception known as publication bias.

Evaluation of herbal medicine research

A formal procedure for the systematic evaluation of a research project or programme may greatly contribute to its success. Evaluation should be done at all stages of the study, from the design, through its implementation and completion.

Research studies

The following elements of the programme or project should be examined: goals, conformity of the protocols with goals, progress of the research towards intended goals, and impact of research.

Technology transfer and education

Herbal medical research

Training in such fields as phytochemistry and pharmacology, which contribute to the rational use of herbal medicines, will help to build a core of competent researchers for the study of herbal medicines. The productivity of such researchers will be enhanced by workshops, seminars, lectures, study tours, and scientific exchange programmes with colleagues from other countries.

The health care professions

Productive use of herbal medicines will be enhanced if the medical, dental, pharmacy and nursing professions provide continuing education on herbal medicines, introduce the subject to their students and include it in their curricula.

The public

The public, too, will benefit if herbalists, manufacturers and distributors of herbal medicines have access to unbiased information about herbal medicines.

4. USING THE GUIDELINES

These research guidelines for evaluating the safety and efficacy of herbal medicines are intended to facilitate the work of research scientists and clinicians in this field and to furnish some reference points for the governmental, industrial and non-profit organizations that provide financial support for their work. It is hoped that these guidelines will be found general enough to enable each Member State to modify them to meet its own specific needs. It must be emphasized that these guidelines are offered as a summary of scientific standards governing various aspects of the study of herbal medicines. As such, they may be useful to the regulatory authorities who control the sale of these products and the governmental agencies and medical authorities who supervise their use in the health care system.

A. Guidelines for quality specifications of plant materials and preparations

To ensure the reliability and repeatability of research on herbal medicines, the identity and quality of the plant material or preparation must be determined and stipulated according to the following headings.

Information for fresh, dried and processed plant materials

Name and characteristics

- name of the plant material in Latin, native languages and English whenever applicable.
- scientific name of the plant with reference to the authors and the family to which it belongs.
- part of the plant used and its condition (such as fresh aerial parts, dried root and rhizome, sliced or decorticated).
- time and method of collection, preliminary preparation and drying. If the material has been processed, the method of processing (such as steamed, stir-baked, carbonized) should be indicated.
- a brief description of the distribution and habitat of the plant; growing wild or cultivated (including possible pesticide used). If more than one plant species is concerned, their differences should be indicated. Drawings or photographs of the plants should be provided.

- characterizing compounds of the plant materials, which may also be the biologically or therapeutically active principle, should be quantified and described with their structural formulae, particularly if they are uncommon. For processed plant material, changes in the quantities of these characterizing compounds should be described.

Quality specifications

Authenticity. A description of the macroscopic, microscopic and sensory characteristics of the plant should be provided, including drawings or photographs if possible. A description should be provided of the physical or chemical tests done to identify the plant substances and chromatogram of the active fraction or characterizing compound should be provided. If this is not possible, it should be sufficient to identify a characteristic mixture of substances ("finger print") of the plant material.

Purity. Limits of foreign organic matter (such as stem and rachis fragments in the leaves or leaflets, leaf fragments in the flowers, etc.) and foreign mineral matter (such as sand and soil adhering to the plant material) should be specified; ash determinations should be provided.

Assay. A physical, chemical or biological assay of any known or active fractions should be described and the biological activity of the plant materials expressed in terms of this assay along with an acceptable range for the assay results.

Packaging, labelling and storage

The conditions for packaging, labelling and storage should all be recorded.

Information for medicinal preparations of plant materials

Among the medicinal preparations now widely used are powders, granules, pills, extracts, tablets and injections. Traditional powders and pills are made of powdered plant materials; tablets, granules, ointments and newer types of pills are mostly made of extracts; injections are made of purified extracts or pure active constituents isolated from the plant material. There are also certain medicinal preparations made of both powdered plant materials and extracts.

Name and formula of the product

- Name in Latin, English and native languages.
- Formula including the name of each ingredient and the quantities used for 1000 g or 1000 ml of the product. A quantity may be given as a range corresponding to a definite quantity of assayed active constituents. Any excipient used should be specified.
- Method of preparation to make 1000 g or 1000 ml of the product. The description of the method should include details of any process, such as solvent used, time and temperature of an extraction and concentration, as well as the process used to reduce the level of microbial contamination.
- The active constituents, as far as they are known, should be stated and their structural formulae given. Any chemical or pharmacological incompatibility should be mentioned.

Quality specifications

Authenticity. A description of macroscopic and sensory characteristics should be given and, if powdered plant materials are used as ingredients, their microscopic characteristics should be described

together with drawings or pictures. Physical or chemical identification tests should be described and thin-layer chromatographic procedures for the characterizing compounds should be described. A drawing or photograph of the chromatogram should be included. For compound preparations, the most important ingredients including the use of a "finger-print" should be obtained by either thin-layer chromatography or high performance liquid chromatography.

Purity. Limit tests for heavy metals in extracts and the test for freedom from methanol in alcoholic preparations should be specified. Limit tests for contaminants such as microorganisms, mycotoxins and pesticides may be needed.

Assay. The content of biologically or therapeutically active constituents, particularly those which influence the efficacy of the product, should be determined and an acceptable range specified. For herbal mixtures, the most characterizing compounds possible should be assayed.

Tests related to the form of the preparation for both non-clinical and clinical tests should follow any available regulatory requirements of Member States or the World Health Organization guidelines.

Packaging, labelling and storage. The conditions for packaging, labelling and storage should all be recorded.

B. Guidelines for pharmacodynamic and general pharmacological studies of herbal medicines

Herbal medicines have various pharmacological effects. The appropriate methods for evaluating the particular herbal medicine tested should be applied. The guidelines present basic concepts and principles which should be of utmost concern.

