

Regulatory Situation of Herbal Medicines

A worldwide Review

FOREWORD

Although modern medicine is well developed in most of the world, large sections of the population in developing countries still rely on the traditional practitioners, medicinal plants and herbal medicines for their primary care. Moreover during the past decades, public interest in natural therapies has increased greatly in industrialized countries, with expanding use of medicinal plants and herbal medicines.

The many and various forms of traditional medicinal products have evolved against widely different ethnological, cultural, climatic, geographical, and even philosophical backgrounds.

The evaluation of these products and ensuring their safety and efficacy through registration and regulation present important challenges.

The purpose of this document is to share national experiences in formulating policies on traditional medicinal products and in introducing measures for their registration and regulation, and to facilitate information exchange on these subjects among Member States. The document, at present, only covers 52 countries, but after a few years it will be updated and expanded in the light of experience. Further contributions from governments, institutions, and others would be greatly appreciated.

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REGULATORY SITUATION OF HERBAL MEDICINES
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I. INTRODUCTION

Traditional Herbal Medicines and Human Health

Herbal medicines which formed the basis of health care throughout the world since the earliest days of mankind are still widely used, and have considerable importance in international trade. Recognition of their clinical, pharmaceutical and economic value is still growing, although this varies widely between countries [1].

Medicinal plants are important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds. Regulation of exploitation and exportation is therefore essential, together with international cooperation and coordination for their conservation so as to ensure their availability for the future [2].

The United Nations Convention on Biological Diversity states that the conservation and sustainable use of biological diversity is of critical importance for meeting the food, health and other needs of the growing world population, for which purpose access to and sharing of both genetic resources and technologies are essential [2].

Legislative controls in respect of medicinal plants have not evolved around a structured control model. There are different ways in which countries define medicinal plants or herbs or products derived from them, and countries have adopted various approaches to licensing, dispensing, manufacturing and trading to ensure their safety, quality and efficacy [2].

Despite the use of herbal medicines over many centuries, only a relatively small number of plant species has been studied for possible medical applications. Safety and efficacy data are available for an even smaller number of plants, their extracts and active ingredients and preparations containing them [3].

Regulation and Registration of Herbal Medicines

The legal situation regarding herbal preparations varies from country to country. In some, phytomedicines are well-established, whereas in others they are regarded as food and therapeutic claims are not allowed. Developing countries, however, often have a great number of traditionally used herbal medicines and much folk-knowledge about them, but have hardly any legislative criteria to establish these traditionally used herbal medicines as part of the drug legislation.

For the classification of herbal or traditional medicinal products, factors applied in regulatory systems include: description in a pharmacopoeia monograph, prescription status, claim of a therapeutic effect, scheduled or regulated ingredients or substances, or periods of use. Some countries draw a distinction between "officially approved" products and "officially recognized" products, by which the latter products can be marketed without scientific assessment by the authority [2].

The various legislative approaches for herbal medicines fall into one or other of the following categories [2]:

- same regulatory requirements for all products;
- same regulatory requirements for all products, with certain types of evidence not required for herbal/traditional medicines;
- exemption from all regulatory requirements for herbal/ traditional medicines;
- exemption from all regulatory requirements for herbal/ traditional medicines concerning registration or marketing authorization;
- herbal/ traditional medicines subject to all regulatory requirements; and
- herbal/ traditional medicines subject to regulatory requirements concerning registration or marketing authorization.

Where herbal medicines and related products are neither registered nor controlled by regulatory bodies, a special licensing system is needed which would enable health authorities to screen the constituents, demand proof of quality before marketing, ensure correct and safe use, and also to oblige licence holders to report suspected adverse reactions within a post-marketing surveillance system [4].

WHO Policy and Activities

The WHO Traditional Medicine Programme

The World Health Assembly (WHA) has adopted a number of resolutions drawing attention to the fact that a large section of the population in many developing countries still relies on traditional medicine, and that the work force represented by traditional practitioners is a potentially important resource for primary health care. In 1978, the Declaration of Alma-Ata recommended, *inter alia*, the inclusion of proven traditional remedies into national drug policies and regulatory measures.

The policy of the World Health Organization regarding traditional medicine was presented in the Director-General's report on Traditional Medicine and Modern Health Care to the Forty-fourth World Health Assembly 1991, which stated that "WHO collaborated with its Member States in the review of national policies, legislation and decisions on the nature and extent of the use of traditional medicine in their health systems." Based on the relevant WHA resolutions, the major objectives of the Traditional Medicine Programme are: to facilitate the integration of traditional medicine into national health care systems; to promote the rational use of traditional medicine through the development of technical guidelines and international standards in the field of herbal medicine and acupuncture; and to act as a clearing house for the dissemination of information on various forms of traditional medicine.

In resolution WHA42.43 (1989), the Health Assembly urged Member States: to make a comprehensive evaluation of their traditional systems of medicine; to make a systematic inventory and assessment (pre-clinical and clinical) of the medicinal plants used by traditional practitioners and by the population; to introduce measures for the regulation and control of medicinal plant products and for the establishment and maintenance of suitable standards; and to identify those medicinal plants, or remedies derived from them, which have a satisfactory efficacy/side-effect ratio and which should be included in national formularies or pharmacopoeias.

In recent years, many developed countries have shown growing interest in alternative or complementary systems of medicine, with a resulting increase in international trade in herbal medicines and other types of traditional remedies. A stimulus consequently exists, in both developed and developing countries, to assess and rationalize practices, and to control commercial exploitation through over-the-counter sale of proprietary labelled herbal and other "natural" medicines.

Herbal medicines have been included in the International Conference on Drug Regulatory Authorities (ICDRA) since the Fourth Conference in 1986. Workshops on the regulation of herbal medicines moving in international commerce were held at the Fourth and Fifth ICDRA Conferences in 1986 and 1989, both confining their deliberations 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 and registration [5].

A WHO consultation in Munich, Germany, June 1991, drafted Guidelines for the Assessment of Herbal Medicines which were adopted for general use by the Sixth ICDRA in Ottawa, October 1991 [6]. These guidelines (WHO/TRM/91.4) define basic criteria for the evaluation of quality, safety and efficacy of herbal medicines to assist national regulatory authorities, scientific organizations, and manufacturers to undertake an assessment of the documentation, of submissions and/or the dossiers in respect of such products. A general rule of such assessment is that traditional experience in their use and the medical, historical, and ethnological background of these products shall be taken into account, through detailed descriptions in the medical or pharmaceutical literature or documented accounts of their applications [6].

These guidelines contain basic criteria for the assessment of quality, safety, and efficacy and important requirements for labelling and the package insert for consumers' information. The requirements for pharmaceutical assessment cover issues such as identification, galenical forms, analysis and stability. Safety assessment should at least cover the documented experience of safety and toxicological studies, where indicated. The assessment of efficacy and intended use includes evaluation of traditional use through appraisal of the literature and evidence to support the indication claims. Special chapters on combination products and on requirements for product information for consumers are included. The WHO Guidelines are intended to facilitate the work of regulatory authorities, scientific bodies and industry in the development, assessment and registration of herbal medicines, reflecting scientific results which could be the basis for future classification of herbal medicines and would also accommodate cross-cultural transfer of traditional herbal medicinal knowledge between different parts of the world [6].

In 1994, the WHO Regional Office for the Eastern Mediterranean published Guidelines for Formulation of National Policy on Herbal Medicines [7]. As the majority of the world population seeks treatment with traditional

medical practices, especially herbal medicine, and as herbal medicines are of particular value in gastrointestinal problems, upper respiratory tract ailments, urinary tract diseases and skin diseases, the need to formulate national policies on traditional medicines and to encourage co-operation between Member States in this regard is evident. The aim of such national policies would be to develop regulatory and legal reforms to ensure good practice, and to extend primary health care coverage, while ensuring the authenticity, safety and efficacy of these medicines. Main objectives include the recognition of traditional medicine as an integral part of national health care systems, co-operation between modern and traditional medicine, promotion of the rational use of products, the introduction of quality assurance systems, the guarantee of regular supplies, the promotion of research and development of regulatory measures. It has been recommended to countries that a National Expert Committee be established, which would be the appropriate authority to identify the steps and plans needed to formulate national policy in this area and then to develop, direct and monitor the various phases of its implementation. The functions and activities of the National Expert Committee should include drawing up a national list of essential herbal medicines, preparing guidelines on registration requirements, advising on a national licensing system, advising on means of reporting adverse reactions, and proposing suitable methods of communication and co-operation with the Ministry of Health. Criteria for selection of essential medicinal herbs should be mainly safety, efficacy, health needs and availability for supply. Based on the approved list of medicinal plants of each country, the policy should indicate clearly how the supply of these medicinal plants would be secured. The supply procedure should include collection, cultivation, local production and processing, imports and preservation of the national flora. Within a national quality assurance system, standards and regulations should be set to ensure the quality of all medicinal plants and their preparations that are available in the market. The guidelines contain a special chapter on criteria for research on traditional herbal medicines and on criteria for their rational use [7].

As most herbal medicines still need to be studied scientifically, Member States have been seeking the co-operation of WHO in identifying safe and effective herbal medicines for use in their national health care systems.

To develop criteria and general principles to guide research work on evaluating herbal medicines, the WHO Regional Office for the Western Pacific, in 1992, organized a meeting of experts to develop guidelines for research on herbal medicines. Basic scientific principles and special requirements related to their use in traditional practice are incorporated in these guidelines, the main objectives of which are to ensure their safety and efficacy, to promote their rational use, and to provide research criteria for their evaluation. The guidelines provide a basis for Member States to develop their own research guidelines, and for the exchange of research experience and other information so that a body of reliable data for the validation of herbal medicines may be built up. The adoption of such policy was intended to help to overcome legal barriers against the use of herbal medicines [8].

Research approaches should differentiate between herbal medicines with a long documented experience and those the "traditional" use of which has not yet been established. In accordance with the WHO Guidelines for the Assessment of Herbal Medicines (WHO/TRM/91.4), traditional experience with the respective preparation, which includes long-term use as well as the medical-historical and ethnological background, should be taken into consideration as a general rule in conducting research [8].

Herbal medicines have two special characteristics which distinguish them from chemical drugs; use of crude herbs and prolonged usage. A single herb may contain a great many natural constituents and a combination of herbs even more. Experience has shown that there are real benefits in the long-term use of whole medicinal plants and their extracts, since the constituents in them work in conjunction with each other. However, there is very little research on whole plants because the drug approval process does not accommodate undifferentiated mixtures of natural chemicals, the collective function of which is uncertain. To isolate each active ingredient from each herb would be immensely time-consuming at unsupportable cost, and is almost impossible in the case of preparations.

The summary and recommendations of the Sixth ICDRA prompted WHO to continue to develop pharmacopoeial monographs on herbal medicines on the basis of the Guidelines for the Assessment of Herbal Medicines. In response to the request from Member States, WHO's Traditional Medicine Programme decided to prepare a technical document entitled "WHO Monographs on Selected Medicinal Plants" for primary health care. The information in the monographs includes two parts: Part I consists of summaries of the botanical characteristics, major active chemical constituents and quality control of each plant; Part II consists of summaries of clinical

applications, pharmacology, posology, possible contraindications and precautions, and potential adverse reactions.

A WHO consultation on "WHO Monographs on Selected Medicinal Plants" took place in Munich, Germany 1996. After discussion and review, 28 monographs were adopted. The purpose of this document is: to provide scientific information on the safety, efficacy and quality control of widely used medicinal plants; to facilitate the proper use of herbal medicines; to provide models for Member States to develop their own monographs on these and additional herbal medicines; and to facilitate information exchange. The 28 monographs were presented at the Eighth ICDRA meeting in Bahrain, November 1996. Another 32 monographs are being prepared.

II. REGULATORY SITUATION

Africa

Mali

The Division of Traditional Medicine, a collaborating centre of WHO and recognized by the Organization of African Unity, has started the industrial exploitation of medicinal plants, carrying out activities such as: a survey of practitioners; identification of natural areas of growth of medicinal plants in Mali; botanical, chemical and pharmacological studies; development of improved traditional medicines; improvement of quality control; and training in traditional medicine. Since 1974, associations of traditional therapists have been established [9].

Mauritius

Between 1992 and 1994, a survey was carried out in Rodriguez and Mauritius in the course of a study funded by the European Union under the aegis of the Indian Ocean Commission "Inventory and study of medicinal and aromatic plants of the States of the Indian Ocean". In the course of this study, more than 600 plants entering the traditional pharmacopoeia were identified. The results give a good indication of the distribution and the use of medicinal plants. Phytochemical, botanical, ethno-botanical and bibliographic information is available together with details of physicochemical properties of some additional plants and tests of some of the extracts for their pharmacological properties. Considering the high value of medicinal plants for primary health care, measures for control of this plant material and public information and professional education are required to guarantee the safe and correct use of these products [10].

South Africa

Importance of herbal medicines

A large number of South Africans consult traditional healers, mostly in addition to medical practitioners. There are about 200 000 traditional healers in the country, and indigenous herbal medicines are in the main materia medica. Herbal medicines are also used for self-care.

Legal Status

The trade in crude indigenous herbal products is completely unregulated. However, once a health-related claim is made for a finished product, it has to go through the full drug evaluation procedure in the Medicines Control Council (MCC) before marketing [11].

