



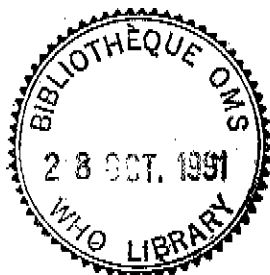
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REPORT OF  
THE CONSULTATION TO REVIEW THE DRAFT GUIDELINES FOR THE  
ASSESSMENT OF HERBAL MEDICINES

Munich, Germany, 19-21 June 1991



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## 1. INTRODUCTION

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. It was concluded that the World Health Organization should consider preparing model guidelines containing basic elements of legislation designed to assist those countries wishing to develop appropriate legislation and registration. The draft document now presented, represents the Organization's response to this request.

Earlier drafts of the guidelines were sent to Information Officers in countries. These are senior government officials designated by their ministries to assist WHO in its task of promoting the exchange of information on drugs. Their constructive suggestions were submitted to the Consultation for consideration.

### 1.1 Objective

The objective of the guidelines is basically to define the criteria for the evaluation of safety, efficacy, and quality 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.

### 1.2 The Guidelines

The document deals first with pharmaceutical assessment and covers such issues as those related to the identification of plant material, galenic forms, analytics and stability.

Safety assessment is, no doubt, the most singular concern for the registration of any manufactured herbal remedy and should minimally cover documentation of safety based on experience of usage and toxicological studies, where indicated. For example, where chronic toxicological events have not been noticed by practitioners or patients.

Assessment of efficacy and intended use covers all important aspects of efficacy assessment, including evaluation of traditional usage through evaluation of the literature, and evidence required to support indications.

Combination products and additives are issues that are important to regulatory authorities, especially the addition of pharmacologically-active compounds such as steroids into herbal preparations.

Product information and promotion protect the consumers and manufacturers and should therefore be focussed on as a condition for registration.

Lastly, the Organization believes that a refined version of the guidelines should be useful to drug regulatory authorities and industry alike and could be adapted as required for the assessment of other traditional medicines derived from different sources.

### 1.3 The outcome

The results of this Consultation should not and could not represent the final word on the subject. WHO will circulate the finalized guidelines widely to countries for adoption to particular national situations and in their present form they should not be considered as an authoritative statement with legal force.

Since the request for WHO to prepare guidelines for the assessment of herbal medicines came from the 5th International Conference of Drug Regulatory Authorities in Paris in 1989, it follows that the report of this Consultation including the finalized guidelines will be presented to the 6th International Conference on Drug Regulatory Authorities in Ottawa in October 1991.

## 2. OPENING SESSION

The meeting was opened by Dr O. Akerele, who welcomed the participants on behalf of the Director-General of the World Health Organization (see Annex II).

Mr J. Burges, Chairman, World Federation of Proprietary Medicine Manufacturers, also welcomed participants and introduced the Bavarian Government authority inviting him to address the meeting.

On behalf of the Bavarian Government, Alfonse Reithmeier of the Bavarian Ministry of the Interior also welcomed the participants to Munich. He observed that the Interior Ministry is the supreme health authority in Bavaria and is in charge of all pharmaceutical affairs (see Annex III).

Dr F.H Kemper, Germany was elected Chairperson and Mrs M. Garman Kasperek, Rapporteur.

## 3. SAFETY AND QUALITY CONTROL ISSUES ASSOCIATED WITH OVER-THE-COUNTER HERBAL MEDICINES

Based on a selection from representative scientific literature, Dr Norman Farnsworth introduced his background paper (Annex IV) noted that over-the-counter herbal medicines do not usually present a major problem with regard to toxicity. However, this does not minimize the need to have quality assurance procedures in place for products being offered to the public, that are intended to have a palliative or curative effect on selected disease states.

In Annex IV examples are cited of some potential problems in this area of safety and quality control of over-the-counter herbal medicines. The Consultation concurred that it should not be difficult to develop guidelines that could be applied to the quality control of these herbal medicines that would adequately minimize the potential problems cited in the Annex. However, it was agreed that a greater problem was the acceptance and implementation of such guidelines on a national or global basis.

## 4. OVERVIEW OF CURRENT ACTIVITIES BY COUNTRIES

Presentations on the regulation, development and control of herbal medicines were made by participants of 11 countries, two from the Americas, four from Asia and five from Europe and also by a participant from the WHO Regional Office for the Eastern Mediterranean. Extracts from these presentations may be found in Annex V.

5. THE PHARMACEUTICAL ASSESSMENT OF HERBAL REMEDIES

A Working Group of the participants considered in detail the pharmaceutical assessment of herbal medicines including questions on purity and contamination.

6. THE SAFETY AND EFFICACY OF HERBAL MEDICINES

A further Working Group of the participants studied the assessment of the safety and efficacy of herbal medicines, and the necessary information for the consumer on these products. Combination products were given special attention since herbal medicines often contain more than one ingredient. Prophylactic use of these medicines was also briefly discussed.

7. FURTHER ACTION

The participants of the Consultation having reviewed the draft guidelines for the assessment of herbal medicines and amended them, recommended that the amended guidelines as printed below, should be widely distributed to Member States by WHO and submitted for consideration to the Sixth International Conference of Drug Regulatory Authorities to be held in Ottawa in October 1991.

8. GUIDELINES FOR THE ASSESSMENT OF HERBAL MEDICINES

8.1. 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.

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.

## 8.2. Assessment of quality, safety, and efficacy and intended use

### 8.2.1 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).

#### 8.2.1.1 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.

#### 8.2.1.2 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.

#### 8.2.1.3 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.

#### 8.2.1.4 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.

#### 8.2.2 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.

##### 8.2.2.1 Toxicological studies

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

##### 8.2.2.2 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.

#### 8.2.3 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.

#### 8.2.3.1 Activity

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

#### 8.2.3.2 Evidence required to support indications

The indication(s) for the use of the medicine should be specified. In the case of traditional medicines, the requirements for proof of efficacy shall depend on the kind of indication. For treatment of minor disorders and for nonspecific indications, some relaxation is justified in the requirements for proof of efficacy, taking into account the extent of traditional use; the same considerations may apply to prophylactic use. Experience with individual cases recorded in reports from physicians, traditional health practitioners, or treated patients should be taken into account.