Animals

Species

Appropriate animals may include mice, rats, guinea pigs, rabbits, cats, dogs, etc. Characteristics of the animals such as strain, sex, age and holding conditions should be specified.

Disease model

Disease models can be made by treating animals with certain chemicals or other modalities. For example, immunologically depressed mice can be made by treating them with an immunosuppressive agent, such as cyclophosphamide. Such animals can be used to evaluate immunostimulating activity of a test medicine.

Animals with genetic defects can also be useful: for example the autoimmune mouse (NZB W/F1, MRL/1) and the hypertensive rat (SHR), etc. For study of those herbal medicines which are used under the principles of traditional medicine, animal models may need to be established according to those principles.

Test assays can use

- whole animals;
- isolated organs and tissues;
- blood and its components;
- *ex vivo* and tissue culture cells; and
- subcellular constituents.

Careful attention must be given to the selection of the test system since *in vitro* assays, although less expensive, may not provide such factors as metabolic activation which may be necessary for the biological activity of a herbal medicine. On the other hand, body fluids from test animals may contain such biologically active metabolites and be used successfully in less complex test systems.

Special attention should be given to the sensitivity, reproducibility and general acceptance of the test animals or test systems selected.

An examination of the literature may help to select the species and test systems considered to be most predictive of clinical results and therefore provide the most useful information.

Administration

Route of administration

Since oral dosage forms of herbal medicines are usually used clinically, the oral route of administration is ordinarily the most suitable for use with test animals. Additional routes may be used to approximate the intended route of administration in man.

Frequency of administration

Ordinarily, doses selected for a study should be established by means of a dose-response relationship but since such relationships often cannot be demonstrated with herbal medicines in whole animals, it may be sufficient to select one or more doses that provide a desired effect.

Selection of doses for animal studies should be in accordance with customary clinical doses.

Control group

It is essential that all studies include a negative (vehicle only) control group of animals and, if possible, a positive control group, that is, a group of animals in which the effect of a drug known to be positive is examined.

C. Guidelines for toxicity investigation of herbal medicines

These guidelines are intended to indicate the standard methods of non-clinical toxicological studies related to assessing the safety of herbal medicines. Not all tests are necessarily required for each herbal medicine intended for human study.

Acute toxicity test

Animal species

Some regulatory agencies require that at least two species be used, one of them to be selected from rodents and the other from non-rodents.

Sex

In at least one of the species, males and females should be used.

Number of animals

In the case of rodents, each group should consist of at least five animals per sex. In the case of non-rodents, each group should consist of at least two animals per sex.

Route of administration

Ordinarily, the oral route is sufficient as this is the normal route of clinical administration. However, some regulatory agencies suggest in addition a parenteral route of administration.

In cases where it is proposed to administer the herbal preparation to a human subject by the parenteral route, it may be sufficient to use this route alone for animal testing.

Dose levels

A sufficient number of dose levels should be used in rodents to determine the approximate lethal dose. In non-rodents, sufficient dose levels should be used for the observation of overt toxic signs.

Frequency of administration

The test substance should be administered in one or more doses during a 24-hour period.

Observation

Toxic signs and the severity, onset, progression and reversibility of the signs should be observed and recorded in relation to dose and time. As a general rule, the animals should be observed for at least seven to fourteen days.

Animals dying during the observation period, as well as rodents surviving to the end of the observation period should be autopsied.

If necessary, a histopathological examination should be conducted on any organ or tissue showing macroscopic changes at autopsy.

Long-term toxicity test

Animal species

Many regulatory agencies require that at least two species be used, one a rodent and the other a non-rodent.

Sex

Normally, the same number of male and female animals should be used.

Number of animals

In the case of rodents, each group should consist of at least ten males and ten females. In the case of non-rodents, each group should consist of at least three males and three females.

When interim examinations are scheduled, the number of animals should be increased accordingly.

Route of administration

Normally, the expected clinical route of administration should be used.

Administration period

The period of administration of the test substance to animals will depend on the expected period of clinical use. The period of administration of the toxicity study may vary from country to country, according to its individual regulations.

The following table reflects commonly used ranges of administration periods:

<i>Expected period of clinical use</i>	<i>Administration period for the toxicity study</i>
Single administration or repeated administration for less than one week	2 weeks to 1 month
Repeated administration, between one week to four weeks	4 weeks to 3 months
Repeated administration, between one to six months	3 to 6 months
Long-term repeated administration for more than six months	9 to 12 months

As a rule, the test substance should be administered seven days a week. Administration periods for the toxicity study must be recorded in each result.

Dose levels

Groups receiving at least three different dose levels should be used.

One dose level should not cause toxic changes (no-effect dose) and one dose level that produces overt toxic effects should be included. Within this range the addition of at least one more dose may enhance the possibility of observing a dose-response relationship for toxic manifestations. All studies should include a vehicle control group of test animals.

Observations and examinations

Observations and examinations should be performed on the following items (from 1 to 6):

1. General signs, body weight and food and water intake.

For all experimental animals, the general signs should be observed daily and body weight and food intake should be measured periodically. If useful, water intake should also be determined. The frequency of measurements should normally be as follows:

- Body weight: before the start of drug administration, at least once a week for the first three months of administration, and at least once every four weeks thereafter.
- Food intake: before the start of drug administration, at least once a week for the first three months of administration and at least once every four weeks thereafter. If the test substance is administered mixed in the food, the intake should be measured once a week.

6. In order to maximize the amount of useful information that can be obtained during the administration period, all moribund animals should be sacrificed rather than allowed to die. Prior to sacrifice, clinical observations should be recorded and blood samples collected for haematological and blood chemical analysis. At autopsy, a macroscopic examination of organs and tissues and measurement of organ weights should be recorded. A full histopathological examination should be performed in an attempt to characterize the nature (severity or degree) of all toxic changes.