Specific regulations for registration and control of new "traditional" herbal medicines do not exist. Old medicines including some well-known herbal medicines, such as Senna or Aloes, are already registered by the MCC, according to internationally accepted standards of efficacy and safety. Pharmaceutical standards need to be consistent with those of the United States Pharmacopoeia (USP) or the British Pharmacopoeia (BP) [11]. At present, there is no possibility for an abridged application procedure, and there is neither a list of therapeutic indication claims suitable for treatment with traditional medicines, nor a national herbal medicines formulary of a pharmacopoeia [11].

Development Programme

The present regulations of the MCC with respect to traditional herbal medicines are comparable to those of the FDA prior to the Dietary Supplement Health and Education Act of 1994 [11].

Traditional medicines are included in the drug policy section of the government's Reconstruction and Development Programme. The Traditional Medicines Programme (TRAMED) at the Department of Pharmacology, University of Cape Town, participated in formulating an outline proposal for the registration and control of traditional medicines in 1994. The aims of TRAMED are promotion of the use of safe, effective and high quality "essential" traditional medicines, promotion of the documentation of traditional medicines and their scientific validation, contributing to primary health care through the provision of appropriate information to traditional healers and health professionals, support of industrial development in this sector by local industry, and contributing to the training of traditional healers [12].

The Americas

Antigua and Barbuda

Antigua and Barbuda became involved in a project on the economic biology of under-exploited tropical plants (EBUTROP) in October 1983 which was terminated in 1989. This project focused on development of herbaria, data bases, studies on plants for medicinal and nutritional use, training especially in phytochemical analysis, and information exchange including publications. The main objectives of this project were to compile a list of plants used traditionally in Antigua and Barbuda for medicinal purposes, to sensitize the public with respect to the advantages or disadvantages of using these plants, to train staff in phytochemical screening, to carry out phytochemical screening of a selected number of these plants, and to acquire appropriate scientific material [13].

There are no regulations existing on traditional medicines at present. The Ministry of Health is examining the possibility of establishing guidelines through the recently inaugurated Pharmacy Council to regulate the import and sale of herbal medicines. An extensive list of the plants traditionally used for medicinal purposes in Antigua and Barbuda exists which makes reference to local names, scientific names and reported uses [14].

Argentina

Distribution

In Argentina medicinal plants are available through different distribution channels, of which only the pharmacies, herboristerias and the pharmaceutical industry are controlled by pharmacists, in accordance with the law describing the responsibilities of a pharmacist, the Drug Law and the National Pharmacopoeia. Herboristerias are authorized to sell vegetable drugs but not mixtures. They have to employ a pharmaceutical technical director. Mixtures of vegetable drugs are controlled, together with preparations made by industry, under the Drug Law No. 16.463. It is relevant to mention a project of the Provincia de Buenos Aires to oblige the herboristerias to act only as wholesalers. Furthermore, persons who grow medicinal plants should have an authorization by the Ministry of Health [15].

Legal Status

For the marketing authorization of a new medicinal product, it is in general required to have a laboratory and to fulfil the legal requirements of article 27 of the Law No. 16.463. There is no difference between herbal medicines and chemical drugs. When the active principle is described in the Pharmacopoea Nacional Argentina, reference can be made to such a monograph. If not, a "Pre-monografia" has to be presented for approval by the Instituto Nacional de Farmacologia y Bromatologia which is responsible for drugs and food. A certification number will be granted which allows sale at a national level. But, at provincial level, each "provincia" has its own system of approval for medicinal drugs, and the certification number is only valid when accepted by a provincia. With respect to the documentation needed to fulfil article 27, the Instituto Nacional de Farmacologia y Bromatologia has issued an information sheet [15].

Lack of controls for raw materials

Prior to 1993, the following were important problems:

- there was no control for the collection in the wild of medicinal plants;
- there were no scientific criteria for the collection of these plants;
- there was no control of the methods of drying, conservation or grinding;

- although herboristerias were controlled by law, the sale of medicinal plants through other distribution channels was completely uncontrolled, which might be of critical importance where potentially toxic plants are sold;
- although pharmacognostic methods are described in the Pharmacopea Nacional Argentina, no methods for the determination of active principles, e.g., quantitative assay, were indicated;
- there was no official definition of what is a medicinal plant and what is not, some plants being used as food although they were included in the pharmacopoeia; and
- with respect to the Law No. 16.463, it was not clear which requirements had to be fulfilled to apply for registration of a new medicine based on medicinal plants.

Although scientific knowledge on medicinal and toxic plants was growing, it was necessary to gain more information about the utilization of 700-800 species. There was no academic specialization for the control and the processing of medicinal plants [15].

For these reasons, the need for future legislation to remedy the unsatisfactory situation relating to medicinal plants became evident [15].

In November 1993, a regulation for registration and commercialization of medicinal plants was published by the Health Ministry of the Provincia de Buenos Aires. With this regulation, an obligation for the registration of medicinal herbs was established. The herboristerias had to register their products within 180 days, together with documentation containing e.g., name of the plant, part of the plant, active principles, identification, and indications. In the case of a mixture of herbs, the benefit of the combination had to be demonstrated. The certificate issued by the Laboratorio Central de Salud is valid for five years, and a prolongation must be applied for 30 days before expiry [16].

The Pharmacopea Nacional Argentina

Within the Pharmacopea Nacional Argentina, there are three categories of plants and their preparations: crude drugs; extracts or fractions with a complex chemical composition extracted directly from a medicinal plant, e.g., fixed or essential oils or resins; and pure active principles. The total number of such monographs is 899. The monographs do not consider pharmaceutical preparations such as extracts, tinctures, aromatic waters etc. Of the 899 monographs, 56 describe crude drugs, and 33 describe extracts or fractions [15].

Canada

Herbal medicines are regulated as drugs in Canada and must therefore conform to labelling and other requirements as set out in the Food and Drugs Act and Regulations, which means that, in contrast to the USA, large numbers of herbal medicines with indication claims are legally on the Canadian market. Prior to assignment of a registration or drug identification number, scrutiny of the composition and the labelling of medicine is required.

On 13 August 1987, following a long discussion between interested parties and experts, an Information Letter was issued by the Canadian Health Protection Branch containing a list of herbs considered hazardous or requiring cautionary labelling. It was reported that products may be sold as foods, drugs or even cosmetics depending on their properties, claims and the manner in which they are used. At that time, herbs and botanicals were acceptable as drugs on the basis of acknowledged claims and quantitative statements of the active ingredient. As a general practice, herbal remedies used for minor self-limiting conditions may be allocated Drug Identification Numbers (DIN), based on a logical pharmacological rationale and bibliographic references which include verified traditional uses that have not been superseded by more recent research and study. Furthermore, the need to provide a specific framework for the registration of herbs and botanical preparations has been identified, and a concept of review involving "Standardized Drug Monographs (SDM)" has been proposed to facilitate registration of those drugs containing herbs that meet the requirements of the monographs. Products making reference to such an SDM would require less individual pre-market scrutiny on a product-by-product basis and would result in more rapid issuance of DIN, but would be balanced with additional post-market compliance monitoring and activity. Combinations of herbs outlined in such monographs would be accepted if justified on sound therapeutic principles. Claims in respect of prevention or treatment of serious diseases and those which are inappropriate for self-diagnosis and treatment are prohibited within this procedure [17].

On 5 January 1990, another Information Letter was issued to clarify the policy of the Health Protection Branch on herbal medicines, to outline the regulatory requirements, and to advise on the mechanisms for applications for DIN for these products. It was clearly stated that the most important factors in determining whether a herbal

product is considered to be a food or a drug are the pharmacological activity of the ingredients, the purpose for which the product is intended, and the representations made regarding its use. Herbal medicinal products are in this Information Letter classified into two major groups:

- Herbs listed in pharmacopoeias and major pharmacological reference works; they generally have their properties, dosage, indications, and contra-indications for a well established use. Products containing such herbal ingredients are reviewed in the same manner as other drug products and are widely available on the market either on prescription or as non-prescription drugs.
- Herbs which have received relatively little attention in scientific literature and therefore may not be well known in Canada. Nonetheless, there is literature available on their traditional use on an empirical basis, and these references are considered to be useful in supporting the acceptability of herbal drug products. It was expected that herbal medicines from this group would be used for minor self-limiting conditions. These products which are based on traditional or folkloric use should be designated as traditional medicines, and some details for application for DIN have been announced.

The review of DIN applications involving standardized drug monographs (SDM) should enable a manufacturer to certify that products meet the conditions outlined in the SDM [18].

In October 1990, guidelines on "Traditional Herbal Medicines" were published by the Health Protection Branch, by authority of the Minister of National Health and Welfare, to assist manufacturers in completing applications for a DIN and in labelling products that fall within the category of Traditional Herbal Medicine (THM), as outlined in the Information Letter of 5 January 1990. Applications must include a draft version of the label with a clear claim or indication for the use of the traditional herbal medicine. The claim should be supported by references. If an SDM is available for a herb, and if the proposed claims are within the scope of the monograph, a statement to this effect is an acceptable replacement for other references. Terms such as "tonic, supplement, purifier, depurative" and other similar wordings are not accepted. Some combinations of herbs that seem illogical e.g., diuretics combined with laxatives and those with contradictory effects are regarded as questionable.

The assessment is primarily based on traditional references for efficacy and dosage. The claims are restricted to those that are acceptable for self-monitoring. If there are safety concerns, modern research will be taken into account instead of traditional references [19].

Chile

In August 1992, the Unidad de Medicina Tradicional was established with the objective to incorporate traditional medicine with proven efficacy into health programmes, and to contribute to the establishment of their practice. A regulation for the control of the practice of alternative medicines was developed, and a legal basis was created (La Ley no. 19.253 of October 1993) which takes into consideration the role of traditional medicine in public health [20].

Legal Status

Natural products are legally differentiated as follows (Código Sanitario):

- drugs intended to cure, alleviate, or prevent diseases (article 97);
- food products for medicinal use and with therapeutic properties (article 98); and
- food products for nutritional purposes (article 108).

According to a regulation for the control of drugs, food products for medicinal use, and cosmetics (decreto no. 435/81), herbal products with therapeutic indication claims and/or dosage recommendations are considered to be drugs. Their distribution is restricted to pharmacies and drugstores which need a special authorization from the Ministry of Health. A registration for marketing authorization is needed for herbal products, homoeopathic products, and other natural products as defined in article 24 of the regulation. An application for registration consists of the complete formula, the labelling, samples of the product, and a monograph which permits identification of the formula and characteristics of the product [20].

Colombia

In July 1990, an order was issued by the Ministry of Health setting out detailed legal requirements for natural products and pharmaceutical preparations thereof that have traditionally been used. A natural product is defined as a material of a natural origin that has traditionally been used for therapeutic purposes, and that has only been treated (processed) by physical methods. A pharmaceutical preparation is defined as a product thereof with a pharmaceutical form and a traditional empiric use for therapeutic purposes, used only orally or administered topically. Products with therapeutic indications have to be registered as medicines, herbal teas are registered as food. Detailed requirements are given that the plant material has to fulfil with respect to cultivation, collection, drying, etc. For the manufacturer of pharmaceutical preparations, a special licence is needed. Plant material is allowed to be brought into the market, individually packed and not mixed, with a special authorization, and a therapeutic use must not be indicated. Pharmaceutical preparations need a registration that has to be applied for with a technical dossier containing documentation on the manufacturing process, quality control and, if necessary, toxicity studies, together with monographs on the material, including its traditional use, method of application, dose, contra-indications, adverse reactions, and a bibliography. If already registered in two or more countries (which are specifically listed), reference may be made to such a previous registration with respect to the documentation of efficacy. In the case of a medicinal plant product, it has to be certified that the plant is included in an official plant list. Drafts of a label and a leaflet have to be submitted. The registration is valid for ten years and may be renewed [21].

In August 1990, a resolution published by the Ministry of Health listed 17 plants, their common and botanical names, the parts used, and their traditional use which has been officially accepted, and to which reference may be made [22].

Mexico

Traditional medicine represents a culturally accepted link between past and present in Mexico. Pre-Hispanic cultures developed an original and powerful way of classifying knowledge. Research has individualized Pre-Hispanic Mexican medicine, bringing understanding of its classification systems, and recognition of the validity of aspects never included in Western thought. During its long history, traditional medicine was repeatedly outlawed and its practices prohibited. However, Mexican traditional medicine has survived, despite these measures, the political tendency to give modern scientific medicine an absolute priority, and the scientists' tendency to minimize traditional knowledge [23].

Nicaragua

In 1985, during the war, the Ministry of Health started a project to revitalize popular and traditional medicine, as a strategy in the search for self-sufficiency in response to the difficult situation in this country. As the majority of supplies of chemical and pharmaceutical materials had to be imported at high prices, a search for alternative therapies was started.

In April 1989, the Ministry of Health established a National Centre of Popular and Traditional Medicine with the following objectives:

- to organize investigations on popular and traditional medicine;
- to train health promoters and medical and paramedical persons in these fields;
- to promote the cultivation and commercialization of medicinal herbs.

Considerable work was done in agrotechnological research, cultivation, and use of appropriate technology. All products have been subjected to quality control, and the products have been distributed through a national network of popular pharmacies for medicinal plants, which offers them to the public at very low prices.

The Centre forms a part of the National Commission for Essential Investigation, along with the National Autonomous University of Nicaragua, and other institutions under the leadership of the Minister of Health.