Where traditional use has not been established, appropriate clinical evidence should be required.

#### 8.2.4 Combination products

As many herbal remedies consist of a combination of several active ingredients, and as experience on the use of traditional remedies is often based on combination products, the assessment should differentiate between old and new combination products. Identical requirements for the assessment of old and new combinations would result in an inappropriate assessment of certain traditional medicines.

In the case of traditionally used combination products, the documentation of traditional use (classical texts such as Ayurveda, Traditional Chinese Medicine, Unani, Sida) and experience may serve for documentation of efficacy.

An explanation of a new combination of well-known substances including effective dose ranges and compatibility should be required in addition to the documentation of traditional knowledge of each single ingredient. Each active ingredient must contribute to the efficacy of the medicine.

In order to justify the efficacy of a new ingredient and its positive effect on the total combination, clinical studies may be required.

#### 8.2.5 Product information for the consumer

The labelling of the products and the package insert should be understandable to the consumer/patient. The package information should cover all necessary information on the proper use of the product.

The following elements of information usually suffice:

- name of the product
- quantitative list of active ingredient(s)
- dosage form
- indications
- dosage (if appropriate, specified for children and the elderly)
- mode of administration
- duration of use

- major adverse effects, if any
- overdosage information
- contraindications, warnings, precautions and major drug interactions
- use during pregnancy and lactation
- expiry date
- lot number
- holder of the marketing authorization

Identification of the active ingredient(s) by the Latin botanical name, in addition to the common name in the language of preference of the national regulatory authority, is recommended.

Not all information that is ideally required may be available. Therefore, drug regulatory authorities should determine their minimal requirements.

#### 8.2.6 Promotion

Advertisements and other promotional activities to health personnel and the lay public should be fully consistent with the approved package information.

#### 8.3. Utilization of guidelines

WHO guidelines for the assessment of herbal medicines are intended to facilitate the work to be carried out by regulatory authorities, scientific bodies and industry in the development, assessment and registration of such products. The assessment should reflect the scientific results gathered in past years in that field that could be the basis for the future classification of herbal medicines in different parts of the world. Other types of traditional medicines in addition to herbal products may be assessed in a similar way.

The effective regulation and control of herbal medicines moving in international commerce also require close liaison with appropriate national institutions that are able to keep under regular review all aspects of their production and use, as well as to conduct or sponsor evaluative studies of their efficacy, toxicity, safety, acceptability, cost and relative value compared with other drugs used in modern medicine.

#### 9. CLOSURE OF MEETING

Dr O. Akerele closed the meeting thanking the participants for their contribution (Annex VI).

LIST OF PARTICIPANTS

Dr Abd El Hamid Abd El Aziz, Under Secretary of State of Pharmaceutical Affairs, Ministry of Health, Cairo, Egypt<sup>(\*)</sup>

Mr Mark Blumenthal, Editor, Herbal Gram, The Herb Research Foundation, P.O.Box 201550, Austin, Texas 78720, United States of America

Dr Attilio Bonati, Scientific Director, Via Ripamonti 99, 20141 Milan, Italy

Mrs M. Carman Kasperek, Director, Bureau of Nonprescription Drugs, Drugs Directorate, Health and Welfare Canada, Place Vanier, 333 River Road, Vanier, Ontario, K1A 1B8, Canada (Rapporteur)

Dr Norman Farnsworth, University of Illinois at Chicago, College of Pharmacy, 833 South Wood Street, Chicago, Ill. 60612, United States of America

Dr Djoko Hargono, Head of Traditional Remedies Control Directorate, Directorate General on Drugs and Food Control, Jalan Percetakan Negara 23, 416726 Jakarta, Indonesia

Dr F.H. Kemper, Institut für Pharmakologie und Toxikologie, Domagkstrasse 12, 4400 Munster, Germany (Chairman)

Mr Kang-Choo Lee, Director of the Bureau of Pharmaceutical Affairs, Ministry of Health and Social Affairs, Seoul, Republic of Korea

Dr G.M.P. Mwaluku, Muhimbili Medical Centre, University of Dar es Salaam, Dar es Salaam, Tanzania<sup>(\*)</sup>

Dr Pakdee Pothisiri, Food and Drug Administration, Ministry of Public Health, Devaves Palace, Bangkok 10100, Thailand

Dr Jean-Pierre Reynier, Faculté de Pharmacie, Institut de Pharmacie galénique, 75, Boulevard Jean Moulin, 13005 Marseille, France

Dr G.G. Sikipa, Secretary for Health, Ministry of Health, Harare, Zimbabwe<sup>(\*)</sup>

Dr Wang Xianjin, China Proprietary Medicine Association, SPAC Bld, A38, Beilishilu Road, Beijing 100180, People's Republic of China

(\*) Unable to attend

Observers

Dr S. Blatt, Institut für Pharmazeutische Biologie, Arzneimittellehre der Universität, Karlstrasse 29, 8000 Munich 29, Germany

Dr Lars Bohlin, Department of Pharmacognosy, Biomedical Center, Uppsala University, Box 579, 751 23 Uppsala, Sweden

Mr Peter Bradley, Chairman of the Scientific Committee of the British Herbal Medicine Association and the European Scientific Cooperative for Phytotherapy, 2, Imber Park Road, Esher, Surrey KT10 8JB, England

Mr Johannes Burges, Chairman, World Federation of Proprietary Medicine Manufacturers, Georg-Kalb-Strasse 5-8, 8023 Grosshesselohe/Munich, Germany