All survivors should be autopsied at the end of the administration period or of the recovery period after taking blood samples for haematological (including blood chemistry) examinations; organs and tissues should be examined macroscopically and organ weights measured. Histopathological examination of the organs and tissues of animals receiving lower dosage should also be performed, if changes are found on gross or macroscopic examination of their organs and tissues of these animals, or if the highest dose group reveal significant changes. On the other hand, histopathological examination of all rodents will further improve the chances of detecting toxicity.

Recovery from toxicity

In order to investigate the recovery from toxic changes, animals that are allowed to live for varying lengths of time after cessation of the period of administration of the test substance, should be examined.

Local toxicity test

Skin sensitization test

Dermatological preparations to be tested

- solid preparations:
To be prepared by wetting the preparation with water or a suitable solvent to provide a uniform application.
- semi-solid preparations:
To be tested as undiluted preparations.
- liquid preparations:
To be tested as undiluted preparations. However, an aerosol agent can be diluted if necessary.

Experimental animals

Use a species with high susceptibility. Guinea-pigs are considered the most suitable experimental animals.

Test methods (in alphabetical order)

1. Adjuvant and patch test
2. Buehler test
3. Draize test
4. Freund's complete adjuvant test
5. Maximization test
6. Open epicutaneous test

7. Optimization test

8. Split adjuvant test

It is recognized that the above-mentioned methods differ in their probability and degree of response to sensitizing substances. However, it is generally accepted that the use of Freund's complete adjuvant increases sensitivity and therefore the possibility of detecting substances with weak sensitizing potential.

Evaluation of test results

The skin reaction of each animal should be evaluated according to the assessment standard of the particular test method used.

Other local toxicity tests

Other local toxicity tests may be conducted if the herbal medicine is intended for such use i.e. vaginal, rectal, respiratory, etc. irritations tests.

Special toxicity tests

Mutagenicity test

Test methods

I. Reverse mutation test in bacteria

1. Strains:

Salmonella typhimurium TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* WP2 uvr A, are the most commonly used bacteria.*

2. Dose levels:

At least five dose levels should be employed.

* See Notes, page 84.

3. Control groups:

A solvent group should normally serve as a negative control. Authentic mutagens which require S9 (9000 g supernatant) mixture, as well as those which do not require S9 mixture, should be employed as positive control groups.

4. Metabolic activation:

Tests in the presence of S9 mixture should also be performed.

5. Test methods:

Either a preincubation method or a plate incorporation method should be used.

6. Presentation of results:

The actual number and mean value of revertants should be presented in tables.

II. Chromosomal aberration test with mammalian cells in culture

1. Cells:

Primary or established cell lines of mammalian cells in culture should be used.

2. Dose levels:

At least three dose levels should be employed.

3. Control groups:

Normally a solvent group should serve as a negative control. A substance known to cause chromosomal aberrations should be employed as a positive control.

4. Metabolic activation:

Tests should also be performed with a suitable method of metabolic activation (such as, S9 mix)

5. Experimental procedure:

- a. Chromosomal preparations should be made at an appropriate time after treatment.
- b. At least two plates should be used for each dose level. Examination should be made for chromosomal structural aberrations and polyploid cells on 100 metaphase cells per plate.

6. Presentation of results:

The relative frequency of cells with chromosomal aberrations and the frequency of chromosomal aberrations per cell should be presented in tables.

III. Micronucleus test with rodents

1. Animals:

Male mice should normally be used.

2. Number of animals:

Each group should consist of at least five animals.

3. Route of administration:

Administration should be intraperitoneal or via the expected clinical route.

4. Dose levels:

At least three dose groups should be employed.

Guidelines for toxicity investigation of herbal medicines

5. Control groups:

As a general rule, a solvent group should serve as a negative control. A positive control group should receive a substance known to induce micronuclei.

6. Frequency of administration:

Single or repeated administration may be employed.

7. Experimental procedure:

- a. Animals should be sacrificed at an appropriate time after administration of the test substance, and bone marrow smears prepared.
- b. Normally, observation should be made of the incidence of micronuclei in 1000 polychromatic erythrocytes per animal. The relative frequency of polychromatic erythrocytes and total erythrocytes should also be calculated.

8. Presentation of results:

The incidence of polychromatic erythrocytes with micronuclei and the frequency of polychromatic erythrocytes per total erythrocytes should be presented in tables.

Carcinogenicity test

Experimental animals

1. Species and strains of the animals should be selected in consideration of such factors as resistance against infectious disease, life span, spontaneous tumour incidence, and sensitivity to known carcinogens.
2. Animals of the same species and strain should be used for preliminary and full-scale carcinogenicity studies with the same test substance.

Experimental method

1. Preliminary carcinogenicity study

This study is performed to set the dose levels for the full-scale carcinogenicity study. However, if sufficiently reliable data are available, some or all of the following studies may be omitted.

(1) Single dose toxicity studies

These studies are performed on a small number of animals in order to determine the highest dose to be used in the following repeated dose studies.

(2) Repeated dose toxicity studies

These studies are performed in order to determine the highest dose to be used in the full-scale carcinogenicity study

a. Animals:

At least two species of animals of both sexes should be used. It is desirable to initiate studies with normal animals of the same age, but no more than six weeks in rodent.

b. Number of animals:

Each group should contain about ten males and ten females.

c. Route of administration:

The same route of administration should be used as for the full-scale carcinogenicity study.

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d. Dose levels:

At least three dose groups and a control group should be established for each sex.

e. Administration period:

The administration period should be 90 days with the dose usually administered seven days a week. However, if the test substance has delayed toxicity or a cumulative effect, administration for a longer period may be necessary.

f. Experimental procedure:

1. For all animals in each group, the general signs should be observed daily and body weight measured at least once a week.