In 1991, the integration of popular and traditional medicine into Nicaragua's local health systems began by training nurses, and developing courses in basic plant therapy and health anthropology in the nursing schools. After the change of government in the same year, the National Centre for Popular and Traditional Medicine became a non-profit foundation, independent from the Ministry of Health, with the following objectives:

- to recover, preserve, and develop the resources, techniques and procedures of popular and traditional

- medicine;
- to ensure the application of technical resources and knowledge acquired by investigation and interchange of information on popular and traditional medicine;
- to design and implement a national programme for the promotion of the use of medicinal plants and the prevention and cure of illnesses; and
- to create a network for distribution and commercialization of medicinal plants and their derivatives through popular, private, and state pharmacies.

The Ministry of Health has included herbal products in the basic list of medicines to be made available through community pharmacies in the local health systems. This is considered to be a significant step towards the integration of traditional medicines into the national health care system of Nicaragua [24].

United States of America

Market Importance of Herbal Products

The use of herbal medicines in the USA is less widespread than in the majority of developed nations. The reason is that their distribution has mostly been limited to health food stores which are frequented by only a small proportion of the population. Wider distribution through pharmacies is difficult because no medical claims may be made and consumers are dependent on advice from pharmacists who, in a majority of cases, have little knowledge about medicinal herbs [25].

Legal Status

In the late 1930s, the Food, Drug and Cosmetic Act was passed and, from that time on, the Food and Drug Administration (FDA) has regulated as drugs any products which claim to treat, cure, mitigate or prevent a disease. Thus, for any herbal medicine claims to be allowed, the same procedures must be followed as for a chemical drug. Most natural products in the United States are regulated as foods or food additives even though many are used by consumers as folk medicines. As such, most of the regulatory action occurs in the area of safety. Where a herb is "generally recognized as safe" (GRAS), this means ensuring that no claims are made and products are not being misbranded or adulterated. Natural products theoretically have GRAS status, so long as qualified experts confirm this and are not contradicted by other experts. According to a court case in 1983, the requirement of "common use in food" was not restricted to use in the USA, but applied also to herbs without a history of use in the USA [25].

Some better known medicinal herbs are listed by the FDA for over-the-counter status. However, an 18-year review of over-the-counter drugs has resulted in most of those medicinal herbs being dropped, mainly because the US herbal industry failed to submit evidence to support their use as such. In November 1992, the FDA established a new advisory committee of outside experts for over-the-counter drugs [25].

New Legislation

Since 1976, following the "Proxmire Bill", a civil regulation for the Health Food Market states that foods, including dietary supplements and herbs, are not drugs. This law kept the FDA from making monographs on dietary supplements, vitamins, minerals and herbs, as has been done for several kinds of drugs [25].

In 1990, Congress passed the Nutrition Labelling and Education Act (NLEA) which required that all food products must have nutritional labelling, and that the FDA has to establish criteria for approving health benefit labelling for foods. An exemption to the NLEA was introduced noting that vitamins, minerals, herbs and similar nutritional substances are consumed differently from conventional food and thus should be subject to more lenient standards of evidence for their health benefits. Congress gave the FDA one year to receive public comment as to how to establish standards and procedures for the assessment of health claims for the supplements that were exempted from the rest of the NLEA. A proposal submitted by the American Herbal Product Association was rejected by the FDA [25].

Dietary Supplements, not Food Additives

In October 1994, the Dietary Supplement Health and Education Act [26] recognized that dietary supplements have been shown to be useful in preventing chronic diseases and therefore help limit long-term health care costs. Herbs and other botanicals, vitamins and minerals now fall under the definition of a dietary supplement which is presented in a dosage form such as capsules, tablets, liquids etc., and which is not represented as a conventional food, but which is labelled as a dietary supplement. Dietary supplements do not include

substances first sold as drugs and later as dietary supplements, nor do they include substances undergoing clinical studies which were not first sold as dietary supplements. The law provides that a dietary supplement is considered to be a food which does not need pre-market approval by the Food and Drug Administration (FDA), and not as a food additive which needs a pre-market approval by the authority. A statement on the label of a dietary supplement is allowed if a benefit is claimed related to a classical nutrient deficiency, if the role of the nutrient or dietary ingredient is described, or if the documented mechanism of action to maintain a function is characterized. In addition, however, it must be clearly stated that this statement has not been evaluated by the FDA, and that this product is not intended to diagnose, treat, cure or prevent any disease. Furthermore, the ingredients, and the plants or parts of plants respectively, and their quantity must be clearly listed. If the supplement claims to conform to an official compendia standard (USP) for which there is an official specification, and fails to meet that standard, the product is regarded as misbranded. This also applies in the case of a product which is not covered by an official compendium, but which fails to have the identity, strength, quality, purity which it may claim to have.

The new law provides for the establishment of an Office of Dietary Supplements within the National Institutes of Health, which should explore the role of dietary supplements to improve health, and should promote scientific studies of the benefits of the dietary supplements [26].

The signing into law of the Dietary Supplement Health and Education Act in October 1994 may accelerate the recognition and increase the importance of herbal products in the US market, because the law may give an opportunity to market these products as dietary supplements, providing there are data to show that the products are safe and to support any claims with reasonable substantiation. The chances, however, to market a herbal product as a drug and to give it medicinal claims are low, because at present the FDA does not accept bibliographic evidence of effectiveness, but prefers randomized controlled trials as evidence of efficacy [27].

Eastern Mediterranean

Oman

In the Sultanate of Oman, the following groups of traditional medicines are in the market:

- Chinese herbal medicines available through Chinese clinics;
- Indian herbal medicines available through Ayurvedic clinics;
- traditional homoeopathic medicines available through homoeopathic clinics; and
- traditional treatments of illnesses in villages or rural areas.

Until a new framework for regulatory control becomes available, which is expected in the near future, the few controls which exist are regulated by guidelines issued for import and traditional drugs in 1995. These guidelines state which documents have to be submitted to the Directorate General of Pharmaceutical Affairs and Drug Control to receive permission for marketing these products:

- free sale certificate issued by the country of origin together with a GMP certificate;
- labelling including active ingredients, quantitative composition, route of administration, date of manufacture and expiry, badge number, and storage conditions;
- a scientific report from the manufacturer indicating the origin of each ingredient, its pharmacological effect and therapeutic uses, side effects, adverse reactions, precautions, overdose effects and antidotes, and a list of countries where the product is marketed;
- a guarantee that the product does not contain other drugs such as corticosteroids, sex hormones, or impurities such as insect parts or other products [28].

Saudi Arabia

In accordance with articles 44 and 50 of the Act for the Practice of the Pharmacy Profession and Trade in Pharmaceuticals and Medical Products, issued by the Royal Decree No. M/18 of 18/03/1398, registration of medicinal products by the Ministry of Health is obligatory. Paragraph 13A of the special provision of regulation for registration which was amended through the Ministerial Resolution No. 1214/20 dated 17/06/1409 subjects to registration, in addition to drugs, products with medicinal claims or containing active ingredients with medicinal effects such as herbal preparations, health and supplementary food, medicated cosmetics, antiseptics or medical devices. A herbal preparation is defined as a product prepared for therapeutic and/or prophylactic use, the active ingredients of which are of plant origin. The definition is limited to preparations to be administered locally, orally, rectally, or by inhalation [29].

In accordance with the "Regulations for Registration of Herbal Preparations, Health and Supplementary Food, Cosmetics and Antiseptics that have Medicinal Claims" issued by the Ministry of Health of the Kingdom of Saudi Arabia, the formal application for registration which is submitted to the General Directorate of Medicinal and Pharmaceutical Licences at the Ministry of Health is based on the registration of the product in the country of origin. For this reason, documents such as manufacturing licences, free sales certificates, and GMP certificates have to be submitted with information on composition, therapeutic category, certificate of analysis, percentage of alcohol and, in the case of ingredients of animal origin, the kind of animal. Furthermore, full specifications and methods of analysis of the finished product, data on stability studies and storage conditions, six samples of the product and of the outer package and label, together with abstracts of scientific references testifying to the efficacy and safety of the product have to be submitted [47]. Handling of locally produced or imported products is prohibited before registration by the Ministry of Health. After registration it is not allowed to make any change in the composition, specification, method of manufacturing, indications, container or package unless it has been approved by the authority. A registration may be cancelled by the authorities under certain pre-conditions. The registration committee reviews registered products after three years from the date of registration, or as deemed necessary, to consider the need for re-registration [29].

Europe

General aspects

The European Community has developed a comprehensive legislative network to facilitate the free movement of goods, capital, services and persons in the Community. According to Directives 65/65/EEC [30] and 75/318/EEC [31], pharmaceutical products require pre-marketing approval before gaining access to the market. Requirements for the documentation of quality, safety, and efficacy, the dossier and expert reports are laid down in Directive 91/507/EEC [32]. Article 39 para 2 of Directive 75/319/EEC [33] obliged Member States to check all products on the market at that time, with a deadline of 12 years, to determine whether they met the requirements of these directives. Countries have taken different approaches in reviewing phytomedicines.

Attempts to Meet the Need for Harmonization

To achieve free movement of medicines within the common market of the European Union, and a centralized system of marketing authorization (e.g., for new chemical entities) with the possibility of application at national level only, a system of mutual recognition of marketing authorization decisions has been installed [34]. This "decentralized procedure" provides, as a general rule, that an assessment by one national authority should be sufficient for subsequent registration in other Member States. Under this procedure, the so-called "Summary of product characteristics (SPC)" approved by the first authority must be taken into account. If differences in evaluation occur between national authorities, a decision will be reached by an EC procedure. In accordance with the new EC Directive, this decision is binding from the beginning of 1995, and may - in case of a negative result - have a negative rebound effect on the first registration in an EC Member State, this registration being annulled if the applicant does not withdraw the application for recognition of the dossier. As uniform criteria at a European level regarding the assessment of safety and efficacy do not exist, there is only a guideline for quality of herbal remedies [35]. The harmonization of scientific assessment is considered a precondition for adjustment of different marketing authorization decisions, particularly in the field of phytomedicines in which there are different national viewpoints and traditions.

The European Scientific Cooperative on Phytotherapy (ESCOP) was founded in 1989, the main objectives being to establish harmonized criteria for the assessment of phytomedicines, to support scientific research and to contribute to the acceptance of phytotherapy at a European level [36]. In October 1990, the first five monographs were presented at a symposium in Brussels and were officially handed over to representatives of the European Community. After a thorough assessment, the Committee on Proprietary Medicinal Products (CPMP) published four monographs on anthraquinone laxatives in May 1994 [37], but no decision was made in case of *Matricariae flos* and *Valerianae radix*. Although this was disappointing for ESCOP, it was decided to continue preparing harmonized SPC proposals so as to fulfil an obligation to the European Union for 50 monographs by end of December 1996. Criteria for the selection of medicinal plants and the preparation of draft SPCs by the Scientific Committee are mainly their importance in European countries and their inclusion in the European Pharmacopoeia or a national pharmacopoeia. The draft is then discussed thoroughly by the Scientific Committee, sometimes with external experts from universities or companies. When a harmonized draft is regarded as finalized by the Scientific Committee, it is circulated to an independent Board of Supervising Editors. Members of this Board are scientists and teachers from European universities, mainly active in the field of pharmacognosy and pharmacology [38].

To be in line with the CPMP requirements laid down in European guidelines, the drafts which are planned to be submitted to the CPMP have the format of a Summary of Product Characteristics (SPC). An SPC describing a medicinal plant and its preparations refers to a Pharmacopoeia monograph with respect to quality, and lists the main constituents that may possibly contribute to the effect claimed. The most important parts of an SPC are the therapeutic indications, the dosage and the pharmacological properties. The latter paragraph gives as many details as possible on pharmacodynamic properties, pharmacokinetic properties and preclinical safety data, each statement supported by references. The SPC text is followed by a list of references, sometimes more than 80, describing in detail all the papers that have been used for the evaluation of safety and efficacy of the respective medicinal plant and its preparations [38].

ESCOMP hopes that the CPMP will perform an assessment of further drafts in the near future, but the members are not too optimistic because at a European level different priorities in the evaluation of medicines have to be set. Nevertheless, ESCOMP is of the opinion that all the drafts that have been prepared in the past years might be of great interest as scientific papers, and for this reason 20 monographs were published in March 1996, and further publications are planned [39].

Austria

The Austrian drug law does not distinguish between medicinal products made from chemical substances and those made from plants or natural substances. An abridged registration is possible for certain non-prescription medicines. This is laid down in section 17a of the Austrian Drug Law [40]. This means that with respect to quality and safety a detailed assessment is not performed. A list of active substances and excipients qualifying for the abridged procedure was published in 1989 [41] and was last modified in 1992 [42]. It lists some 500 substances and medicinal plants/ parts of plants/ essential oils etc., for which the simplified procedure according to section 17a can be used. The requirements for the documents that have to be submitted are listed in sections 15 and 17a of the Austrian Drug Law.

In principle, medicinal products can only be sold in pharmacies. An exemption is laid down in section 59, para 3 of the Austrian Drug Law stating that certain products which do not have any risk are allowed to be sold outside pharmacies, e.g., in drug stores. A list of these products of which many are medicinal plants has been published officially, and contains a description of the medicinal plant/ part of plant, the wording for the indication and the dosage recommendation [43].