Dr Il-Moo Chang, Natural Products Research Institute, Seoul National University, Seoul 110460, Republic of Korea

Dr Hubertus Cranz, Chairman of the Committee for Traditional Medicine of the World Federation of Proprietary Medicine Manufacturers, 7, Avenue de Tervuren, 1040 Brussels, Belgium

Dr B. Eberwein, Chairman of the Executive and the Scientific Committee of the European Scientific Cooperative for Phytotherapy, Ubierstrasse 73, 5300 Bonn 2, Germany

Dr Rainer Friedel, Professor for Biochemistry, Ludolfinger Platz 5, 1000 Berlin 28, Germany

Mr L.W. von Hebel, European Scientific Cooperative for Phytotherapy, Chairman of the Committee on Strategy, P.O.Box 33, 8080 AA Elburg, Netherlands

Mr Ho-Young Maeng, Senior Pharmacist, Bureau of Pharmaceutical Affairs, Ministry of Health and Social Affairs, Seoul, Republic of Korea

Dr M. Nicoletti, Dipartimento di Biologia Vegetale, Università degli studi "La Sapienza", P.le Aldo Moro 5, 00185 Rome, Italy

Mr Victor Perfitt, Director and Treasurer of the British Herbal Medicine Association, 3, Amberwood House, Amberwood Gardens, Christchurch, Dorset, BH23 5RT, England

Dr Jurgen Reimann, Member of the Board of the German Society for Vitamin Research, Georg-Kalb-Strasse 5-8, 8023 Grosshesselohe, Germany

Dr J. Reinstein, Director-General, World Federation of Proprietary Medicine Manufacturers, 15 Sydney House, Woodstock Road, London W4 1DP, England

Observers

Dr Ingrid Riess, Kooperation Phytopharmaka, Georg-Kalb Strasse 5-8,  
8023 Grosshesselhoe, Germany

Dr Georg Seidel, Secretary to the Scientific Committee of the European  
Scientific Cooperative for Phytotherapy, Ostmerheimer Strasse. 198,  
5000 Cologne 91, Germany

Dr K.H. Stumpf, Member of the Commission of the German Pharmacopoeia,  
Willmar-Schwabe-Strasse 4, 7500 Karlsruhe 41, Germany

Mr T. Tomlinson, Morris Arboretum of the University of Pennsylvania,  
9414 Meadowbrook Avenue, Philadelphia, PA 19118, United States of America

Secretariat

Dr O. Akerele, Programme Manager, Traditional Medicine, World Health  
Organization, Avenue Appia, 1211 Geneva 27, Switzerland (Secretary)

Miss J. Dadzie, Secretary, Traditional Medicine, World Health Organization,  
Avenue Appia, 1211 Geneva 27, Switzerland

Dr B. Deutscher, Consultant, Traditional Medicine, World Health Organization,  
Avenue Appia, 1211 Geneva 27, Switzerland

Dr M. ten Ham, Senior Scientist, Pharmaceuticals, World Health Organization,  
Avenue Appia, 1211 Geneva 27, Switzerland

Ms Y. Maruyama, Associate Professional Officer, Traditional Medicine, World  
Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland

Dr Abdel Azziz Saleh, Chief, Health Protection and Promotion, Pharmaceuticals  
Diagnostic and Therapeutic Substances, World Health Organization, Regional  
Office for the Eastern Mediterranean, P.O.Box 1517, Alexandria 21511, Egypt

Welcome Address

by

Olayiwola Akerele  
Programme Manager, Traditional Medicine  
World Health Organization, Geneva, Switzerland

It gives me great pleasure to take the floor at the opening of this WHO Consultation to review the Draft Guidelines for the Assessment of Herbal Medicines.

On behalf of Dr Hiroshi Nakajima, Director-General of the World Health Organization and indeed, on my own behalf, I welcome all of you to this beautiful city of Munich. I would like to take this opportunity to express my thanks and sincere appreciation to all the people who have collaborated with us in making it possible to host this important consultation in Munich. Special thanks must go to Mr Johannes Burges, the Chairman of the World Federation of Proprietary Medicine Manufacturers, for his personal efforts and contributions to the organization of our meeting.

During the last decade or so, there has been a resurgence of interest in the use of plant-derived medicines. One of the major consequences of this shift in consumers' preference has been increased communication in the subject. Much has been written on the use of medicinal plants in recent times. What has been written ranges from unduly critical to over-enthusiasm in promoting the use of plant-derived medicines. The appraisal of the place of medicinal plants in health care and responsible self-medication is now one of the major topics of discussion in many international forums, such as at the occasion of the Forty-fourth World Health Assembly. The debate of the subject at the Assembly in May, 1991 resulted in resolution WHA44.34 which, inter-alia, urges Member States "to intensify activities leading to cooperation between those providing traditional medicine and modern health care, respectively, especially as regards the use of scientifically proven, safe and effective traditional remedies to reduce national drug costs."

In any country in which herbal and other traditional remedies are in common use, several requirements need to be met if the maximum benefit is to be obtained and if misuse and unwarranted claims are to be kept to a minimum.

These include the following:

- Preparations should be registered, their contents should be known, and the claims made for them should be substantiated;
- The public should be kept well informed, through the media or school education, of those common conditions for which self-medication is safe, effective, and appropriate;
- The health professions should be encouraged to accept self-medication, where appropriate, as natural and beneficial, and desirable in reducing demands on professional health care; and

- The suppliers of medicinal plant remedies should observe an agreed code for safe manufacturing practices, clear labelling, and avoidance of exaggerated and/or unjustified claims for their products.

That is the reason why the World Health Organization has convened this Consultation to Review the Draft Guidelines for the Assessment of Herbal Medicines. Our Consultation will review and refine these requirements and outline strategies and approaches for their development in countries.