2. Autopsy and gross observations on organs and tissues should be performed on dead animals on each occasion and on surviving animals at the end of the administration period. Organs and tissues with gross changes should be examined histopathologically.

g. Results:

1. The dose in the preliminary carcinogenicity study that inhibits body weight gain by less than 10% in comparison with the control and causes neither death due to toxic effects nor remarkable changes in the general signs and laboratory examination findings of the animals. This is the highest dose to be used in the full-scale carcinogenicity study.

2. It is desirable that the highest dose should be set for each species and sex.

2. Full-scale carcinogenicity study

a. Animals:

At least two species of animals of both sexes should be employed. It is desirable to use animals with normal growth of the same age, up to the age of six weeks.

b. Number of animals:

Each group should comprise at least 50 males and 50 females. Allocation of the animals to each group should be made with the proper random sampling method based on body weight, etc.

c. Route of administration:

The expected route of clinical application should be used, if possible.

d. Dose levels:

At least three dose groups and a control group should be employed for each sex.

e. Control group:

i. A negative control group should be included.

ii. If various vehicles or emulsifiers are required to administer the test substance, the negative control group should receive such vehicles or emulsifiers alone. It is also desirable to establish an untreated control group.

2. Haematological examination

For rodents, blood samples should be taken before autopsy. For non-rodents, blood samples should be taken before the start of drug administration, at least once during the administration period (for studies of longer than one month), and before autopsy.

For both haematological and blood chemistry examinations, it is desirable to include as many parameters as possible.

3. Renal and hepatic function tests

Since the liver and kidneys are the usual organs of metabolism and excretion, they are easily affected by potentially toxic agents; their functions should be monitored in long term toxicity studies.

For rodents, a fixed number of animals from each group should be selected and urinalysis should be performed before the start of drug administration, and at least once during the administration period.

4. Other function tests

If appropriate, ECG and visual, auditory tests should be performed. For rodents, ophthalmological examination should be performed on a fixed number of animals from each group at least once during the administration period; for non-rodents, examination should be performed on all animals before the start of drug administration and at least once during the period of administration.

5. Animals found dead during the examination should be autopsied as soon as possible. A macroscopic examination should be made of organs and tissues. In addition, where possible, organ weight measurements and histopathological examinations should be performed in an attempt to identify the cause of death and the nature (severity or degree) of the toxic changes present.

measure red and white blood cells as well as to prepare smear specimens. The smear specimens should be examined in cases suggestive of blood disorders such as anaemia or pathology of lymph nodes, liver or spleen.

iv. At the end of the study, the survivors should be autopsied immediately, the organs and tissues of all animals in each group should be examined macroscopically. Histopathological examination should be performed on all animals in the highest dose group and the control group. If the incidence of neoplastic lesions between organs and tissues of the highest dose group and the control group are found to differ, the relevant organs and tissues of all animals in other dose groups should be examined histopathologically and blood examined as in (iii) above.

Evaluation of results

A test substance is considered to be positive for carcinogenicity when any of the following types of response has been observed in the carcinogenicity study:

1. Development of tumours of a type not seen in the control group.
2. Development of tumours seen with greater frequency in the test group, compared with the control group.
3. Greater varieties of organs and tissues are involved in tumour development in the test group, compared with the control group.
4. Earlier development of tumours in the test group, though in the absence of any significant difference in the incidence of tumours between the test group and the control group.

Reproductive and development toxicity test

Experimental animals

1. Species and strains should be selected in consideration of reproductive and developmental information such as fertility, incidence of spontaneous malformation, and susceptibility to substances known to affect reproduction and development.
2. It is desirable to select species and strains with a low incidence of spontaneous malformations.
3. It is desirable that animals used in studies referred to as Segment I, II and III studies be of the same strain and species.

Experimental methods

1. **Segment I. Study on administration of the test substance prior to and in the early stages of pregnancy.**
 - a. **Animals:**

At least one species of animal of both sexes such as rats or mice should be used.
 - b. **Number of animals:**

In the case of rats or mice, each group should consist of at least 20 males and 20 females.
 - c. **Route of administration:**

The route of administration ordinarily will be the expected clinical route of administration.
 - d. **Dose levels:**

Groups with three different doses plus a control group should be employed.

e. Control group:

- i.** A negative control group should be employed. A positive or a comparative control group is desirable.
- ii.** When vehicles or emulsifiers are required for the administration of the test substance, a negative control group should normally receive such vehicles or emulsifiers alone. A positive control group should receive a substance known to have potent reproductive and developmental toxicity, and a comparative control group should receive a drug with a similar chemical structure or pharmacological effects as the tested drug.

f. Administration period:

When rats or mice are used, males at least 40 days of age should be dosed daily for 60 days or more before mating, and administration should be continued until successful copulation. Sexually mature females should be dosed daily for at least 14 days before mating, during mating and after successful copulation until the beginning of organogenesis.

g. Experimental procedure:

- i.** During the experimental period, mortality should be recorded, general signs noted and body weights and food intake should be measured.
- ii.** A treated male and a treated female should be housed together and observed daily for confirmation of successful copulation.
- iii.** The mating period between the male and female pairs should be about two weeks. If necessary, a treated male and a non-treated

female, or a treated female and a non-treated male should be housed together and observed daily for confirmation of successful copulation.

- iv. After successful copulation, females should be autopsied at term, and examined for the number of corpora lutea, successful pregnancies and mortality of fetuses. Additionally, a gross examination of the organs and tissues for all dams should be made.
- v. Males used for mating and females without successful copulation should be autopsied at an appropriate time, and gross observation on organs and tissues should be made.

