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GUIDELINES FOR THE ASSESSMENT OF HERBAL MEDICINES

PROGRAMME ON TRADITIONAL MEDICINES
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Introduction

For the purpose of these guidelines "HERBAL MEDICINES" should be regarded as:

Finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plants, or other plant material, or combinations thereof, whether in the crude state or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and any other substances of this nature. Herbal medicines may contain excipients in addition to the active ingredients. Medicines containing plant material combined with chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines.

Exceptionally, in some countries herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients which are not of plant origin.

The past decade has seen a significant increase in the use of herbal medicines. As a result of WHO's promotion of traditional medicine, countries have been seeking the assistance of WHO in identifying safe and effective herbal medicines for use in national health care systems. In 1989, one of the many resolutions adopted by the World Health Assembly in support of national traditional medicine programmes drew attention to herbal medicines as being of great importance to the health of individuals and communities (WHA 42.43). There was also an earlier resolution (WHA 22.54) on pharmaceutical production in developing countries; this called on the Director-General to provide assistance to the health authorities of Member States to ensure that the drugs used are those most appropriate to local circumstances, that they are rationally used, and that the requirements for their use are assessed as accurately as possible. Moreover, the Declaration of Alma-Ata in 1978 provided for *inter alia*, the accommodation of proven traditional remedies in national drug policies and regulatory measures. In developed countries, the resurgence of interest in herbal medicines has been due to the preference of many consumers for products of natural origin. In addition, manufactured herbal medicines from their countries of origin often follow in the wake of migrants from countries where traditional medicines play an important role.

In both developed and developing countries, consumers and health care providers need to be supplied with up-to-date and authoritative information on the beneficial properties, and possible harmful effects, of all herbal medicines.

The Fourth International Conference of Drug Regulatory Authorities, held in Tokyo in 1986, organized a workshop on the regulation of herbal medicines moving in international commerce. Another workshop on the same subject was held as part of the Fifth International Conference of Drug Regulatory Authorities, held in Paris in 1989. Both workshops confined their considerations to the commercial exploitation of traditional medicines through over-the-counter labelled products. The Paris meeting concluded that the World Health Organization should consider preparing model guidelines containing basic elements of legislation designed to assist those countries who might wish to develop appropriate legislation and registration.

The objective of these guidelines, therefore, is to define basic criteria for the evaluation of quality, safety, and efficacy of herbal medicines and **thereby to assist national regulatory authorities, scientific organizations, and manufacturers to undertake an assessment of the documentation/submission/dossiers in respect of such products**. As a general rule in this assessment, traditional experience means that long-term use as well as the medical, historical and ethnological background of those products shall be taken into account. Depending on the history of the country the definition of long-term use may vary but would be at least several decades. Therefore the assessment shall take into account a description in the medical/pharmaceutical literature or similar sources, or a documentation of knowledge on the application of a herbal medicine without a clearly defined time limitation. Marketing authorizations for similar products should be taken into account.

The foregoing guidelines for the Assessment of Herbal Medicines were finalized at a WHO Consultation in Munich, Germany, from 19 - 21 June 1991. The request for WHO to prepare these guidelines came from the Fifth International Conference of Drug Regulatory Authorities (ICDRA) held in Paris in 1989. The finalized guidelines were presented to the Sixth ICDRA in Ottawa in 1991.

These efforts concentrate on herbal medicines, but might at a later stage be the basis for the assessment of other traditional medicines not covered by these guidelines. In the meantime, it is up to the national authorities to adapt the guidelines for assessment of traditional medicines and other herbal drugs.

Prolonged and apparently uneventful use of a substance usually offers testimony of its safety. In a few instances investigations of the potential toxicity of naturally-occurring substances widely used as ingredients in these preparations have revealed previously unsuspected potential for systematic toxicity, carcinogenicity and teratogenicity. Regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing the suspect substance, or by rescheduling the substance in order to limit its use to medical prescription.