WHO chose Germany as an appropriate venue for this important consultation for a number of reasons. As you all know, Germany has a long tradition in the use of herbal medicines which has existed side by side with modern medicine through the ages. Munich combines, in a very unique way, traditional and modern life-styles and is therefore an appropriate venue for our deliberations. Our German hosts have gone to a great deal of trouble in making the necessary arrangements to ensure that our Consultation will be an enjoyable as well as a valuable experience for all concerned. I wish to express again my deep appreciation to all concerned.

Distinguished Ladies and Gentlemen, I now have pleasure in declaring open the WHO Consultation to Review the draft Guidelines for the Assessment of Herbal Medicines. It is a pleasure and great honour for me to now call on speakers from Bavaria and the city of Munich to address us.

Address by

Alfonse Reithmeier  
Bavarian Ministry of Interior  
Munich, Germany

It's a great pleasure for me to welcome you on the occasion of your Consultation to Review the Draft Guidelines for the Assessment of Herbal Medicines in Munich. Especially I would like to convey to you the best regards and wishes of the Bavarian State-Minister of the Interior, Dr Edmund Stoiber. That pleasure is the more on my side as our department - the Bavarian Ministry of Interior - is the supreme health authority of Bavaria that is in charge of all pharmaceutical affairs. This is why the specific problems of pharmaceuticals are familiar to us. So you can count on us as an interested and open-minded partners. I would also like to welcome you on behalf of the German Ministry of Health that wishes our meeting good progress and substantial results.

Health is the most precious thing we have. To preserve it to old age is every citizen's dearest wish. This is why public interest is specially focused on health policy. It is the aim of the Bavarian Government to preserve, promote and improve health in all spheres of life and to provide sufficient rehabilitation programmes. In doing so, we optimistically rely on each citizen's cooperation and responsibility.

Self-medication, that is self-treatment by the individual with medicines not prescribed by the doctor, has its firm place in our liberal health system. It serves as a link between mere health precautions and medical therapy. And herbal medicines are especially suited for self-medication. But herbal medicines are also firmly established in medical therapy. In traditional medicine, phytopharmacy, for example, is employed as the only kind of medical treatment.

We therefore welcome the Resolution of the Executive Board of the World Health Organization on Traditional Medicine and Health Care and support its aims. The Resolution will certainly make clear the growing importance of herbal medicines for public health.

As today people no longer feel illness and pain as an inevitable fate, they place particularly high expectations on the quality of medicaments. It is not surprising therefore that medicaments are again and again severely criticized. The public is certainly aware of the beneficial effects of medicaments to preserve health, to cure diseases, to soothe pain and to prolong life, but it is often rather the side-effects of these medicines, the danger of drug addiction or therapeutical failures that fill the headlines.

Small wonder then that people are increasingly returning to natural remedies, which has led to a renaissance of herbal medicines. According to a survey on the attitude of the German population towards natural medicaments,

nine out of ten patients consider them as good as or even better than chemical medicines. This attitude is not at all surprising as it shows how strongly people feel about living in a natural and intact environment and learning about natural cures. On the other hand, it must also be said that not all illnesses can be treated by medicines to the extent people appreciate these cures. And of course, natural medicines cannot generally be said to be without any dangers. Equally, chemical medicines cannot generally be said to necessarily include dangers.

A rational therapy with herbal medicines assumes effectiveness in the required therapeutic indications. Moreover, the relation between the success of therapy and possible risks must be acceptable. Therefore, we embrace and encourage the first steps back to the traditional methods of naturopathy - by way of science, of course.

The science of the healing power of plants, phytotherapy, has a tradition thousands of years old. There are compilations of recipes from China, India and ancient Egypt which give detailed descriptions of the effects of herbs, roots and fruit. The Greek physician Hippocrates edited a compilation of proven recipes and made a list of medicinal herbs.

Emperor Charles the Great even ordered the farming of medicinal herbs by law. The physician and pharmacist Paracelsus - an important figure of the German Renaissance in the 16th century - first extracted medicinal substances from herbs by distillation. He wrote: "Alle Wiesen und Matten, alle Berge und Hügel sind Apotheken" (All pastures and meadows, all mountains and hills are pharmacies).

However, as science succeeded in producing large amounts of medicaments synthetically at the beginning of this century, phytotherapy was more and more neglected. At the same time, medicine followed a course that was governed by chemistry and physics. Let it be said clearly, there should not be any doubts whatsoever about the tremendous success of scientific medicine. Its achievements are generally accepted and irreplaceable, and they are by no means put into question if people today increasingly resort to natural medicines.

Thus a great number of functional disturbances, minor illnesses, but also chronic sufferings can be treated better by herbal drugs than by strong synthetical medicaments. Herbs alone, however, cannot be called medicaments in their full sense. It is pharmaceutical progress that sorts out the often incalculable effects and reactions of different drug components and guarantees medicaments of reliable and constant quality. Therefore generally accepted criteria as to their quality, their effectiveness and safeness are absolutely necessary.

The Guidelines for the Assessment of Herbal Medicines which you are going to discuss and to decide on will make a valuable contribution in the establishing these criteria.

In this sense I wish all of you who are attending this meeting to gain ample professional and personal benefit from your stay in Munich. I hope you will also find enough time to make your personal choice among the rich cultural offers of our capital.

Summary of the Presentation on the Safety and Quality  
Control Issues Associated with Over-the-Counter  
Herbal Medicines

by N.R. Farnsworth

Although this summary is concerned only with safety and quality control issues pertinent to over-the-counter herbal medicines, the same basic principles apply to plant medicines, used primarily, but not exclusively, in developing countries by large segments of the population. Over-the-counter herbal medicines imply that a manufacturer is associated with the products; such may not be the case in developing countries where the herbalist or other practitioner may gather herbs in the wild and sell them or use them directly for treatment.