2. Segment II. Study on administration of the test substance during the period of organogenesis.

a. Animals:

Females of at least one species of rodent and a non-rodent such as rabbits should be used.

b. Number of animals:

Each group should consist of at least 30 animals for rats or mice and at least 12 animals for rabbits.

c. Route of administration:

The route of administration should ordinarily be that expected clinically.

d. Dose levels:

At least three different dosage groups plus a control group should be employed.

e. Control group:

i. A negative control group is necessary and a positive or a comparative control group is generally desirable.

ii. When vehicles or emulsifiers are required for the administration of the test substance, a negative control group should normally receive such emulsifiers alone. A positive control group should receive a substance known to have potent reproductive and developmental toxicity and a comparative control group should receive a drug with a similar chemical structure or pharmacological effects.

f. Experimental procedure

i. During the experimental period, mortality, general signs, body weights and food intake should be measured for all dams.

ii. In the case of rodents such as rats or mice, approximately 2/3 of the dams in each group, and in the case of non-rodents such as rabbits, all the dams in each group should be autopsied at term. They should be examined for successful pregnancy and mortality of fetuses. Body weight measurement and morphological examinations should be made on live fetuses. Gross observations on organs and tissues should be made for dams.

iii. For rats or mice, etc., the remaining approximately 1/3 of the dams should be allowed to deliver their offspring. Dams should be examined for abnormality on delivery.

iv. Litter size, mortality, sex and external changes of neonates should be examined, and body weights should be measured.

v. Offspring should be examined for growth and development, appearance of specific signs, reproductive performance, etc. Growth and development should be recorded and morphological, functional and behavioural examinations should be made. Reproductive performance of the offspring, that is, the ability to establish pregnancy, should be examined. If necessary, observation for a longer period should be made.

vi. At an appropriate time, autopsy and gross observation of the organs and tissues of treated dams should be made on treated dams. If necessary, an examination of the second litters should be done.

3. Segment III. Study on administration of the test substance during the perinatal and lactation periods

a. Animals:

At least one species of female animals such as rats or mice should be used. Species should be selected from among those used in the study of administration of the test substance during organogenesis specified in the segment II study.

b. Number of animals:

Each group should consist of at least 20 animals for rats or mice.

c. Route of administration:

The route of administration should be the expected clinical route as a rule.

d. Dose levels:

At least three dose groups plus a control group should be employed.

e. Control group:

- i. A negative group should be employed. A positive or a comparative control group may be employed, if necessary.
- ii. When vehicles or emulsifiers are required for administration of the test substance, a negative control group should normally receive such vehicles or emulsifiers alone. A positive control group should receive a substance known to have potent reproductive and developmental toxicity and a comparative control group should receive a drug with a similar chemical structure or pharmacological effects.

f. Administration period:

- i. During the experimental period, all the dams in each group should be examined for mortality and general signs and body weights and food intake should be measured.
- ii. All the dams in each group should be allowed to deliver and nurse their offspring. Dams should be examined for abnormality on delivery.
- iii. Litter size, mortality, sex and external changes of neonates should be examined, and body weights should be measured.
- iv. Offspring should be examined for growth and development, appearance of specific signs, reproductive performance, etc. For observation of growth and development,

morphological, functional and behavioural examinations should be made. Reproductive performance of offspring should be examined on the basis of establishment of pregnancy. If necessary, observation for a longer period should be made.

- v. At an appropriate time, autopsy and gross observations on organs and tissues should be made on treated dams. If necessary, an examination of the second litters should be done.

Analysis of results

1. The results obtained should be presented in the form of tables and figures with discussion of the results. For presentation, summary tables which give an overview of the results of all groups should be prepared. In addition, appendix tables which provide data for individual animals in each group should be prepared for reference.
2. For statistical analysis of the data obtained before weaning, it is desirable that the litter, instead of the individual fetus or offspring, serve as the unit for analysis.
3. The discussion should address the no-effect dose level of the test substance concerned with the reproduction of the parent animals and development of the next generation. It is desirable to compare the reproductive and developmental toxicity with that of similar drugs.

**WORLD MEDICAL ASSOCIATION
DECLARATION OF HELSINKI***

**RECOMMENDATIONS GUIDING PHYSICIANS
IN BIOMEDICAL RESEARCH
INVOLVING HUMAN SUBJECTS**

**ADOPTED BY THE 18TH WORLD MEDICAL ASSEMBLY
HELSINKI, FINLAND
JUNE 1964**

**AND AMENDED BY THE
29TH WORLD MEDICAL ASSEMBLY
TOKYO, JAPAN
OCTOBER 1975**

**35TH WORLD MEDICAL ASSEMBLY
VENICE, ITALY
OCTOBER 1983**

AND

**THE 41ST WORLD MEDICAL ASSEMBLY
HONG KONG
SEPTEMBER 1989**

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Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

1. *Basic principles*

1.1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

1.2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

1.3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

1.4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is

in proportion to the inherent risk to the subject.

1.5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

1.6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

1.7 Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

1.8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

1.9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

1.10 When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a

dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

1.11 In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

1.12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

2. *Medical research combined with professional care (Clinical research)*

2.1 In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2.2 The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

2.3 In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

2.4 The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

2.5 If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

2.6 The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

3. *Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)*

3.1 In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

3.2 The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3.3 The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

3.4 In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REPORT OF THE MEETING OF THE WORKING GROUP ON THE SAFETY AND EFFICACY OF HERBAL MEDICINE

Summary

The Working Group on the Safety and Efficacy of Herbal Medicine met in Manila, Philippines, from 5 to 9 October 1992. The main objective of the meeting was to develop research guidelines for evaluating the safety and efficacy of herbal medicines and to make recommendations on further collaboration and activity on the safety and efficacy of herbal medicines.

The meeting was attended by 15 members from ten Member States, two consultants, two secretariat staff from the WHO Regional Office for the Western Pacific and one observer from Japan. Dr Nelia Cortes-Maramba was elected Chairperson, Dr G.N. Vaughan as Vice-Chairman, and Dr Kit Lam Chan and Professor Yun Cheong Kong as Rapporteurs. Dr S.T. Han, WHO's Regional Director for the Western Pacific, delivered addresses at both the opening and the closing ceremonies.