Assessment of quality, safety, and efficacy and intended use

Pharmaceutical assessment

This part should cover all important aspects of the quality assessment of herbal medicines. However, if a pharmacopoeia monograph exists it should be sufficient to make reference to this monograph. If no such monograph is available, a monograph must be supplied and should be set out in the same way as in an official pharmacopoeia.

All procedures should be in accordance with Good Manufacturing Practices (GMP).

Crude plant material

The botanical definition, including genus, species and authority should be given to ensure correct identification of a plant. A definition and description of the part of the plant from which the medicine is made (e.g., leaf, flower, root) has to be provided as well as an indication as to whether fresh, dried or traditionally processed material is used. The active and characteristic constituents should be specified and, if possible, content limits defined. Foreign matter, impurities and microbial content should be defined or limited. Voucher specimens, representing each lot of plant material processed, should be authenticated by a qualified botanist and should be stored for at least a ten year period. A lot number should be assigned and this should appear on the product label.

Plant preparations

Plant preparations include comminuted or powdered plant materials, extracts, tinctures, fatty or essential oils, expressed juices and preparations whose production involves a fractionation, purification or concentration process. The manufacturing procedure should be described in detail. If any other substance is added during the manufacture, to adjust the plant preparation to a certain level of active or characteristic constituents or for any other purpose, the added substances should be mentioned in the procedure description. A method for identification, and where possible assay of the plant preparation should be added. If the identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g., "chromatographic fingerprint") to ensure consistent quality of the preparation.

Finished product

The manufacturing procedure and formula including the amount of excipients should be described in detail. A finished product specification should be defined. A method of identification, and where possible quantification, of the plant material in the finished product should be defined. If the identification of an active principle is not possible, it should be sufficient to identify a characteristic substance or mixture of substances (e.g., "chromatographic fingerprint") to ensure consistent quality of the product. The finished product should comply with general requirements for particular dosage forms.

For imported finished products, confirmation of the regulatory status in the country of origin should be required; the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be applied.

Stability
The physical and chemical stability of the product in the final marketing container should be tested under defined storage conditions and the shelf-life should be established.

Safety assessment
This part should cover all relevant aspects of the safety assessment of a medicinal product. A guiding principle should be that if the product has been traditionally used without demonstrated harm no specific restrictive regulatory action should be undertaken unless new evidence demands a revised risk-benefit assessment.

A review of the relevant literature should be provided with original articles or references to the original articles. If official monograph/review results exist, reference can be made to them. However, although experience on long-term use without any evidence of risks may indicate harmlessness of a medicine, it is not certain in some cases to what extent reliance can be placed solely upon long-term usage to provide assurance of innocuity in the light of concern generated in recent years over long-term hazards of some herbal medicines.

Reported side-effects should be documented according to normal pharmacovigilance principles.

Toxicological studies
If any toxicological studies are available, they should be part of the assessment. Literature should be indicated as above.

Documentation of safety based on experience
As a basic rule, documentation of a long period of use should be taken into consideration when the safety is being assessed. This means that, when there are no detailed toxicological studies, documented experience on long-term use without evidence of safety problems should form the basis of the risk assessment. However, even in cases of long-used drugs, chronic toxicological risks may have occurred, but may not have been recognized. If available, the period of use, the health disorders treated, the number of users, and the countries with experience should be specified. If a toxicological risk is known, toxicity data have to be submitted. Risk assessment, whether it is independent of dose (e.g., special danger or allergies), or whether it is a function of dose, should be documented. In the second instance the dosage specification must be an important part of the risk assessment. An explanation of the risks should be given, if possible. The potential misuse, abuse, or dependence have to be documented. If long-term traditional use cannot be documented, or doubts on safety exist, toxicity data should be submitted.

Assessment of efficacy and intended use
This part should cover all important aspects of the efficacy assessment. A review of the relevant literature should be carried out and copies provided of the original articles or proper references to them. Research studies, if they exist, should be taken into account.

Activity
The pharmacological and clinical effects of the active ingredients and, if known, their constituents with therapeutic activity should be specified or described.