Belgium

On 10 February 1995, a regulation of the Health Ministry was published describing the requirements for the registration dossier for herbal medicines [44]. This new regulation replaced the previous one published in 1989 [45]. According to this regulation, a simplified registration procedure for herbal medicines may be used if reference is made to the plants listed in Lists I - XIX. A list of indications for which the different groups of plants are traditionally used is also available. However, since the new regulation became effective, the indications are no longer introduced by the term "traditionally used in...." as was done previously. Combination products are not accepted if they contain more than three plants of one list or if the plants belong to different lists [44].

Bulgaria

In April 1995, a new Drug Act became effective, which closely resembles the EU regulations for the pharmaceutical sector. The law does not distinguish between medicinal products made from chemical substances and those made from plants or natural substances. Under the law, proof of quality, safety and efficacy became an essential pre-condition for the registration of drugs. Registration of borderline products was expected to be published in 1996. Some plant-based products are included under a simplified procedure. These consist only of non-prescription products with restricted claims, which are suitable for self-medication [46].

Denmark

Under the Danish Ministry of Health Order No. 790 of 21 September 1992 [47], natural remedies covered by the authorization system are defined as follows:

- Natural remedies shall be understood to mean medicinal products in which the active substance (content) exclusively comprises naturally occurring substances in concentrations that are not substantially greater than those in which they are found in nature.
- The order applies to natural remedies intended for oral use or application on skin or mucous membranes. It does not apply to remedies containing prescription-only drugs, nor to homoeopathic medicines.

Combinations of natural remedies with added vitamins and/or minerals cannot be marketed as natural remedies. Proof of quality, safety and efficacy must be given; a bibliographic application with respect to therapeutic use is accepted if it contains descriptions in the relevant scientific literature of Europe or North America [47,48].

Estonia

On April 1 1996, the "Medicinal Products Act" became effective, laying down the general requirements of the procedure for registration of medicinal products and approval of variations to the terms of registered medicinal products [49]. For the application, a special form has to be used and additional documents concerning chemical, pharmaceutical, biological, pharmacological-toxicological and clinical information has to be submitted, with a summary of product characteristics and information concerning price and design of the package [49]. Special rules governing application for herbal medicines are in preparation.

Finland

Administrative regulation 9/93 [50] regulates the status of herbal products in Finland. It takes into account the provisions of Directives 65/65/EEC [30] - especially article 4.8 (a) (ii), 75/318/EEC [31], and 75/319/EEC [33] with later amendments. Herbal products contain traditionally used plants or their parts as such or in dried form, extracts or tinctures prepared from them, or traditionally used essential or fatty oils.

In accordance with the European Directive 75/319/EEC [33], an expert report shall be submitted on the pharmaceutical and chemical characteristics. With regard to these, a summary based on the application material shall be submitted which briefly describes the main indications for the products, the usual dose, mechanism of action, side effects, interactions with other medicinal products, and other facts which the manufacturer considers to be of significance in the evaluation of the application [50].

The documentation on pharmaceutical and chemical characteristics shall be presented in accordance with the European Directives 75/318/EEC [31] and 91/507/EEC [32] which are applicable for all kinds of medicinal products. The particulars on the quality and manufacture of herbal remedies shall further take into account the European guideline "Quality of Herbal Remedies". Raw materials have to meet the requirements of the pharmacopoeia or, if there are none, detailed quality requirements shall be drafted in accordance with the model of the monographs of the European Pharmacopoeia. Quality requirements for intermediate and finished products have to be presented, the latter covering, for example, identification and determination of active ingredients with validated methods, and a purity test. If the product contains more than one herbal remedy, these shall all be identified e.g., by the TLC finger print method.

The applicant shall present a proposal for the indications of the product, its dosage and, where necessary, its instructions for use. If the herbal remedy or its active ingredient has been used for a long time in Europe or in countries close to Europe with regard to their health care traditions, the safety and proposed indication of the product can normally be explained by information available in scientific literature, which shall be verified in accordance with the European Directive 91/507/EEC [32]. If this cannot be reliably verified, an application for a marketing authorization with a full dossier shall be made. Where a bibliographic application is made, copies of the references in the scientific literature verifying the safety and indications of the product shall be submitted. The application shall also include a bibliography of the material that is appended or otherwise referred to in the application. Proposals for labelling and the package leaflet and the Summary of Product Characteristics shall be submitted to the National Agency for Medicines together with the application. The label of a herbal remedy clearly states that it is a herbal remedy [50].

Herbal products are normally sold in pharmacies with the exception that, if they are not registered as

medicines, they can be sold as health products in pharmacies, department stores and health shops [50].

France

Herbal medicines are defined as medicines the active ingredients of which are exclusively plants or plant extracts. In 1987, the Ministry of Health published the first "Avis aux fabricants" (advice to manufacturers) taking into account the fact that the directives of the EC which define pharmacotoxicological and clinical criteria required for a marketing authorization are not applicable for most herbal remedies, and the fact that frequently their efficacy cannot be demonstrated on the basis of bibliographical data. To give a better defined status to plant-based medicinal products, a list was drawn up of vegetable drugs which could be registered according to an abridged dossier. Their safety, with an optimum benefit-risk ratio, was taken into account as well as historical proof of their widespread traditional use and their well established use in self-medication. These guidelines were completed in 1990, and cover applications for marketing authorizations for new products and the validation of products already on the market [51].

This guideline includes a list of 174 plants and parts of plants with approved therapeutic indications, a list of 35 accepted therapeutic indications for minor ailments (17 for oral use, 9 for external use and 9 for both uses) with a low indication level which is introduced by "Traditionnellement utilisé dans..." ("Traditionally used in ..."). Furthermore, a list of fixed combinations of plants is available and a special section on laxative herbs. The guideline is completed by a detailed description of the content of the dossier, a list of toxicological recommendations according to the preparations concerned (with special recommendations for laxatives), and rules for labelling and packaging of herbal medicines [51].

Germany

Market Importance of Herbal Medicines

Herbal remedies represent an important share of the German pharmaceutical market. According to an Institut für Medizinische Statistik (IMS) report [52], presented during an ESCOP Symposium in Brussels in October 1990, the German herbal medicines market was worth US\$ 1.7 billion (incl. VAT) in 1989, which was equal to 10% of the total pharmaceutical market in Germany. A representative study carried out by the Allensbach Institute [53] among the German population in June 1989 confirmed that a large number of people use natural medicines. The study showed that 58% of the population had taken such remedies, 44% of them within the previous year. It could also be shown that over the years the number of younger people using natural medicines had increased significantly. According to the study report, natural medicines were generally considered to be more harmless than chemical drugs. A majority among the German population (85%) believed that the experience of physicians, practitioners, and patients should be accepted as a proof for the efficacy of natural medicines [53].

Herbal medicines are distributed through over-the-counter sales in pharmacies and other distribution channels and on medical prescription through pharmacies. They are, in principle, reimbursable by the health insurance system unless special criteria for their exclusion apply, for example, specified indications such as common cold or laxatives, or substances, with a negative assessment by Commission E. Except for a few preparations, herbal medicines are not prescription-bound but can be prescribed by physicians or practitioners for reimbursement.

The total turnover of non-prescription-bound herbal medicines in pharmacies was DM 4.5 billion in 1995 (public price level), which is equal to almost 30% of the total turnover of non-prescription-bound medicines (DM 15.2 billion). Preparations sold on prescription amounted to DM 2.4 billion and those purchased through self-medication to DM 2.1 billion of the total turnover of non-prescription-bound phytomedicines [54]. Herbal medicines can be found among the 2 000 most important drugs prescribed by medical doctors and reimbursed by health insurances [55].

Legal status

In terms of legal status, herbal medicines are fully considered as medicines. This legal position was confirmed by the European Court of Justice in 1992. On 1 January 1978, the Second Medicines Act came into force which set new standards for the granting of marketing authorization in accordance with the European framework for the handling of medicines [56]. Under this new regulation, proof of quality, safety, and efficacy became an essential pre-condition for the registration of medicines. Article 39 para 2 of Council Directive 75/319/EEC [33] directed Member States to check all products on the market at that time, within a deadline of 12 years, to determine whether they were in accordance with the European Directive. These products were

allowed to continue being marketed with a so-called "fiction marketing authorization" for this 12-year transitional period, that is until 31 December 1989 (later extended to 30 April 1990) [56]. To meet the requirements of the new Medicines Act, the authorities were obliged to carry out a review process [57]. The review of existing products was a two step procedure. It began in 1978 and was partly stopped by the fifth amendment to the Medicines Act in 1994. The two steps of the procedure were first a review of active principles, which resulted in monographs, and, second a product-specific verification of pharmaceutical quality and conformity with the published monographs [58-65]. Due to the large number of products on the market, the review was focused on active ingredients and not on individual products. The concept underlying the procedure was to establish clear, *a priori* criteria for active ingredients and to make it transparent to industry which products would have a chance to be authorized. The review of herbal remedies was done by a pluridisciplinary commission of experts, the so-called Commission E, with pharmacists, pharmacologists, toxicologists, clinical pharmacologists, biostatisticians, medical doctors from hospitals, and general medical practitioners [62,66]. This commission was responsible for the evaluation of more than 300 medicinal plants, and the results - the monographs - have been published in the Bundesanzeiger (Federal Gazette) [67] since 1984 [58-65,68]. These monographs cover most of the ingredients of industrially prepared herbal medicines on the market.

All data available to the health authority (data from pharmaceutical companies interested in a particular drug, new data from pharmacological and clinical research, data from the international side-effect monitoring system, publications, etc.) were collected and forwarded to Commission E. Their work was also supported by the "Kooperation Phytopharmaka", which collected scientific information on a large number of important medicinal plants, which was presented in the form of expert reports to Commission E for evaluation. On the basis of this large documentation, the material was screened, discussed in the Commission's meetings, and then pre-published as a draft monograph. Within a certain deadline, companies and other interested parties were allowed to make statements or remarks, often in co-ordination with the pharmaceutical associations. At a later stage, the monograph text was published officially in the Bundesanzeiger, and this scientific evaluation formed the basis for the marketing authorization and review decisions of the Federal Institute for Drugs and Medical Devices (BfArM). An ideal situation is reflected in the so-called "positive monograph" covering all relevant indications for the package leaflet or consumer information such as composition of the drug, form of application, indications, contra-indications, warnings, dosage [57,62,66,68]. Because there was a growing interest to use monographs for applications for new marketing authorization and because the fourth amendment to the Medicines Act in 1990 allowed manufacturers to change completely the composition of herbal medicines on the basis of published monographs, the texts published in 1991-1994 had to be much more detailed than the earlier texts, sometimes focusing only on specific preparations the efficacy of which had been established in clinical studies.

There are also a substantial number of "negative monographs" where there were risks from active ingredients or absence of reasonable proof of efficacy [60]. Marketing authorizations of a number of herbal remedies had to be withdrawn or to be modified because of serious risks to public health. The work of all review commissions, including Commission E, regarding the evaluation of bibliographic data and the preparation of monographs was finalized with the fifth amendment of the Medicines Act [69]. The main reason was that the most relevant active principles were covered by monographs and the remaining products could be assessed more economically on a case by case basis. The commissions will now be advisory boards to the health authority in making decisions on the registration of new drugs, and in the individual assessment of old medicinal products already on the market, as the second step of review process [69]. By 1996, this second step had not been completed, due to an overload of work for the authority to check all the dossiers that had been submitted during the past years by manufacturers [68].

Requirements for Marketing Authorizations for Herbal Remedies

The Federal Institute for Drugs and Medical Devices, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), since 1994 one of the successor institutes of the former Bundesgesundheitsamt (BGA), is responsible for the assessment of medicines and the verification of submitted dossiers with respect to quality, safety and efficacy. Criteria for registration are set out by European directives and guidelines, such as the Note for Guidance on Quality of Herbal Remedies, the European Pharmacopoeia, and national guidelines and directives such as the guidelines for testing of drugs following section 26 of the Medicines Act (Arzneimittel Prüfrichtlinien) [70]. Bibliographic data on the well established use of herbal medicines are accepted. Criteria developed by Commission E and positive monographs are widely used to document safety and efficacy of herbal remedies [58-65]. Monographs can to a large extent replace pharmacological, toxicological and clinical documentation,

as can bibliographic data. Earlier monographs often require an update of literature. The quality dossier is checked in each case individually.

Medicines or groups of medicines which do not pose a direct or indirect risk to the health of man or animal can be exempted from the requirement for an individual marketing authorization according to section 36 of the Medicines Act. To ensure their quality, safety and efficacy, each such medicinal product referring to this procedure must comply exactly with a monograph of a standardized marketing authorization published by the Ministry of Health. The monographs include analytical test requirements and also the texts for labels and package leaflets (279 monographs of standardized marketing authorizations have been published, mainly for herbal teas). An applicant referring to such a monograph does not need to present any documentation to the Federal Institute for Drugs and Medical Devices (BfArM) [62].