The members presented their papers to review the current status of research works on herbal medicine, and to introduce methodology used for evaluating the safety and efficacy of herbal medicines. The drafts of guidelines for evaluating safety and efficacy of herbal medicines were discussed extensively. The issues covered in the discussion included: the definition of terms used in the guidelines; the development of a coherent scheme for describing various herbal medicines and the plant substances from which they are formulated; the means of incorporating ethical considerations into

the guidelines; the standards for non-clinical and clinical studies; the philosophical difficulties of evaluating herbal medicine remedies outside the system of medical thought in which they were developed; and the financial and technical difficulties liable to be encountered in carrying out the terms of the guidelines.

In the course of these discussions, the Working Group developed the research guidelines for evaluating the safety and efficacy of herbal medicines and made recommendations for promoting the dissemination of these guidelines. A summary of these recommendations follows:

- (1) WHO and the Member States should help to promote the use of scientifically validated herbal medicines for the purpose of providing medical care in a cost-effective manner with the goal of validating claims for herbal medicines now in use and seeking collaborative solutions to common national and regional problems. In addition, programmes should be established to disseminate research on herbal medicine, not only to research workers, but to health planners and health care practitioners as well as students in the health care professions.

Member States are also encouraged to make national policies that encourage the rational use of herbal medicine and promote their safety and quality. In addition, national policies should be made to preserve the environment that provides valuable medicinal plants.

- (2) WHO should disseminate these guidelines as widely as possible among Member States and their institutions concerned with herbal medicines to solicit their comments and recommendations, so that the guidelines can be revised and made as helpful as possible to each country in forming its own guidelines to meet its own specific needs.

Introduction

Humankind has used plants as therapeutic agents for thousands of years and continues to rely on them for health care, particularly in developing countries where they are usually prescribed by traditional medical practitioners who are respected members of the community. WHO has recognized the potential significance of the practice of traditional medicine, the therapeutic practices of which are based almost entirely on the use of traditional herbal remedies. Thus, resolutions have been adopted both by the the World Health Assembly and the Regional Committee for the Western Pacific to encourage the appropriate development of traditional systems of medicine and to examine the therapeutic properties of their herbal remedies.

Approximately 40% of the world's population lives in the countries served by the WHO Regional Office for the Western Pacific. This Office has actively examined how the resources of herbal medicines, which have a particularly rich tradition in many of its member countries, might be mobilized to help achieve the goal of health for all by the year 2000.

With a view to providing safe and effective herbal medicines and promoting research on herbal medicines for their scientific development, WHO constituted a Working Group on the Safety and Efficacy of Herbal Medicine which met from 5 to 9 October 1992, in Manila.

Objectives

The objectives of the meeting were as follows:

- (1) to review the current status of attempts to evaluate the safety and efficacy of herbal medicines;

- (2) to discuss the methodology for evaluating the safety and efficacy of herbal medicines;
- (3) to outline principles and approaches to be used in developing guidelines for the safety and efficacy of herbal medicines; and
- (4) to develop research guidelines for evaluating the safety and efficacy of herbal medicines and to make recommendations on further collaboration and activity on the safety and efficacy of herbal medicines.

Participants

The working group comprised 15 temporary advisers, two consultants and two members of the WHO secretariat. One observer from Japan also attended the meeting. The list of participants is in Annex 3.

Organization

Dr Nelia-Cortes-Maramba and Dr G.N. Vaughan were elected Chairperson and Vice-Chairman respectively of the Working Group and Dr Kit Lam Chan and Professor Yun Cheong Kong were elected as Rapporteurs.

Opening ceremony

Dr S.T. Han, Regional Director of the WHO Regional Office for the Western Pacific Region opened the meeting by pointing out how herbal medicines, which have contributed to human health for thousands of years, continue to do so, particularly in the Western Pacific Region where herbal medical traditions are particularly rich and still vital. He reminded the Working Group that WHO was fully aware of the continuing importance of herbal medicines for the

health of a very large sector of the world's population and that WHO encouraged the use of herbal medicines which have been proven to be safe and effective. He noted that the Working Group had the responsibility to develop the first guidelines in the Region to be applied to research on the evaluation of herbal medicines.

Proceedings

The Working Group recognized its task to develop Research Guidelines for Evaluating Herbal Medicines and was aided by working papers provided by the members of the Working Group and by draft guidelines provided by two consultants and members of the secretariat.

Presentation

The current status of research on herbal medicine in the Region and the methodology used for evaluating the safety and efficacy of herbal medicines were outlined by the members during the presentation of their working papers in the Meeting. The papers are summarized below:

Dr Chen Ken, WHO-WPRO Medical Officer, Traditional Medicine, gave a summary of various global and regional WHO resolutions regarding traditional medicine. He emphasized that the aim of WHO's Traditional Medicine Programme is to promote the appropriate utilization of traditional medicine in relation to a country's health care system, and reviewed WHO's role in developing a comprehensive approach to herbal medicines that includes utilization and administration, inventory survey and conservation, training and research, cultivation and pharmaceutical production, legislation and registration.

In another paper, Dr Chen Ken reviewed the research carried out on herbal medicines within the Western Pacific Region. Such research was classified according to the materials examined, the disciplines involved and the purpose and place of research. The difficulties of carrying out research on the safety and efficacy of herbal medicines were also pointed out. These include inadequate technical facilities, financial shortages, and in some cases different approaches to problems as a result of different cultural and ethical norms. He outlined a set of principles for the development of research guidelines for evaluating the safety and efficacy of herbal medicine.

Mr Noriaki Shigeno, WHO-WPRO Scientist, Pharmaceuticals, outlined the basic requirements for the quality control of both prescription drugs and non-prescription drugs and suggested that herbal medicines may be considered non-prescription drugs.