1. Types of herbal medicines

There are several categories of over-the-counter herbal medicines based on the nature of the manufacturing or packaging processes involved. These may be categorized as follows:

- Dried plant material that is sold in bulk form, or in the form of tea bags;
- Dried plant material that is reduced to a powdered form and is used as such, either in bulk form or placed in a hard gelatin capsule;
- The manufacturer "advances" the herbal medicines either by extraction with ethanol, selling them as tablets or capsules, or by extraction in hot water, freeze-drying and lyophilization.

"Advanced" herbal medicines and "teas" are primarily marketed in Europe; whereas crude formulations powdered or powdered in gelatin are used in North America and crude or powdered forms in the Far East.

2. Side-effects and toxic reactions to herbal medicines

Based on published reports, side-effects or toxic reactions associated with over-the-counter herbal medicines in any form are rare. Most of the adverse effects reported for herbal medicines are associated with "crude drugs" or powdered forms of plant material, that is, not with "advanced" forms of herbal medicines. Adverse effects reported for herbal medicines fall into one or more of the following categories.

2.1 Allergic reactions

There is no way to completely eliminate the possibility of any substance, including prescription drugs, herbal medicines or cosmetics, from producing allergic responses in susceptible persons exposed to them.

## 2.2 Over-the-counter herbal medicines containing normal toxic substances

There are a large number of plants containing appreciable levels of chemical substances which are normal biosynthetic products of the plant and which are toxic to humans or animals, for example:-

- Pyrrolizidine alkaloids; reported from six plant families and causing liver veno-occlusive disease and some being hepatocarcinogenic;
- Aristolochic acid; existing probably in all members of the Aristolochiaceae; the acid is mutagenic and carcinogenic;
- Phorbol esters; diterpene esters having tigliane or daphnane skeleta are tumour promoters and vesicants to the skin.

## 2.3 Over-the-counter herbal medicines found toxic because of intentional or unintentional mislabelling.

## 2.4 Over-the-counter herbal medicines reported toxic because of the intentional addition of unnatural toxic substances

Where for example, synthetic anti-inflammatory drugs have been added to multicomponent Chinese herbal remedies for arthritis.

## 2.5 Over-the-counter herbal medicines containing natural toxic contaminants

Plant material becoming contaminated, for example, by animal excreta containing pathogenic organisms, such as Salmonella typhosa.

## 2.6 Interactions involving the use of synthetic prescription drugs and over-the-counter herbal medicines

Since many herbal medicines are also used as foods, it may be anticipated that some chemical constituents in the herbal medicines might react adversely with normal prescription drugs.

Extract from Papers Presented by Country Representatives and  
Others on the Regulation, Development and Control of Herbal Medicines

CANADA<sup>(1)</sup>

Large numbers of manufactured herbal medicines are legally on the Canadian market. Herbal medicines, loosely defined as products of a botanical source claiming or possessing pharmacological activity, are regulated as drugs under the Canadian Food and Drugs Act, C.7 RCS 1985. Scrutiny of the composition of the medicine and its labelling is required prior to the assignment of its registration number or drug identification number.

Assessment is primarily based on traditional references for efficacy and dosage, and claims are restricted to those amenable to self-monitoring using readily recognizable terminology. However recently elucidated safety concerns may be used to override traditional references. Quality control is usually not assessed, but Good Manufacturing Practices are enforced through post-marketing inspections. Recent reviews of Good Manufacturing Practice for botanicals has focused on microbiological contamination. Manufacturers and distributors are inspected on a cyclical basis for compliance of dosage forms.

Multiple function products are not usually acceptable and noncontributory herbs in amounts greater than 10% of an accepted active level are not permitted.

CHINA<sup>(2)</sup>

It is more than 4000 years since Chinese traditional medicines were first recorded in the Chinese literature. The Government of the People's Republic of China has set great store in the Chinese traditional medicine. The constitution stipulates that modern and traditional medicine should be developed simultaneously. So there has been no difficulty in the production and distribution of Chinese patent medicines, if the product accorded with the requirements of the Drug Law.

Since 1963 the Chinese Pharmacopoeia has been divided into two parts, the first of which is specially for recording of traditional Chinese medicines, including medicinal materials and patent medicines. The monographs in this part record, according to the variety and dosage, the name resource, prescription, method of preparation, shape and properties, identification, examination, extraction, content determination, effects and channel-trophism, function and main indication, methods of use and dosage, cautions, specification, storage and dosage forms.

The 1990 edition of the Pharmacopoeia has been published and implemented from 1 July 1991. For products manufactured before this date the standards are controlled by those of the 1985 edition of the Pharmacopoeia, but for newer

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(1) Summary of the presentation by Mrs M. Garman Kasperek.

(2) Summary of the presentation by Wang Xianjin.

products, the manufacturer must submit materials for application according to the new standards to the appropriate health department for checking and reviewing.

The Chinese Pharmacopoeia is compiled by the Pharmacopoeia committee of the Health Ministry of the People's Republic of China according to Rule 23 of the Drug Administration Law. New drugs are examined and approved according to the procedure laid down in the Drug Administration Law and if approved the manufacturer is issued with a Certificate of New Drug.

Traditional Chinese medicines usually contain a combination of several herbal medicines and these are recognized as they have been used for thousands of years.

#### FRANCE<sup>(3)</sup>

A revised Notice to Manufacturers of Herbal Medicines was issued by the French Ministry of Health in 1990, taking into account the recommendations of the European Community and includes a notice to applicants for marketing authorizations and an explanatory notice on vegetable drugs. The notice is intended to ensure that herbal medicines respond to quality criteria, quality constants, safety and efficacy. It is not restrictive, leaving the applicant a certain innovation flexibility and allowing the possibility of bringing all the technical and scientific arguments needed to support the request.