Fifth Amendment of the German Medicines Act

In August 1994, the fifth amendment of the German Medicines Act became effective. It provides a new procedure with respect to proof of quality, safety and efficacy, widening the scope of existing legislation for products, including herbal medicines, already on the market. Traditional usage instead of reasonable proof of efficacy is accepted for a certain category of products, mostly sold outside pharmacies. This is why many products with a negative assessment by Commission E are included in this regulation. All these products have to be labelled as "traditionally used". In accordance with section 109a of the Medicines Act, the BfArM has compiled lists stating which preparations are allowed to refer to this regulation and which traditional indications can be claimed [71-75]. This new system may offer a legal possibility for a large number of preparations without sufficient scientific documentation as proof of efficacy to be re-registered under such a simplified procedure [76]. On a "higher" level, "non-traditional" indications will be admissible as before, provided that these are based on monographs or on individual clinical studies with defined preparations.

In contrast to herbal medicines, the quality dossiers of "traditional" products are not checked by the health authority. The regulation contrasts with EU requirements for the marketing of medicinal products. This is why the new regulation may offer a legal possibility for herbal and non-herbal preparations to stay on a strictly national market without sufficient documentation as proof of efficacy and safety and without thorough control of pharmaceutical quality.

Greece

A new regulation for herbal medicines was published 1 April 1994 by the Ministry of Health [77], according to which, herbal medicines are medicines which contain as active ingredients only plants or preparations of plants. The regulation does not apply to plant products used in food or beverages and which are regulated as such, unless indication claims are made or they are advertised as medicines, in which case they are regarded as medicines and have to fulfil the requirements of the regulation.

The regulation contains a detailed description of the requirements of the dossier which comply with the European legislation. The dossier has to be submitted to the National Pharmaceutical Office (EOF) which will grant or reject the registration. Furthermore, there are detailed instructions for the content of the package leaflet and labelling [77].

Hungary

Pharmaceutical legislation in Hungary already takes into account several of the EU directives. The Medicines Law is in a developmental stage, and the classification of medicines will change in accordance with these directives. For the moment, medicines are classified into four groups: non-prescription medicines, prescription medicines, medicines prescribed by specialists only, medicines used in hospitals only. A fifth group includes herbal and other plant-based preparations which, due to insufficient clinical data, cannot be classified as medicines in Hungary. This group is called "Preparations having therapeutic effect but not considered to be medicines", and is designated by the term "parapharmaceuticals" [78].

Iceland

An Executive Order on natural remedies in Iceland was expected to be implemented in 1996 [48].

Ireland

The Medical Preparations (Licensing, Advertisement and Sale) Regulations 1984 provide a common statutory licensing system for all medicines, both proprietary and non-proprietary, taking into account the respective European directives. In general, a product authorization is required for a medical preparation to be imported or placed on the Irish market [79].

In August 1985, "Guidelines for Application for Product Authorization of Herbal Products" were issued by the National Drugs Advisory Board (replaced by the Irish Medicines Board in 1996) giving information on the requirements for their assessment [80]. These guidelines contain detailed requirements for the plant raw material and also for finished products, but have been largely superseded by the European note for guidance, particularly in relation to the quality of herbal remedies. Safety and efficacy requirements are consistent with those required for conventional pharmaceutical products. Experimental animal studies have to be undertaken to delineate the effects of the contained substances and of the medicinal product. Where possible, comparative studies should be made with a pure drug substance having a similar effect. The tests should generally include examinations in rodents as well as in humans. In the case of a drug substance which is likely to be used in association with other drugs, account should be taken of the potential for interaction in terms of the therapeutic effects, side effects and toxicity of each drug substance concerned. Each active ingredient should make a relevant and reasonable contribution to the overall therapy, and the quantity of each active ingredient must be effective, safe and appropriate to the recommended use and range of dosage. Detailed requirements for tests of acute and chronic toxicity have to be fulfilled, e.g., a test for acute toxicity in at least three mammalian species, and a detailed list of requirements for the tests of chronic toxicity [80].

Until the end of 1995, it had not been possible to identify a simplified procedure for dealing with assessment of such products based upon the waiving of any requirement for efficacy and/or safety. It was hoped to address this as part of the remit of the Irish Medicines Board in 1996 [81].

An information sheet on Borderline Products was issued by the Department of Health in 1988 [79] attempting to explain the position of these products under the regulations. Products containing herbal ingredients are considered to be medical preparations under the regulations when the labelling or accompanying or associated literature makes any preventive, curative or remedial claim, or any of the herbal ingredients present is recognized as having medicinal properties. An illustrative list of such herbs is included as an annex listing about 100 herbs with these properties. Preparations consisting of dried, crushed or comminuted herbs labelled in a manner which specifies the herb and the process of production are excluded from the scope of the regulations provided no other name is given to the preparation and no recommendation as to use as a medicinal preparation is made. Examples of such exempted products would include Senna leaves, Senna pods and Carrageen moss [79]. The information memorandum on borderline products issued by the Department of Health in 1988 was updated in 1990. However, principles alluded to in the 1988 document remain valid [81].

In December 1993, the Food Safety Advisory Committee prepared a Report on Food Supplements and Health Foods to the Minister for Health and the Minister for Agriculture, Food and Forestry [82]. The report addresses the question of an appropriate policy for the control of products which are on the borderline between foods and medicines, including natural materials the composition and status of which may have not been established, such as herbal extracts, herbal teas, essential oils. These products should be subject to authorization by the regulatory authority prior to marketing. Reference is made to the memorandum of the Department of Health on Borderline Products [79]. With respect to herbal teas, a regulatory framework is recommended to ensure that no potentially toxic plants are marketed as herbal teas, that all the plant materials comply with stringent quality standards, and that problems of environmental contamination of herbal materials (e.g., the need for statutory controls on levels of pesticides, heavy metals and radionuclides in teas) are taken into account. Where medicinal benefits are claimed or imaginative labelling suggests such benefit for herbal teas, they should be regarded as medicines and therefore regulated by the National Drugs Advisory Board (replaced by the Irish Medicines Board in 1996). Materials for use as herbal teas should not be permitted by the appropriate regulatory authority unless they have GRAS (generally recognized as safe) status, or are recommended as acceptable for inclusion in food by the Council of Europe, or have been approved for food use by another authoritative body. Quality control should be guaranteed in accordance with the European Pharmacopoeia. With respect to essential oils, it is recommended that they should not be permitted unless they have been approved for use as flavouring substances and natural sources of flavourings by the Council of Europe, have been granted GRAS status, or have been accepted for food use by other authorities. Furthermore, it is recommended that the regulatory authority draw up a list of herbal substances which are toxic under normal conditions of use. All products included in this category of natural materials, the composition and status of which may not have been established and which are marketed for their health giving properties such as herbal

extracts, herbal teas, essential oils etc., should be subject to prior authorization to establish their quality and safety before gaining access to the market [82].

The Food Safety Advisory Committee report on food supplements and health foods has not yet been formally implemented in terms of national legislation. The NDAB, up to the end of 1995, was still applying the recommended dietary allowance cut-off point for vitamins and mineral substances, above which these products were classified as medicinal products requiring authorization before marketing. This is another area being addressed by the Irish Medicines Board in the context of more recent European legislation [81].

Italy

On 8 January 1981, a guideline was issued by the Italian Health Authority classifying herbal products as medicines or health food products respectively [83].

The first type of herbal product covers plants traditionally used as food or flavour. They serve for nutritional purposes and are not allowed to claim therapeutic indications. They are classified as dietetic products and do not need an approval, but the authority has to be notified of the label. These products are allowed to be sold outside pharmacies, in so-called "erboristerias" which are also regulated in this guideline. The responsible person for the "erboristeria", the "erborista", is not allowed to give recommendations on the use of herbal products. The "erborista" can sell herbal products which are not pharmacy-bound, but is not allowed to prepare mixtures of these products.

Herbal products that make therapeutic claims, that have a particular pharmacological activity or that might be toxic, are considered as medicines and are only allowed to be sold through pharmacies. Mixtures of herbs, such as herbal teas or similar preparations, with a brand name and/or therapeutic indications have to be registered as medicinal products. They are only allowed to be sold by a pharmacist in a pharmacy. The "erborista" is not allowed to sell medicinal plants for therapeutic purposes, whereas the pharmacist is allowed to prepare and to sell mixtures of medicinal plants to the public.

The guideline contains two annex lists, one for medicinal plants which may only be sold in pharmacies, and a second list of plants that may be sold outside pharmacies.

When registered as a medicine, a herbal product needs a leaflet which gives information on indication claims, risk, dosage, etc. According to this guideline, the application dossier must contain a technical-analytical documentation. With respect to the pharmacological, toxicological, and clinical documentation, a bibliographic application in accordance with the Directive 65/65/EEC is possible [83].

Netherlands

Herbal products (products containing only plants and/or plant extracts) consist of two categories: officially registered pharmaceuticals; and non-registered products which are classified as foodstuffs and for which medicinal claims are not allowed. Herbal products classified as medicinal products have to follow the normal registration procedure [84].

Norway

Herbal products are not classified as medicines unless they have been registered through the marketing authorization process with the Norwegian Medicines Control Authority. A separate guideline, including documentation requirements, has been developed for herbal remedies for which applications are made for marketing authorization as medicines. If these products are not granted a marketing authorization, they can be sold as herbal remedies but no medicinal claims may be made for them [85].

In January 1994, a guideline for the registration of natural remedies was published, based on the European directives and particularly on article 4.8 (a) (ii) of Directive 65/65/EEC [30]. Reference is made to the Notice to Applicants. These guidelines for a simplified registration procedure describe medicinal products containing substances which are not prescription-only, which are suitable for self-medication, and for which there is documentation on their traditional use in Europe or North America. Eardrops, eyedrops and eye-ointments are excluded, together with injections, prescription-only or toxic substances, and isolated chemically defined

substances from medicinal plants. There are detailed provisions laid down in these guidelines which require expert reports and documentation on quality, safety and efficacy [85].

According to "The Guidelines on Marketing Authorizations for Natural Remedies", a natural remedy is defined as a medicine for self-treatment, in its original package, intended for an individual consumer, and in which the active ingredient or ingredients derive from natural sources such as the vegetable or animal kingdom, or in certain cases micro-organisms, salts and minerals. Plant material may include juices, gums, fatty oils, essential oils, extracts or tinctures. Combinations of herbs with vitamins and/or minerals are not regarded as natural medicines, but these constituents are allowed. With respect to quality requirements, reference is made to the European guideline "Quality of Herbal Remedies" as well as to the Notice to Applicants. Tinctures and extracts shall be as described in an official monograph of the European Pharmacopoeia or another pharmacopoeia. Tinctures and extracts which are not described in a pharmacopoeia should be specified according to the medicinal plant and solvent, including the alcohol concentration. In the case of a combination of extracts, each solvent and drug should be specified. The medicinal plants should be described with their Latin name together with the Norwegian name and the part of the plant used. For the manufacture and control of these products, the rules of Good Manufacturing Practice (GMP) are applicable. Quality control consists of e.g., identification check for impurities, and quantitative assay [48,85].

With respect to safety, the requirements are based on the WHO "Guidelines for the Assessment of Herbal Medicines" of 1991, as are the requirements for efficacy. Several examples are given for the wording of indications relating to minor ailments, e.g., improvement of appetite. The documentation on efficacy may consist of a compilation of the relevant literature. This means a summary of all the bibliographic references to the respective ingredients, their medicinal background and traditional use or, if not available, clinical documentation, for example on randomised controlled clinical studies. There are four categories for the documentation of efficacy:

1. Traditional use that is documented in one of the references of an enclosed list.
2. Natural remedies containing additional vitamins and/or minerals for which maximum doses must be taken into consideration.
3. Natural remedies which are not within the scope of categories 1 or 2 and for which a full toxicological and clinical dossier must be submitted.
4. Combination products which must have a justification and documentation such as laid down for category 1.

In the case of herbal teas, active ingredients should not exceed a maximum of 70% by weight, and other ingredients (e.g., aromatics) should not exceed a maximum of 30% by weight. For dosage forms such as tablets, capsules or tinctures, up to five active ingredients are normally accepted.

The Norwegian guidelines also contain requirements for the content of the label and the package leaflet. Registered natural remedies receive a registration number which will appear on the label. The annex to the guidelines consists of a list of 32 references [85].

Portugal

Herbal products were included in specific Portuguese legislation in 1993 on health products which comprise e.g., cosmetics, medicinal plants, dietetic products with therapeutic use, and homoeopathic preparations. They are controlled by the Instituto Nacional da Farmácia e do Medicamento (INFARMED), an authority responsible to the Ministry of Health. A special division of this Institute is entitled to draw up rules for marketing, quality and safety of this group of products [86].

According to the drug law, phytomedicines are subject to the same registration requirements as chemically based medicines [87]. Specific rules on herbal medicines, however, are not part of the Portuguese drug law. The implementation of legislation concerning classification and sale of herbal medicines is urgently required [88].

Spain

The Ministerial Order of 3 October 1973 [89] established a special registration for medicinal plants. Products (1) consisting exclusively of whole, comminuted or powdered medicinal plants or parts thereof have to be registered. Preparations (2) containing a single species or parts thereof which are included in a special list as annex to this order, are exempted and do not need registration.

Medicinal plants with or without obligation for registration (1 and 2) can be controlled by the health authority. For registration of medicinal plants (1), pharmacological and analytical documentation has to be presented including indications, dosage, and the analytical methods. For plants which are not yet included in the list, it is possible to apply for their inclusion [89].

Preparations containing extracts, tinctures, distillates etc., and other galenical preparations, are regarded as medicines which have to fulfil all the requirements of the Spanish Drug Law [90].