Dr Kit Lam Chan emphasized the importance of identifying the biologically active constituents of each plant which forms the composition of a herbal medicine preparation in order to explain the therapeutic properties of the preparation. He reviewed evidence of the value of the brine shrimp as a test system for screening for pharmacological activity prior to the use of more specific and sophisticated bioassays, and pointed out how KB cell cultures may provide preliminary insight into the therapeutic selectivity of plant materials and some measure of the difference between possible therapeutic activity and toxicity in the same host system.

Professor Byung Hoon Han pointed out the need for a systemic approach to, and the importance of evaluating the efficacy of herbal medicines, by both *in vitro* and *in vivo* studies. False-positive and false-negative results are inevitable in the *in vitro* assay systems owing to the wide distribution in plants of simple fatty acids, polyvalent organic acids, tannin and metallic ions. Professor Byung Hoon Han also pointed out that the registration for sale of

herbal medicine preparations by the Korean Government relies almost completely on acceptance of a formulation that follows one of the classic traditional medicine texts.

Professor Hoang Bao Chau, reviewed the progress made at the Institute of Traditional Medicine of Viet Nam since 1960. The Institute has worked towards improving the safety and evaluating the efficacy of traditional drugs, and efforts have been made to standardize drugs and overcome toxicity. In the period from 1990 to 1995, the Institute will focus on the safety and efficacy of some herbal medicine preparations with different functional groups as compared with total extracts. Measures taken to integrate studies from various non-clinical disciplines with clinical practice were also mentioned.

Dr Nam-Jae Kim presented the screening methodology for the biochemical and pharmacological evaluation of herbal medicines. He also summarized the present status of the role of herbal medicines in the health care system of the Republic of Korea. He proposed revising the terminology of traditional medicine into an integrated system that could readily be adapted to modern scientific terms, and which would be in accordance with pathological studies.

Professor Yun Cheong Kong focused on the measures that could improve the quality of both the crude plant materials and proprietary herbal medical products. He concluded that education of the public in the basic concepts of traditional medicine and principles guiding its diagnostic methods is the best way to enable people to make their own evaluation of traditional medical practitioners and of the safety and efficacy of the medicines they prescribe.

Dr Liao Fu-long suggested guidelines for the evaluation of the safety and efficacy of both crude and processed forms and preparations of herbal medicines. He also emphasized the importance of

legislative and administrative policies in determining the approval of new herbal medicines.

Professor Lou Zhi-cen, presented a comprehensive scheme for the evaluation of the safety and efficacy of herbal medicines by considering standards for appropriate pharmacodynamic, toxicological and clinical investigations.

Dr Nelia Cortes-Maramba described the research activities conducted by the National Integrated Research Programme on Medicinal Plants in the Philippines and described a survey of 1207 traditional healers regarding their preparation of herbal medicines, the plants and their parts, the methods of processing, and the dose and frequency of administration for various indications. Pre-clinical studies have been carried out for 30 medicinal plants, and out of 270 plants tested 12 were found to have mutagenic activity.

Dr Motoyoshi Satake described the guidelines for the required types of pharmacological, pharmacokinetic, toxicological and clinical studies that have been developed to assure the quality of herbal medicines (Kampo) registered with the Japanese regulatory authorities. Kampo medicines in Japan are of two types: one, the traditional decoctions prepared from several varieties of chopped herbs, the other specific formulations of extracts compounded on an industrial scale by pharmaceutical manufacturers.

Professor S. Sotheeswaran reviewed the safety and efficacy of some of the plants used in the herbal medicines of the South Pacific and some of their pharmacological activities. He indicated that extracts of many of these medicinal plants have pharmacological properties that confirm their clinical use, such as herbs used to treat wounds that show antimicrobial activity. He also drew attention to the toxic compounds of some of these herbs which have not yet

been fully appreciated and pointed out ways in which the actions of some traditional herbal medicines may interfere with the intended actions of modern drugs.

In the paper of Dr Bounhoong Southavong, the research activities of herbal medicine in Lao People's Democratic Republic were presented. The Research Institute of Medicinal Plants was founded in 1976, and since then has begun to evaluate more than 200 species of newly discovered medicinal plants whose evaluation for safety and efficacy is a continuing activity of the Institute.

Dr Hiroyori Tosa addressed the problem of evaluating the safety and efficacy of Kampo prescriptions, particularly when physicians no longer understand the Kampo philosophy. To increase the accuracy of Kampo prescribing, he proposed that checklists of symptoms, signs, laboratory tests and other examinations should be created and their intensity graded systematically. Composite scores could then be created, which, with statistical analysis, could provide a clinical evaluation of the efficacy of Kampo prescriptions.

Dr G.N. Vaughan reviewed the guidelines and policies at the Therapeutic Goods Administration (TGA), the federal agency in Australia responsible for evaluating the quality, safety and efficacy of all drugs including herbal medicines. "Registration" drugs undergo intensive evaluation to ensure safety, quality and efficacy. "Listed" drugs, on the other hand, which apply to most herbal medicines, undergo an evaluation emphasizing only quality and safety. No therapeutic claims can be made for such drugs. All drugs, however, are subject to Good Manufacturing Practice (GMP).

Professor Wang Bao-qin described how herbal medicines are assessed in the People's Republic of China. In the past five years,

the Government has listed 120 commonly used crude herbal medicines for systematic investigation and strict quality assessment. It is of particular interest that pharmacodynamic studies show that several traditional multi-herbal prescriptions have a greater therapeutic effect than their individual components. Studies are also under way to develop and evaluate new herbal medicines.

Dr Haruki Yamada described his studies on pharmacologically active molecules in Japanese Kampo medicines which call attention to the pharmacological activity of the larger molecules in some of these prescriptions. Several pectic polysaccharides in the "Kampo" prescription, Juzen-Taiho-To, for example, have immunomodulating activity. Such studies support the conviction that attention in the study of classic herbal medicines should not be confined exclusively to compounds of low molecular weight.

Discussion

During the preparation of the guidelines, a number of issues were raised that received particular attention and required considerable discussion.