The Notice confirms the pharmaceutical status for herbal medicines and ensures that they are manufactured and controlled in a reproducible manner according to the usual standards of quality. At least once a year there is a pharmaceutical inspection of all manufacturers and distributors of herbal medicines and samples of the products are assessed by the National health Laboratory.

Dossiers of herbal medicines are submitted by manufacturers and are examined by a special group of the Marketing Authorization Committee.

This Notice to Manufacturers has assisted in herbal medicines gaining respectability and guarantees their quality. They can now be manufactured, controlled, and distributed like any other pharmaceutical speciality.

#### GERMANY<sup>(4)</sup>

The Federal Health office, the Bundesgesundheitsamt (BGA), is responsible for the formal verification of quality, safety and efficacy of drugs. For elaboration of the most important evaluation criteria, the Federal Health office has established special commissions of experts in accordance with the German Drug Law. Of the commissions established, Commission E works on herbal medicines.

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(3) Summary of the presentation by J.-P. Reynier

(4) Summary of the presentation by F.H. Kemper

The legal regulation is based on the fact that drugs, that have to be reviewed, are more or less products containing well-known ingredients with a long-term therapeutic experience, as a consequence of which it is deemed unnecessary, at least for the majority of these drugs, to perform new pharmacological/toxicological/clinical studies. For newly introduced preparations, the Drug Examination Regulations (Arzneimittelprüfrichtlinie) require pharmacological, toxicological and clinical studies to be performed.

A considerable amount of scientific knowledge on a great number of essential medicinal plants marketed in Germany has been drawn up by the "Kooperation Phytopharma" and presented to Commission E for evaluation. After acceptance these have been published by the Federal Health Office as monographs.

In addition to individual marketing authorizations, the German Drug Law also offers the possibility of obtaining a license for marketing a drug by reference to a standard marketing authorization.

Two important issues have still to be finalized by commission E: the evaluation of drug combinations and of drugs that are used for prevention of diseases.

#### INDONESIA<sup>(5)</sup>

In 1960 the Indonesian Basic Health Law No. 9/1960 became operative and consisted of four paragraphs. These covered the drug needs of the population, and the need for the Government to regulate and control the supply, production, storage, distribution and utilization of drugs, drug materials and other health articles, including traditional remedies. It stated that these drugs, etc. should meet the requirements mentioned in the Farmykode Indonesia and other regulations and that traditional remedies should meet these requirements as well.

A further law as the legal basis of the regulation, development and control of traditional remedies in Indonesia in the Pharmasi Law No. 7/1973. It details the efforts for fulfilling the pharmaceutical needs of the people in this respect including production, distribution, research and control efforts. Under this Law, the Minister Regulation No. 246 of 1990 was issued on the Industrial Business Licence and Registration of Traditional Remedies.

Regulation No. 246 defined the traditional remedy and the galenical preparation, laid down the licensing procedure of Traditional Remedy Industrial Business and the Requirements for its application and stated that all traditional remedy industries must comply with Good Manufacturing Practices. Every traditional remedy industry must submit a registration application for each traditional remedy produced by that industry to the Ministry of Health. For the evaluation, the composition of the product, the production process, the quality control process, usefulness of the product, method of utilization, dose, contraindications, etc., have to be stipulated. Among the regulations is one that prohibits the addition of an active chemical ingredient to a traditional remedy.

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(5) Summary of the presentation by D. Hargono

Quality control requirements laid down in the Farmakope Indonesia, the Ekatra Farmakope Indonesia and the Materia Medika Indonesia, and control activities on traditional remedies, begun in 1976, are undertaken by the directorate of Traditional Remedies Control.

#### ITALY<sup>(6)</sup>

In Italy, a product containing medicinal plants and medicinal plant derivatives are considered as proprietary medicinal products if therapeutic effects may be attributed to them. Their marketing is allowed on a specific authorization granted by the Ministry of Health and they are sold only in pharmacies. In order to manufacture any proprietary medicinal product, it is necessary to have the relevant authorization by the Ministry of Health, which is granted on specific request and after ascertaining the ability to produce medicinal specialities according to Good Manufacturing Practices. Manufacturers are periodically inspected by officials of the Ministry of Health.

There is no rule which allows the registration of proprietary medicinal products containing medicinal plants and their derivatives according to an abridged procedure; therefore the relevant registration dossier must comply completely with all ministerial requests as far as quality, safety and efficacy, exactly as for any other proprietary medicinal product.

Generally speaking, the Ministry of Health is not in favour of multiple component medicines; this general attitude includes the multiple component herbal medicines.

In Italy, the use of medicinal plants is becoming more and more popular, but most of these products are sold in herbalist's shops and not in pharmacies.

#### REPUBLIC OF KOREA<sup>(7)</sup>

The use of herbal drugs in Korea originated about 5000 years ago and about 300 species are used. In 1969, the Ministry of Public Health and Social Affairs made Notification No. 233, which acknowledged that a herbal preparation described in 11 classic books containing details of the ancient remedies (8 Korean and 4 Chinese) could be prepared by a pharmaceutical firm according to the same formula described in the classic literature without submitting any clinical or animal toxicity data.

A law, the composite pharmacy law, governs all activities in respect to pharmacy, pharmaceutical industries and suppliers of medicinals including herbal raw materials. There are two official drug compendia: the Korean Pharmacopoeia (5th. Edition) and the Korean Natural Drug Standards.

To produce well-controlled and clean herbal raw materials by manufacturers, the Ministry of Public Health and Social Affairs has made a Notification under

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(6) Summary of the presentation by A. Bonati.

(7) Summary of the presentation of Kang-Choo Lee and of the Abstract of the Paper of Il-Moo Chang

which a new licence will be issued to the Standardized Herbs Manufacturer. Herbal drugs and preparations are mainly produced as over-the-counter products by manufacturers and are standardized and quality controlled according to guidelines described in the Korean Pharmacopoeia, the National Institute of Health and the Ministry of Public Health and Social Affairs. The main information required concerning standardized herbs includes, the taxonomic status, parts used, gross morphology including colour and odour, qualitative assay, purity, total ash, acid-insoluble ash, weight loss due to dryness, content of essential oil, content of extract and grade of quality.