Sweden

The Medicinal Products Act [91] also applies to natural remedies. In November 1994, the Medicinal Products Agency issued a guideline "Information on application for authorization to market natural remedies" [92]. This guideline contains detailed requirements and regulations for obtaining a marketing authorization for natural remedies.

According to the Medical Products Agency's Order and guidelines on marketing authorizations for medicinal products, a natural remedy is defined as follows:

- A finished product intended for administration to human beings or animals for the prevention, diagnosis, relief or cure of diseases or symptoms of diseases.
- A natural remedy denotes a medicine in which the active ingredient or ingredients derive from natural sources such as plants or animals, or consist of a bacterial culture, mineral, salt or salt solution. The active ingredients however must not be processed too highly, e.g., constituents may not be chemically modified, produced by biotechnological methods or in a chemically defined isolated form.

A natural remedy must be suitable and intended for self-medication in accordance with tested national traditions or traditions of countries close to Sweden with respect to the drug use. Products for injection and homeopathic preparations are not covered by the definition [48,92].

A marketing authorization is granted for five years by the Medical Products Agency and may be renewed. The general requirements for medicines of the Medicines Act of 1992 are also applicable to natural remedies. They must have a complete declaration of the contents, an acceptable name, and a clear label. Their manufacture has to follow Good Manufacturing Practice (GMP).

A simplified application procedure, according to Directive 65/65/EEC [30] which describes a bibliographic application, can usually be used. If the use of a preparation has become well established, full documentation of the results of pharmacological and toxicological investigations or clinical trials may be replaced by data from published scientific literature.

The guideline contains detailed requirements for the application dossier and the fees. The documentation should be in accordance with the European Notice to Applicants. The requirements for the documentation on quality take into consideration that natural remedies have special characteristics. For this reason, guidelines for the documentation on quality have been compiled as an annex to the main guideline.

With respect to safety, consideration should be given primarily to the experience of corresponding earlier use of the product or constituents, in which no harmful effects have arisen or been suspected. If satisfactory proof of safety is not provided, then it should be established by means of clinical trials and/or pharmacological and toxicological studies.

As natural remedies are normally intended to treat diseases or conditions suitable for self-medication, the indications depend on the documentation which supports the application. For well documented ingredients for which there is adequate experience, reliable bibliographical data may be sufficient for the efficacy assessment. If the product has not been used traditionally, the application has to be supplemented with a specific product-related documentation, and results of clinical trials and pharmacological studies presented.

Combination products containing several active ingredients need a special explanatory statement in the application. A fundamental precondition for the approval of combination products is that each active ingredient contributes to the overall effect. No restriction has been placed on the number of herbal drugs included in a remedy provided that the documentation is satisfactory with respect to quality, safety and efficacy.

The guideline also contains information on the processing of applications, possibilities of modifications and notifications thereof, and detailed requirements for product information such as labelling and the package

leaflet [92].

Switzerland

In Switzerland medicinal products are classified as follows, depending on toxicity, indications and active ingredient:

- List A - restricted prescription
- List B - prescription-only
- List C - sale limited to pharmacies, without prescription
- List D - sale limited to pharmacies and drugstores, without prescription
- List E - no restriction as to sales outlet.

The active substances are classified by the IKS (Interkantonale Kontrollstelle für Heilmittel) and published in a positive list (Lists AE) [93,94]. Products containing these substances are classified by the IKS in the corresponding sales categories (A - E). Products in categories A, B, and C may be sold in pharmacies only, category D in pharmacies and drugstores, and category E in all shops.

For non-prescription medicines, the composition, mode of action, duration of treatment and method of application must be suitable for self-medication, with the possibility of obtaining specialist advice from the pharmacist or pharmacy staff. For these products, medical diagnosis is not required and their use does not need supervision.

Herbal products are considered as medicines and need a product licence. The national marketing authorization procedure for medicines is based on the Intercantonal Convention on the Control of Medicines of 3 June 1971 [95] and regulations implementing this convention and their amendments. According to the Regulations for the Implementation of the Intercantonal Convention on the Control of Medicines of 25 May 1972 (updated 23 November 1995), article 10, applications can only be submitted by a person or company with Swiss residence and with a cantonal licence for the trade of medicines [96].

Abridged applications for herbal medicines are in principle possible. For medicinal products with active substances which are not new chemical entities or which are already contained in registered products, it is not necessary to submit the complete documentation (no toxicological and only reduced clinical data required). Abridged registration for combination products is also possible if the products are comparable with an already registered combination product. Herbal remedies are defined as drugs that contain as declared components only plants, parts of plants or preparations of plants. Homoeopathic medicines or medicines containing isolated or synthetic active ingredients (even if prepared from raw material of plant origin) are not considered to be herbal remedies [97].

In 1992, the IKS published requirements for leaflets on phytomedicines in Lists C and D [98]. A specially adapted leaflet is required instead of the usual patient information. Product information for health care professionals is required only for herbal medicines in List B and for those containing anthraquinone laxatives. The leaflet is intended to guarantee the correct and safe use of the medicine and to give the relevant information to the consumer in an understandable manner. The leaflet should be in the three official languages (French, German, Italian) and must be approved by the IKS. Its language should be patient-friendly, avoid scientific and foreign words and be printed in minimum 8-point characters. Chapters should not be introduced by titles but by interrogative sentences such as "When should ... not be used or be used with caution?".

With respect to the therapeutic indications, the following standard sentences should be included in the leaflet if no clinical data on therapeutic efficacy are available:

- pharmacological properties: "(the following properties...) have traditionally been attributed to (the constituent plant(s))"
- instruction for use: "... is used in case of..."

If, on the other hand, efficacy has been clinically proven, the properties and use are described as follows: "The constituent plant(s) are effective in ..." and "the product is effective in ..." [98].

Regarding combination products, the Swiss regulations are rather restrictive. In 1990, the IKS issued recommendations for combination products which also partly apply to herbal medicines:

- Combination products should contain only few active ingredients in a suitable dose.
- Each ingredient must have a justification, i.e., it is only accepted if it contributes to the efficacy or improves the formula.
- After major modifications (deletion, reduction, exchange of active substances), a combination product should reapply for marketing authorization. Minor modifications (e.g., elimination of one active ingredient or reduction of its quantity, exchange of excipients) may be treated as a "reformulation" (not requiring a new marketing authorization) [99].

Turkey

Herbal medicines have been used in Turkey traditionally although today modern medical science is utilized all over the country whereas traditional methods have only a limited use. On the other hand, there is a rich flora of medicinal plants in the country, and experienced academic people in this field [100].

Prior to 1984, there were no regulations for herbal products. Crude drugs were sold in "Akthar" shops, where no special training was required for the persons responsible. In 1984, the Fifth Symposium on Crude Drugs, held in Ankara, was the first step for regulatory action on herbal products. A resolution of the symposium described the situation of herbal products, presented ideas for the solution of problems, and recommended a specific regulation for herbal products [100,101], which was followed by appropriate action.

A regulation was published by the Ministry of Health on 1 October 1985 and included a list of plants allowed to be sold in the Akthar shops, mainly crude herbs and their parts. The sale of poisonous plants such as Belladonna or Bulbus Scillae was not permitted. Since 11 March 1986, special permission by the Ministry of Health is required to open an Akthar shop [100,101].

On 17 January 1986, requirements for the establishment of herbal drug manufacturing premises (the GMP rules for herbal products) were published by the Ministry of Health, giving detailed instructions on personnel, equipment, starting materials, manufacturing operations, packaging and labelling, quality control, etc. [102]. Furthermore, a regulation concerning the recall of pharmaceutical and medical preparations, substances, materials, compounds and herbal preparations was published on 15 August 1986 [103]. A regulation on licensing herbal products which have any medicinal indication claim on the label was published 2 March 1995 [100].

The basic principles of these regulations are the following:

1. Each Akthar shop must be registered by the local branch of the Ministry of Health to be able to sell herbs. Promotion of these products with health claims is strictly forbidden.
2. According to the registration procedure, there are three classes of herbal products:
 - products from plants without a risk potential for human health and without any health claim on the label, which are handled according to the food regulation;
 - herbal products presented in pharmaceutical forms such as tablets or capsules, which must be registered by the Ministry in the same way as medicinal products, and require a complete documentation; and
 - herbal teas with health claims on the label, for which registration by the Ministry is needed, but the documentation required is limited to quantitative formulae, specifications, quality control methods, summarized production method, and a sample of the package insert [100].

With the increasing importance of products of plant origin, the Ministry of Health decided to establish a separate commission for registration of herbal medicines, the Herbal Committee which consists of 3 pharmacognosists, 2 technologists, 1 pharmacologist and 1 toxicologist. With the authorization of the Committee, some 40 products, mostly teas with indications, were registered. These products are only available in pharmacies [101]. The Committee prepared regulations for application dossiers for herbal medicines which were published in 1986. The information requested for a complete dossier includes the methods of analysis and the quality control, the manufacturing process, stability tests, pharmacological and toxicological information, indications, contra-indications, and the package leaflet [104].

United Kingdom

The requirements of the licensing system in the United Kingdom are set out in Part II of the Medicines Act 1968. Without the appropriate licence it is an offence to manufacture, sell, supply, export or import a medicine into the United Kingdom, unless some exemption is provided in the Act or regulations [105].

Exemptions from licensing for certain herbal remedies are contained in Section 12 of the Medicines Act, namely:

- the plant has been subjected only to the processes of drying, crushing or comminuting in producing the remedy;
- it is sold or supplied by its botanical name with reference to the process of manufacture; and
- it is sold or supplied without any written therapeutic recommendation [105].

The review of herbal medicines was completed in 1990. An information sheet on the review for licence holders was published in October 1985 by the Medicines Control Agency [106]. Herbal medicines indicated for conditions capable of self-diagnosis were granted a licence when sufficient evidence of efficacy was established, and the authority required the product label to include the statements "a herbal remedy traditionally used for the symptomatic relief of..." and "if symptoms persist consult your doctor". Combination products containing a large number of herbal ingredients or mixtures of herbal and other ingredients were not accepted, and licence holders were invited to consider to which ingredients the therapeutic claim related and to adjust the formulations [106].

Medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist are listed in the General Sales List. The exemption from licensing for certain herbal remedies described above is modified by the Retail Sale or Supply of Herbal Remedies Order [107], the purpose of which is to control the use of toxic plants by removing them from the general sale list category of medicines and making them "pharmacy only", or by limiting the dose or route of administration for use outside a pharmacy setting. The plants listed in Part I of the schedule may only be sold or supplied in a registered pharmacy; those listed in Part II and Part III may be used by practitioners who sell or supply herbal remedies where they are for administration to a particular person following a personal consultation (after being requested by or on behalf of that person to use his own judgement as to treatment required), but are not for retail in circumstances other than through a pharmacy.

In December 1995, "A guide to what is a medicinal product" was published by the Medicines Control Agency. In accordance with Directive 65/65/EEC it tries to give examples for clarification where the borderline lies between medicinal products and products such as cosmetics and foodstuffs, taking into consideration the claims for the product, the properties of its ingredients, the labelling, promotional literature, product form and whether there are similar licensed products on the market. The new guideline does not intend to affect the status of products legally sold without a licence, nor does it affect the current exemptions for herbal remedies [108].

South East Asia

India

Market Importance and Use of Herbal Medicines

In India, a great deal of folk knowledge exists among ordinary people about the traditional use of herbal medicines. It is difficult to quantify the market size of the traditional Indian systems since most practitioners formulate and dispense their own recipes. The present annual turnover of products manufactured by large companies is estimated at approximately US \$ 300 million, compared to a turnover of approximately US \$ 2.5 billion for modern drugs. According to a study on the attitude of modern medicine practitioners towards Ayurvedic products, general practitioners are relatively unfamiliar with Ayurvedic products even though some are prescribed. They are willing to try an Ayurvedic product if its efficacy is scientifically proven, and would try Ayurvedic products if no modern medicinal remedies were available. People use self-medication for minor ailments such as cough, cold, diarrhoea and stomach problems. Patent and proprietary Ayurvedic medicines are sold over the counter in pharmacies. These products appear to represent a major share of branded traditional products in India. Nevertheless, systems like Ayurveda still need to gain an empirical support of modern medical science to make them credible and acceptable for all. An innovative research effort to define the advantages of traditional systems of medicine with respect to their safety and efficacy could result in a better utilization of these complementary systems of medicine [109].

In India, there are currently about 250 000 registered medical practitioners of the Ayurvedic system (total for all traditional systems: approximately 291 000), as compared to about 700 000 of the modern medical system. In every Indian state, about one-third of the governmental medical posts are occupied by physicians who belong to the traditional systems [109].

Legal Status

In India, traditional medicines are governed by the Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of 1945. They regulate the import, manufacture, distribution and sale of drugs and cosmetics. In 1959, the Government of India recognized the traditional Indian systems of medicine and amended the Drugs and Cosmetics Act to include drugs which are derived from traditional Indian medicine. No products derived from traditional systems may be manufactured without a licence from the State Drug Control Authorities. Patent and proprietary medicines derived from the traditional systems must contain ingredients which are mentioned in the recognized books of the above systems, as specified in the Drugs and Cosmetics Act. The government is advised by a special committee and an advisory board for Ayurvedic, Siddha and Unani drugs. Pharmacopoeia committees have been constituted to prepare pharmacopoeias for all these systems [109].