The definition of the term herbal medicines was accepted to refer to the remedy derived primarily from plant material taken by the patient, although it was recognized that such remedies are not always exclusively of plant origin and that the term herbal medicine can be used to refer to the system of medicine based on plant remedies rather than exclusively to the remedies themselves.

Another difficult problem was the development of a coherent scheme for describing various herbal medicines and the plant substances from which they are formulated. Such remedies come from many cultures and are often thousands of years old. The

Working Group recognized, therefore, that there would probably be important exceptions to any scheme proposed, but hoped that its proposed definitions would be a helpful frame of reference that would not unjustly exclude any useful or potentially useful herbal medicine.

Although the Guidelines do not specifically raise the issue of financing the scientific evaluation of the safety and efficacy of herbal medicines, the issue of such financial support was repeatedly raised by members of the Working Group. All members of the Working Group recognized that the goals of the guidelines required research facilities, personnel and supplies that in turn required the necessary financial support.

In addition to general principles such as feasibility, reliability, repeatability and practicality, the following four points were considered by the members of the Working Group in relation to principles for developing research guidelines for evaluating the safety and efficacy of herbal medicine.

The Working Group wished to make clear the importance of ethical considerations relevant to both human and animal research and to the preservation of the environment that allows medicinal herbs to flourish, but wished to incorporate these considerations into the guidelines in a way that would be acceptable to all groups within the Region and elsewhere in the world.

The Working Group also recognized the difficulty of setting standards for non-clinical studies that might be too rigid on the one hand or too vague on the other, since in a sense the task of writing such guidelines forces the Group to solve the very difficult problem of defining "good science".

Randomized, double-blind, placebo-controlled clinical trials have provided much useful information about drugs used in modern

medicine, but their power lies in their ability to eliminate the biases that seem to beset the advocates of any therapy and that make it so difficult to distinguish a true therapeutic response from the variability inherent in clinical medicine. Similarly, statistical reasoning has helped the modern clinician to recognize that an apparent therapeutic success may merely be a chance occurrence. Thus the guidelines on clinical trials were formulated to show the importance of these principles of modern drug evaluation and not to thwart imaginative research protocols that find other ways of convincing the sophisticated observer that bias and chance results have not been confused with therapeutic effect.

Although the Working Group carried out its charge to develop guidelines on the evaluation of herbal medicines, its members were keenly aware of the philosophical difficulties of evaluating remedies used in traditional systems of medicine. This unfortunate philosophical paradox was also one of the reasons why several members of the Working Group felt so strongly that the philosophical rationale of traditional systems of medicine should be made available in the courses taken by students in the health professions and made available to the public as well.

Conclusions and recommendations

Conclusion

The consensus reached by the Working Group on principles, methodologies and technical considerations is set out in the Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines which were developed during this meeting. The recommendations of the working group are outlined below.

Recommendations

The Working Group recommends that WHO and its Member States help to promote the use of scientifically validated herbal medicines for the purpose of providing medical care in a cost-effective manner.

To carry out this overall goal the following more specific recommendations are made:

1. Research on herbal medicines should be encouraged both by WHO and the individual Member States, with the goals of validating claims for herbal medicines now in use; encouraging the convergence of traditional and modern medicine; and providing collaborative solutions to common national and regional medical problems. When planning research projects on the medical value of herbal medicines, the value of this research as a basis for economic development should also be considered.
2. WHO should encourage the establishment of facilities for the dissemination of research and other information about research on herbal medicines with the goal of providing health care workers and planners with the latest information for use in their own countries and to encourage them to establish regional cooperation and collaboration towards the solution of common medical and educational problems. Facilities, which should be equipped with computers, CD-ROM and other modern information technology and stationed within one country should be made accessible to scientists and planners from other countries.
3. WHO and its Member States should foster programmes that enable students and practitioners in the health care professions to learn about traditional medicines and the benefits that herbal remedies can provide. Education of the public about herbal medicine will help in the selection of remedies of the highest standards.

4. All Member States should develop national policies to foster the rational use of herbal medicines including the development of standards for those products that may eventually result in national or regional formularies; and they should foster efforts both to preserve the environment which provides valuable medicinal plants and to increase knowledge about their own medicinal plants.

WHO should disseminate the Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines as widely as possible among Member States and their institutions concerned with herbal medicines to solicit their comments and recommendations, particularly with regard to the value of these guidelines in helping each country to form its own guidelines.

WHO should help the Member States to develop and improve their national health policies on herbal remedies by taking steps to amend these guidelines periodically to reflect both technical and scientific advances and the experience of other Member States.

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NOTES

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These bacterial strains can be obtained from:

American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, 20852 Maryland, USA.

Institute for Fermentation, OSAKA (IFO), 17-85, Juso-Honmachi 2, Yodogawa-ku, Osaka 532, Japan

The accession numbers are as follows:

Strain	Accession Number	
	ATCC	IFO
<i>Salmonella typhimurium</i>		
TA 1535	ATCC 29629	IFO 14209
TA 1537	ATCC 29630	IFO 14211
TA 98	-	IFO 14211
TA 100	-	IFO 14194
<i>Escherichia coli</i>		
WP2 <i>uvr A</i>	-	IFO 14196

Reference: D. Durand et al. *Detection of Carcinogens. MELE in Microbiology (student manual)*, Burgess Publishing Company, Minneapolis: 1982.

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Technical guidelines for pharmaceuticals in the European Economic Community, editor, Duilio Poggiolini, New York: Raven Press, 1983.

The rules governing medicinal products in the European community: Volume III. Guidelines on the quality, safety and efficacy of medicinal products for human use, Luxembourg: Office for Official Publications of the European Communities, 1989.

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"These guidelines are intended to facilitate the work of research scientists and clinicians in the field of herbal medicine. They will also furnish some reference points for the various governmental, industrial and non-profit organizations involved in research and use of herbal medicines."

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