Traditional drugs are essentially in the crude state and a single herb may contain hundreds of natural constituents. Hence where several herbs are combined, hundreds of natural constituents would need to be assayed for quality control. Therefore the National Institute of Health employs proximate assay methods, whereby an important, active natural product or an indicative substance is analysed for the purposes of quality control.

It is expected that the Ministry of Health and Social Affairs will enact a regulation on Good Manufacturing Practices for herbal drugs in 1991.

#### NETHERLANDS (8)

In the Netherlands, from the legislative point of view herbal preparations are in four categories:

- i) A few herbal medicines are formally registered;
- ii) A much larger number is provisionally registered, but these medicines will have to obtain formal registration by 31 December 1991;
- iii) Certain extracts of herbal remedies in the form of tinctures are classified as homeopathics; and
- iv) Certain herbal preparations are considered as food preparation. No claim can be made about their having any therapeutic effect.

Since 1987, the Government of the Netherlands has been discussing with the Dutch Society for Phytotherapy (NvF), the Dutch branch of the Organization of Manufacturers (NEHOMA) and the Dutch Society of Pharmacists (KNMP) the development of formal registration procedures and the three Societies have been working together to formulate self-regulation programmes and tools for registration procedures.

The Dutch Authorities are in favour of the European Community recommendations and of the developments made by the European Scientific Cooperative for Phytotherapy. It is hoped that expanded formal registration procedures will be formulated by the Government within the next few months.

#### THAILAND (9)

In 1969 the Thai Drug Act B.E. 2510 was promulgated. Under this act and its revisions, any person wishing to manufacture or import traditional drugs was

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(8) Summary of the presentation by L.W. von Hebel

(9) Summary of the presentation by Pakdee Pothisiri

first required to obtain a licence. Then application had to be made to the competent official for registration of the drug formulation. Upon the receipt of a certificate of formula registration, the traditional drug could be manufactured or imported. A herbal drug, that is a drug derived from plant, animal or mineral sources, that had not yet been compounded, dispensed or denatured did not require registration.

In accordance with the Drug Act, a Drug Committee is appointed as being responsible for the registration of traditional drugs and the withdrawal or suspension of licences. There are three Subcommittees, on Domestic or Manufactured Traditional Drug Registration Approval, on Foreign or Imported Traditional Drug Registration Approval and on Investigation of Manufacturing Premises and Warehouses Approval, to assist in the evaluation of drug registration and licence applications.

Manufacturers or importers must submit an application form, labels and inserts, to obtain the approval of the Subcommittee on Investigation of Manufacturing Premises and Warehouses, following which licences are granted to manufacture traditional drugs, sell them or import them into the Kingdom.

An important intercountry programme is the Standardization, Quality Control and Utilization of Herbal Medicines, which is part of a project under Technical cooperation among ASEAN countries in Pharmaceuticals. The activity is aimed to assure the quality of herbal medicines used by the people of ASEAN countries and to promote their utilization in primary health care programmes.

#### UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND<sup>(10)</sup>

Control of medicines in the United Kingdom is based on the Medicines Act 1968, from which a large amount of detailed legislation has followed, incorporating all relevant European Community Legislation. A system of Product Licences was introduced in 1972, but companies had a legal right to a provisional Product Licence for any existing product already on the market.

European Community Directives issued in 1965 and 1975 required all medicinal products to be reviewed by 1990. The first review applications from manufacturers of herbal medicines, with full data on quality, safety and efficacy, were submitted to the Department of Health in 1983 and the last in December 1988. Of the products submitted, probably more than 95% of herbal medicines have been granted reviewed Product Licences.

The British Herbal Medicine Association (BHMA), representing the manufacturers, produces the British Herbal Pharmacopoeia as a source of quality standards and other specifications were negotiated in the form of "Master Files" submitted to the Department of Health.

Overall therefore, in the United Kingdom all herbal medicines are fully reviewed for quality, safety and efficacy to the requirements of the European Community. Obviously, for many herbal remedies, adequate clinical evidence of efficacy is not available in the literature. However European Community Directive 65/65 states:

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(10) Summary of the presentation by P. Bradley

"The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if it can be demonstrated by detailed reference to published scientific literature that the constituent or constituents of the proprietary medicinal product have a well-established medicinal use, with recognized efficacy and an acceptable level of safety".

About 1000 herbal medicines have survived the review. However, many other herbal products are on sale, which are legally marketed as "food supplement", but no medicinal claims may be made for such products.

#### UNITED STATES OF AMERICA<sup>(11)</sup>

In the United States of America, regulations governing the labelling and sale of herbs and medicinal plants are still in a developmental state. Currently, most herbs and herbal medicines are unregulated in the USA. That is, most are not regulated as medicines. They are regulated as foods. As such, most regulatory action occurs in areas of safety (i.e. whether the herb is Generally Recognized As Safe, GRAS, or in the area of economic problems. Economic problems include making unproven or unapproved claims, or the misbranding or adulteration of a product.

Because most herbs are marketed as foods, they cannot make therapeutic claims. To do so would be to market an unapproved drug. This situation severely hampers the herb industry which must rely on suggestive labelling or other avenues to "educate" consumers as to the benefits of herb products.

There appears to be a bias against herbs by the Food and Drug Administration (FDA). The agency acts as if herbs are unproven drugs, without a scientific basis. The agency sees the herb industry as part of the health foods industry with which it has had many problems regarding what the agency thinks are unfounded claims for health food products.