In 1993, an expert committee appointed by the Indian government developed guidelines for the safety and efficacy of herbal medicines which were intended to be incorporated into the Drugs and Cosmetics Act and rules. It was proposed that no new herbal medicines other than those authorized by the licensing authorities be allowed to be manufactured or marketed, except for those mentioned in and manufactured in compliance with the formulae given in the "authoritative" books for Ayurveda, Siddha and Unani herbal medicines. A manufacturer of a new herbal medicine must include safety data and appropriate efficacy data in the marketing authorization application. Herbal preparations are defined as natural products in which the predominant active constituents are of plant origin. A classification for herbal medicines was proposed depending on their market availability, and the nature of the herbs:

- Category 1: already in use for more than 5 years
- Category 2: in use for less than 5 years
- Category 3: new medicines.

The classification of herbal medicines depends on whether they contain processed or unprocessed parts of plants and whether they contain potentially poisonous plants. Requirements for safety and efficacy vary according to the classification and market availability of the product. Depending on the nature of herbs and market availability, different requirements exist for submission of clinical trial data and toxicity data [110].

Indonesia

The use of traditional drugs in Indonesia can be traced back to the fifteenth century during the era of the Mataram kingdom. The reliefs on some temples such as Borobudur, Prambanan, Penataran show the pictures of many medicinal plants used at that time. Because written documentation was rarely available, knowledge of the use of these plants was not developed properly.

Legal Status

After national independence, much research was undertaken by the Ministry of Health in various institutions. In 1975, the Directorate of Traditional Drug Control was established under the Directorate General of Drugs and Food Control of the Ministry of Health. At that time, the government gave guidance on all aspects of traditional drugs development. Since 1976, the government has set many requirements for traditional drugs and crude drugs:

- production, distribution and labelling of traditional drugs;
- procedure for registration of traditional drugs and imported crude drugs;
- licensing of traditional drugs and imported traditional drugs; and
- control requirements, such as for a production code, labelling and advertisement [111].

In accordance with a Decree of the Minister of Health dated 17 September 1976, imported crude drugs marketed in Indonesia must be registered at the Ministry of Health by the importer [112]. For this registration a number of requirements have to be fulfilled, e.g., the Latin name of the crude drug must be given on the label according to the Indonesian Pharmacopoeia. The foreign name has to be given, the Latin name of the plant, family name, information on efficacy of the crude drug, description, macroscopic and microscopic elucidation,

chemical identification method, check for impurities, assay, region of origin, and information on the label of the crude drug. The delivery, sale, storage, offer for sale or the sale of imported crude drugs that have not been registered and approved by the Minister of Health is prohibited [112].

The import and the distribution of imported crude drugs and licensed traditional drugs have been regulated in specific guidelines of 2 November 1983 [113]. In principle, foreign traditional drugs are not permitted to be imported into Indonesia, except in the case of a licence being granted. After obtaining the approval, it is allowed for one year to import the traditional drug as a finished drug from the country of origin, the packaging being done in Indonesia. During the following one to two years, the holder of the licence must already have produced these "foreign" traditional drugs in Indonesia using the imported crude drug as raw material. The imported crude drug has then to be substituted by an Indonesian crude drug, and the respective plants have to be cultivated in Indonesia. After this, the import of the traditional drug, in the form of the finished product, is not allowed anymore. Finally, a certificate for marketing is granted after a thorough examination by the National Quality Control Laboratory of Drug and Food [113]. A new decision of the Director General of Drugs and Food Control was issued in 1984 describing more detailed provisions for the registration of imported crude drugs [114].

To protect the public, the Ministry of Health published a Decree dated 31 July 1992 to prohibit the production and distribution of traditional drugs used intravaginally as suppositories or as eye drops. Those products were withdrawn from the market within a period of two months [115]. Drugs or traditional drugs containing more than 1% ethanol have to indicate the ethanol content on the label [116]. A special decree regulates traditional drugs in capsules or tablets [117,118]. These products have to be manufactured under control of a pharmacist in accordance with special requirements on stability, extraction liquid and extraction conditions such as temperature and method of drying.

Besides the "Indonesian Farmacopea", the Directorate General of Drugs and Food Control has also published six volumes of the "Materia Medika Indonesia". These publications discuss the formal requirements for crude drugs and give further information which might be needed e.g., local name, section microscopic drawing, crude drug powder and a crude drug colour picture. The *Materia Medika Indonesia* (Volumes I to VI) contains 350 crude drug monographs and is used as the formal quality requirement book for crude drugs in Indonesia [111].

Labelling

Since 1985, special guidelines on labelling of traditional drugs have been issued [119]. It is required that the labelling states the correct information, that the label is clear and easy to read and that the explanation of traditional drugs is written in the Indonesian language and in Latin letters. Traditional drugs are characterized by a special emblem, e.g., a leaf. The registration number has to be included on the label together with the name and address of the company, composition, indication, method of use and dosage, duration of administration, warnings, contra-indications, storage, expiry date and production code. Similar information is required for the package leaflet.

Good Manufacturing Practices

A Decree of the Minister of Health dated 30 October 1991 regulates Good Manufacturing Practices of Traditional Drugs (GMPTD) [120]. These rules cover the aspects related to the production of traditional drugs with the objective to guarantee that the product always fulfils the requirements. There are general requirements regarding the employees, the responsible persons in the technical field, training in GMPTD, the premises, the area and equipment (machinery and laboratory). Processing and packing also must be carried out with special methods. A periodic self-inspection has to be made and everything has to be documented clearly. If there are concerns regarding safety or quality, these have to be checked and, if no longer adequate, the product has to be withdrawn from the market.

In 1993, the Directorate General of Drugs and Food Control published an English translation of all the regulations relevant for traditional drugs [121]. This book was intended to provide guidance for manufacturers, distributors or institutes, on traditional drugs and crude drugs with respect to their production and distribution so as to ensure products of good quality.

Nepal

Herbal medicines have to be registered by the Department of Drug Administration, at the Ministry of Health. Regulatory requirements are: manufacturing licences issued by the concerned Drug Control Authority, price approval and valid price list, letter of warranty of the manufacturer indicating his/her responsibility for safety, efficacy and quality of his products, authorization for import, export and distribution of the product, and the mode of distribution and promotion. Pharmaceutical requirements are the quantitative formula including all excipients, stability data, shelf-life, bioavailability *in vitro* and *in vivo*, wherever applicable, a description of the product including container and labelling, and a photograph of each product. For medicinal plants, permission is given by the Department of Forests [122].

Thailand

As the use of herbal medicine started to decline at the beginning of this century, the government, aware of the potential of medicinal plants and traditional medicine to treat common diseases and symptoms in primary health care, has adopted a national policy on their utilization, including research and development.

Legal Status

There is no government control on the production and distribution of medicinal plants in Thailand provided that the plants are sold as such. However, in so far as medicinal plants are mixed or put into dosage forms, the distributors are required by law to obtain permission from the Food and Drug Administration [123].

In accordance with the Drug Act B.E. 2510 and its amendment, "traditional drug" means a drug intended for use in the practice of the traditional medicine, and which appears in a pharmacopoeia of traditional drugs notified by the Minister, or a drug notified by the Minister as a traditional drug, or a drug of which the formula has been registered as that of a traditional drug. In contrast, "household medicine" means a modern or traditional drug notified by the Minister as a household medicine, and "herbal drug" means a drug of plant, animal or mineral origin which has not yet been compounded, dispensed or denatured. No one is allowed to produce or sell a traditional drug or to import one without a licence from the licensing authority. This does not apply to the preparation of a traditional remedy by a traditional medical practitioner in accordance with the pharmacopoeia for his own patients or for resale, nor to the sale of a herbal remedy which is not a dangerous drug or the sale of a household medicine.

There are three categories of licences relating to traditional drugs: to produce; to sell; and to import or order. Persons licensed to produce traditional drugs must have premises, staff and equipment to ensure their correct manufacture and control; they have to provide labels corresponding to the registered formula indicating that it is a "traditional drug"; and they have to use labels and accompanying literature corresponding to the registered formula. Any person licensed to produce or import drugs including traditional drugs is required first to apply for the registration of the formula. This, however, does not apply to crude drugs. Within the application for registration of a drug the following particulars shall be given: name of the drug, names and quantities of the ingredients, content, label, leaflet, etc. The Minister is empowered to give notice in the Government Gazette listing pharmacopoeias, substances classified as drugs, dangerous drugs, common household drugs, traditional drugs, etc. [124].

The Thai Pharmacopoeia

Arrangements have been made to control the quality of crude drugs, but not of compound medicines prepared from them because of the complexity of the assay procedures. There are different government agencies involved in quality control and specifications of crude drugs. For example, the Department of Medical Sciences has been appointed to head the Thai Pharmacopoeia Committee with the aim to establish quality control of drugs sold in the Thai market. Monographs on crude drugs are prepared, some with reference to international pharmacopoeias such as the British Pharmacopoeia, and the United States Pharmacopoeia [123].

Western Pacific

Australia

Legal Status

Therapeutic goods for human use which are imported or manufactured in Australia must be included in the Australian Register of Therapeutic Goods, in accordance with the Therapeutic Goods Act 1989. Traditional medicines also need registration. Alternative medicines are allowed to enter this register at a lower level than many other pharmaceuticals. In some cases, e.g., substances about which there are safety concerns, or products which are claimed to treat more serious medical conditions, a higher level of a pre-market registration will be required. The Traditional Medicines Evaluation Committee (TMEC) was established to provide expertise for the evaluation of non-prescription traditional medicines and to give advice to the authority on their registration. The TMEC is appointed by the Minister and consists of six to nine members who are experts in: the clinical practice or teaching of alternative medicine; pharmacy with expertise in pharmacognosy or plant toxicology; the manufacture of alternative medicines; or who are medical practitioners or who have qualifications and experience in clinical pharmacology [125].

According to general requirements for labels of medicines, herbs are included in the List of Australian Approved Names for Pharmaceutical Substances which is published by the Therapeutic Goods Administration in its edition "TGA Approved Terminology for Drugs" dated January 1993, with amendments. There are also special regulations on the expression of quantity or proportion of active ingredients in drug products, with special requirements for herbal ingredients [126].

China

Traditional Chinese medicine (TCM) has a long history of more than 4 000 years. Discovery of medicinal materials in ancient times was closely related to the life and the labour of people and their natural conditions of living. People found out that many natural materials could be used to treat diseases, and great experience in this field has gradually been accumulated.

The Chinese Materia Medica is one of the best documented and most extensive sources, as well as the one that enjoys the most continued use, including more than 7 000 species of medicinal plant.

Market Importance of TCM

The Constitution of the People's Republic of China stipulates that modern and traditional medicine should be developed simultaneously. Therefore, since the founding of the People's Republic of China, traditional Chinese medicine has developed steadily. By the end of 1995, there were 2 522 TCM hospitals with a total of 276 000 beds. Most of the general hospitals have a TCM department. There are 940 factories and plants for the manufacture of herbal medicines. In 1995, the total value of herbal medicine manufactured reached 17.6 billion Chinese yuan, an increase of 213% compared to 1990. The total sales volume of traditional herbal medicines in 1995 was 15 billion yuan, an increase of 123% compared to 1990. From 1978 to 1993, sales of patent herbal medicines and raw plant materials increased by 10.8 and 2.3 times, respectively. The sale of patent herbal medicines represented 24% of the total sale of medicines countrywide in 1993 (14% in 1978). At the same time, sales of raw plant materials for decoctions were just 9% of the total sale of medicines countrywide in 1993 (compared to 18.7% in 1978) [127].

The Chinese Pharmacopoeia

The 1990 edition included 784 articles on traditional Chinese medicines and 509 articles on Chinese patent medicines. The monographs describe the source or the substances used, prescriptions, methods of preparation, identification, examination, extraction, effects and main indications as well as methods of use, dosage, precautions, etc. [128]. Further information on herbal medicines is available in the new edition of the "Pharmacopoeia of the People's Republic of China" [127].

Legal Status

With regard to their legal status, herbal medicines in China are normally considered as medicinal products with special requirements for marketing, for example a quality dossier, safety and efficacy evaluation, and special labelling. New drugs have to be examined and approved according to the Drug Administration Law. After approval, a New Drug certificate is granted an approval number. The factory is then permitted to put the

product on the market. This procedure reflects the respect in which traditional experiences are held, while modern scientific and technical knowledge is used in appraising the therapeutic effects and the quality of the modified traditional medicines, and contributes administratively to the exploitation of traditional Chinese medicine [128].

The Drug Administration Law of the People's Republic of China [129] was enacted on 20 September 1984. Article 3 states "The State encourages the development of both modern and traditional drugs, the role of which in the prevention and treatment of diseases as well as in health care will be fully brought into play. The State protects the resources of wild herbal drugs and encourages domestic cultivation of herbal drugs".

With regard to a drug manufacturing enterprise, Article 5 states that "It should be staffed with an adequate number of pharmacists or technical personnel with a title equivalent to or higher than associate engineer, and skilled workers adaptable to the scale of drug production". However, "Enterprises for the preparation and slicing of raw plant materials should be staffed with pharmaceutical professionals familiar with the property of raw materials and registered with the health bureau above the county level, if pharmacists or technical personnel with a title equivalent to or higher than associate engineer are not available." Article 6 states "processed medicinal plant materials must be prepared and sliced in compliance with the specifications of the Pharmacopoeia of the People's Republic of China or the processing norms stipulated by the health bureau of the province, autonomous region or municipality".