The majority of herb sales in the USA occurs through health food stores, not pharmacies. There are a few herbs that are still approved as non-prescription, over-the-counter (OTC) drugs. However, a recent 18-year review of OTC drugs has resulted in many formerly-used herbal ingredients being dropped. This occurred due an idiosyncrasy in the system. Most manufacturers of herbal products did not submit new data on the individual herbs to prove their safety and efficacy. Without new data, many of these ingredients defaulted to a position called "Category III" meaning that there was not enough information available to make a determination of safety or efficacy. When final monographs are published, Category III ingredients are automatically changed to "Category II" meaning unsafe or ineffective and thus the ingredient is banned from use as OTC drugs. The ingredient is banned for use as an "active" unless a company petitions FDA to reopen the monograph to consider some new evidence.

Critics charge that this situation is partially explained by the FDA bias toward the approval of single chemical drugs, whether for OTC or prescription drugs. Single compounds are often less costly to produce, and they are simpler to assay than complex phytomedicines. This makes herbs in general, plus multiple compounded herbal products, extremely difficult to obtain approval.

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(11) Summary of the presentation by M. Blumenthal

Since 1976, the US FDA has been enjoined from heavily regulating the health food market due to the passage of the so-called "Proxmire Bill" which in effect said that foods (including dietary supplements) are not drugs. This included herbs. This law kept the FDA from pursuing its intention of regulating dietary supplements like vitamins and minerals (and herbs) on a monograph basis, as if they were a form of drugs, as is done in Canada and many European countries. However, recently the Nutrition Labeling and Education Act of 1990 (NLEA) has become law. Among other sweeping reforms in food labelling, this Act will allow specific health messages for foods to be advertised by industry, as long as the claims fall within certain standards and guidelines.

A big issue facing the herb industry currently is whether FDA will accept the proposal of the American Herbal Products Association (AHPA) to establish procedures and guidelines for the evaluation of the safety and appropriateness for health claims for herbs, when sold as foods, not drugs. Thus, the NLEA may not provide an adequate vehicle for the proper labelling of herbs for health claims or therapeutic benefits.

#### EASTERN MEDITERRANEAN REGION OF WHO<sup>(12)</sup>

The Eastern Mediterranean Regional Office of WHO (EMRO) has established a Regional Programme on Traditional Medicine to support national efforts in those countries in which traditional medicine is widely practised. The programme seeks to ensure that useful traditional remedies and practices are incorporated into national health systems, in keeping with the Global Strategy of Health For All by the year 2000.

Member States of EMRO vary greatly in many aspects including population size, Gross National Product, education and available manpower. They also differ with respect to the type and extent to which traditional medicine is practised.

The targets for the Traditional Medicine programme of the Eastern Mediterranean Region are that, by 1995:

1. At least one-third of the countries of the Region will have incorporated useful traditional medicine practices into the health services, especially at the primary health care (PHC) level;
2. In at least one-third of the countries, there will have been a concerted national effort to utilize effectively a selected list of medicinal plants and herbal remedies of proven efficacy;
3. In at least three countries, national capabilities in traditional medicine research will have been strengthened.

Academic institutions will be encouraged to continue research in the following areas: (a) safety and efficacy of medicinal plants used in their countries; (b) standardization and quality control of medicinal plants recommended for medical use; (c) evaluation of national flora; (d) means of integrating traditional practices into the PHC system.

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(12) Summary of the Presentation by Abdel Azziz Saleh.

A model list of 54 medicinal plants that are in common use in most of the countries of the Region was compiled for use at primary health care level during an intercountry meeting held in Kuwait in 1985. The list could be modified by each country to meet local requirements.

Standardization and quality control measures for medicinal plants are essential for wider acceptance of herbal remedies. An act aiming at ensuring the safety and quality of herbal remedies was formulated and has been used by a few countries in the Region.

The Regional Programme is developing general guidelines for use by Member States in formulating national policies on Traditional Medicine. An Intercountry Expert Meeting on Traditional Medicine and Primary Health Care is planned to be held in Cairo, Egypt from 30 November to 3 December 1991 to finalize these guidelines.

Closing Remarks

by

Olayiwola Akerele  
Programme Manager, Traditional Medicine  
World Health Organization, Geneva, Switzerland

Mr Chairman, distinguished friends,

We have come to the end of our deliberations and we have a fine product - one in which each and everyone of us should be proud. The guidelines as they stand, will need some editorial work, but I promise to stay faithful to the text as by everybody.

The report of the Consultation plus the guidelines that we have worked on during the last few days, when completed, will be circulated to all participants for their comments before finalization.

I would like to express the Organization's sincere appreciation and thanks to all participants for all their hard work without which we could never have completed our charged duty on time. We were lucky to have Professor Kemper as our chairman on this occasion. I am sure that all of you will agree with me that he has directed the course of our deliberation with fairness and when necessary, with firmness. These attributes have enabled us to complete our work and to stay in focus to our objectives.

Our scribe and rapporteur Mrs M. Carman Kasperek deserves our sincere thanks and appreciation. It was, in fact, due to her unflinching support and hard work that we had a document for our consideration this morning. Special thanks are also due to our group moderators and rapporteurs for their work which has contributed to the achievements we have been able to make in finalizing the guidelines.

My renewed thanks go to our hosts, particularly Mr Burges, Chairman of the World Federation of Proprietary Medicine Manufacturers, who spared no effort to see that we meet in a conducive atmosphere.

We would like to thank the hotel management and staff for facilitating our work.

The secretariat deserves our thanks for their hard work which they carried out with dedication and charm. I would like to single out Mrs H. Baumhauer-Crane, Miss J. Dadzie and Ms Y. Maruyama.

Mr Chairman, Madam Rapporteur, allow me to end by wishing you all a safe journey home and happy reunion with your families.

Ladies and Gentlemen,

The WHO Consultation to review and finalize the Guidelines for the Assessment of Herbal Medicines is declared closed.