For the control of drug handling enterprises, Article 11 states that a drug handling enterprise should be established with an adequate number of pharmaceutical technicians adaptable to the scale of its business. However, enterprises engaged in the handling of modern drugs may be staffed with pharmaceutical professionals familiar with the property of drugs and registered with the health bureau above the county level, if pharmaceutical technicians are not available. Article 15 states that in the market of country fairs only the sale of medicinal plant materials is permitted, with certain exceptions.

Article 29 states "The Ministry of Public Health has the authority to restrict or prohibit the exportation of medicinal plant materials and patent herbal medicines if they are in short supply in the domestic market". Article 31 states "The sale of medicinal plant materials newly discovered or introduced from abroad is not allowed unless it is approved by the health bureau of the province, autonomous region or municipality" [129].

Documentation for Applications for New Drugs

Based on Article 21 of the Drug Administration Law, "the clinical trial or clinical verification of a new drug should be sanctioned by the Ministry of Public Health or the health bureau of the province, autonomous region or municipality". "A new drug will be approved for clinical use and a licence issued by the Ministry of Public Health, if the clinical trial or clinical verification has been completed and an appraisal of its efficacy has been made." Pursuant to Articles 21 and 22 of the Drug Administration Law, on 1 July 1985, the Ministry of Public Health issued and implemented a regulation for the Approval of New Drugs. "New drugs" are referred to as drugs which have not been produced previously in China, or drugs for which a new indication, a change in the route of administration or a change of dosage form is to be adopted. Any unit or individual engaged in the development, production, distribution, prescription, inspection and surveillance of new drugs must adhere to the provisions of the document. The regulation includes general principles concerning new drugs, their classification, research, clinical trials, approval, and manufacture. Several appendices provide detailed information on the application form, list of documents required, and technical requirements of toxicological and clinical studies on new modern drugs, and new TCM drugs [127].

Based on the Amendment and Supplemental Regulation of Approval of New TCM Drugs, implemented 1 September 1992 [130], new TCM drugs are classified under five categories, as follows:

Category 1

- artificial imitations of TCM herbs;
- newly discovered medicinal plants and their preparations;
- single active principle extracted from TCM plants material and their preparations.

Category 2

- Chinese medicinal herbal injections;
- parts of TCM medicinal plants newly employed as a remedy and their preparations;
- non-single components extracted from TCM and natural plants and their preparations;
- TCM materials obtained by artificial techniques *in vivo* and their preparations.

Category 3

- new TCM preparations;

- combined preparations of TCM and modern medicine in which TCM medicine is the main component;
- cultivated material which traditionally is imported.

Category 4

- new dosage forms or new routes of administration of TCM drug;
- materials introduced from other parts of the country and those for cultivation instead of harvesting in the wild.

Category 5

- TCM products with new and additional indications.

All research on new medicines should provide data on toxicity, pharmacological properties and clinical research, as well as a detailed documentation on the quality of the medicinal material and the pharmaceutical form. For the five categories mentioned above, different requirements have to be fulfilled for the medicinal material as well as for their pharmaceutical preparation. Proprietary medicines included in the national pharmacopoeia and new medicines approved by the Ministry of Public Health are exempted from clinical testing when only the dosage form is changed, such as from powder into gelatine capsules, or from tablets into granular form infused with boiling water, without changes in the indications for cardinal symptoms or dosage.

The report on the medicinal material should contain the following items in applications for clinical research: purpose of research, previous experience or modern research data, source of material, cultivation, processing, properties, data based on Chinese pharmacology and experience, efficacy with respect to cardinal symptoms, pharmacological research data, acute toxicity tests, data on mutagenicity/carcinogenicity/reproductive toxicity (only for category 1), draft on quality standards, stability, and the proposed plan for the clinical research. A separate application for production should include documentation on quality standards, stability tests, a summary of clinical studies, and packaging material.

The report on pharmaceutical preparation has to meet similar requirements as the report on medicinal material, depending on the drug category.

Technical requirements for pharmacological studies are laid down in a special paragraph. The tests on major drug effects shall be designed in such a way that the special characteristics of the traditional Chinese medicine are taken into consideration. Two or more methods shall be selected for research on the major drug actions, based on the effects of the new medicine on the complex of symptoms or the illness. For new medicines in categories 1, 2 and 3, this research shall be sufficient to verify the major therapeutic functions and other important therapeutic effects. For new medicines in category 4, two (or more) tests on the major effects are required, or else well documented material has to be submitted. For new medicines in category 5, only tests on the major effects of the medicine on "new" cardinal symptoms are required. Research on general pharmacology shall be performed on the nervous system, on the cardiovascular system, and on the respiratory system. Technical requirements for studies on toxicity are also laid down in a special paragraph. Here a difference is drawn between a clinical trial and a clinical verification. Clinical trials shall be conducted for new medicines of categories 1, 2 and 3, and clinical verifications are required for new medicines of categories 4 and 5. Clinical trials are divided into three phases, but clinical verification does not have phases.

The purpose of a clinical trial phase I is to study the reaction and the tolerance of the human body to the new medicine and to find out the safe dosage. Medicines in categories 1 and 2 which have either toxic or incompatible compounds have to go through phase I of the clinical trial. For dosage determination, the dosage used in animal tests may be used as a reference. The purpose of phase II of a clinical trial is to obtain an accurate evaluation of the curative effects of the new medicine and its safety. In addition, a comparison has to be made between the new medicine and known drugs, so as to determine its advantages and disadvantages. Phase II consists of two parts, the first applies when the treatment is performed and the second when the treatment is expanded. The dosage used in the clinical trial shall be based on pharmacodynamic tests made beforehand and clinical facts, or the results of phase I. For the selection of cases, there are strict standards on diagnosis, and the diagnosis is based on overall analyses of symptoms and signs, the course, nature and location of the illness and the patient's physical condition, according to the basic theories of TCM. For the performance of a clinical trial, either the single or the double blind method may be used, according to need or the actual circumstances. When the curative effects are determined, four ratings are applicable: clinical recovery, significantly effective, effective and non-effective. The evaluation of curative effects shall be based on the clinical

symptoms (symptoms and physical signs), objective standards for curative effects and the ultimate results on the patient.

The objective of the clinical trial phase III is the further investigation of the safe use or effectiveness of the new medicine on the basis of the findings of phase II. The main purpose is to have clinical trials on a new medicine during its trial production or after it has been put on the market for a period of time. This is to make up for deficiencies in phase II, to observe further the curative effects, and the nature of its effects on cardinal symptoms and adverse reactions.

Clinical verification is applicable for new medicines in categories 4 and 5, the purpose being to observe their curative effects, contra-indications and precautions. Different groups for control and for comparison shall be used. For new medicines that have changed their dosage forms, the control shall be same pharmaceutical form as the original form. For those medicines that have additional curative effects, a known medicine with curative effects on the same illness shall be selected as control.

The summary of the clinical trial shall be objective and comprehensive and shall be an accurate reflection of the whole process. The discussion in the final report shall include the conclusion which is based upon the outcome of the tests, the functions and effects on cardinal symptoms, the scope of application of the new medicine, its administration, the course of treatment, curative effects, safety, adverse reactions (including the measures to be taken), contra-indications and precautions. An objective evaluation on the characteristics of the new medicine shall also be made.

Technical requirements for studies on quality standards for Chinese medicinal material and medicines are laid down in a special chapter. The source (original plant, part of the plant, harvesting conditions), the properties, the identification, the test for impurities, the assay and the processing have all to be described. The quality standards for Chinese medicines shall include the prescription, the way of processing, the properties, the identification, the examination and the assay in accordance with the general guidelines laid down in the pharmacopoeia. A further special paragraph describes the technical requirements for studies on stability, and which items have to be checked for which dosage form. [130]

Hong Kong

Recommendations for the Use and Practice of TCM

In August 1989, the Secretary for Health and Welfare appointed a Working Party on Chinese Medicine (WPCM) to review and to make recommendations on the use and practice of traditional Chinese medicine (TCM) in Hong Kong. The objectives were to ensure patients' safety, promote the proper use and good practice of TCM, recognize the role of TCM in the health care system, and facilitate its further development. The development of TCM based on the strength of its heritage was identified as a guiding principle. The report of the Working Party on Traditional Medicine was published in October 1994 [131].

While Western medicine remains the mainstream of the health care system in Hong Kong, TCM continues to enjoy considerable popularity. Drinking herbal teas or herbal tonics made from Chinese medicinal materials is a common practice among people of the community. The number of TCM practitioners in Hong Kong is estimated between 4 000 and 10 000. Most of them (76%) have practised in Hong Kong for more than 10 years, 42% more than 25 years. Mostly, they have gone through some form of training, e.g., full time TCM courses or apprenticeship. At present, there is no established system of TCM courses or schools [131].

More than 59% of the traditional Chinese medicines are imported, mostly from China, including about 80% of proprietary Chinese medicines and 80-90% of raw or processed medicinal materials. At present, there are some 30 processing workshops and 60 manufacturing establishments, 100 wholesalers of raw or processed Chinese medicinal material, 200-300 wholesalers of proprietary Chinese medicines, and 1 600 retail herbal shops. Proprietary Chinese medicines are available from pharmacies, drugstores and herbal shops [131].

Controls on the quality of Chinese medicinal materials and proprietary medicines are only incidental, e.g., the Pharmacy and Poisons Ordinance (Cap 138) requires control for adulteration with Western drugs (control only for proprietary Chinese medicines). Labelling is regulated under the Public Health and Municipal Services Ordinance (Cap 132) which prohibits the sale of drugs with indications that are not appropriate. As there is no specific control on traditional Chinese medicines for the purposes of import and export, registration, sale, dispensing, purchase, over-the-counter sales of Chinese medicines without prescription from TCM practitioners are common. Licences are only required for Chinese medicinal materials in proprietary form, not for raw or processed Chinese medicinal materials [131].

The Working Party on Chinese Medicines recommended [131] registration of TCM practitioners to safeguard the patients' interests and to provide a framework for the future development of TCM, and this was widely supported. From the Working Party's point of view, registration will help to enhance the status of TCM practitioners and increase public confidence in this profession.

About one third of the almost 5 800 Chinese medicinal materials listed in the Chinese Herbal Medicines Dictionary is available in Hong Kong. The Working Party on Chinese Medicines regards them as safe for general use, except for about 50 herbs with a narrow safety margin, which might be toxic and should be brought under control. It was recommended to draw up a list of these herbs and to license manufacturing establishments, because control on processors and manufacturers of Western drugs under the Pharmacy and Poisons Ordinance could not be automatically extended to those of Chinese medicines. Licences should be issued annually for the processing and manufacture of traditional Chinese medicines at registered premises. The Working Party also recommended a licensing system for proprietary Chinese medicines which could be based on certification from the place of origin, where such certification is considered by the respective government as evidence of scientific assessment, clinical trial and relevant research [131].

Macao

Traditional Chinese medicine (TCM) is a popular form of health care in Macao. Many of the people still consult doctors and practitioners of TCM. In addition, a very high percentage of the population regularly uses TCM in preparing soups, herbal teas or herbal tonics as supplementary food. In view of this situation, the Health Authority realized several years ago that it was crucial to establish laws and other regulations to improve the quality, efficacy and safety of these medicines, and to define the professional backgrounds and technical skills for trading in and dispensing pharmaceutical products, the most important aspects.

The first Chinese traditional pharmacy was registered in the Health Department in 1936, and by 1990, there were already 102 licensed traditional Chinese pharmacies. Since the law regulating licensing was very old, it could not deal with updated technological requirements developed in the last two decades. The new law, Decreta-Lei n 53/94/M, was enacted in November 1994 and aimed at better public health through adequate licensing of medicines, import, export and wholesalers companies, dispensing pharmacies, and pharmacists and other technicians of traditional pharmacies. Based on this law, a list which includes 456 types of traditional medicinal material which may only be sold in Chinese pharmacies of Macao was prepared. The list consists of two sub-lists: Part 1. - toxic traditional Chinese materials; and Part 2. - common therapeutic traditional Chinese materials. Under this law, a simple but effective registration system for imported traditional medicines, the so-called "alternative registration system" started to be implemented. Only traditional medicines which have been registered in a country can be imported into the Macao market; but for those from Hong Kong, Singapore and other countries without a registration system at the moment, the importer must provide analytical certificates issued by the manufacturer or recognized laboratories [127].

Fiji

Traditional medicine has a long history in Fiji and is still used today. Practitioners include herbalists, masseurs, and bone setters.

Legal Status

In addition to Fijian traditional medicines, traditional medicines from other countries, e.g., China, India, and Korea are imported. The existing Pharmacy and Poisons Act of Fiji permits importation of traditional medicines for use by ethnic communities. The Pharmacy and Poisons Board issues import certificates for herbal medicines provided that they make no therapeutic claims. If a therapeutic claim is made on the label or any accompanying leaflet, the Board does not approve an import certificate. The importer is requested to present information which proves the therapeutic claims [132].

The Fiji National Drug Policy recommends that the government encourage and support research in traditional medicines. The existing legislation is being re-drafted and is intended to recognize herbal medicines so that their quality, safety, and efficacy may be controlled. The Ministry of Health recognizes the potential danger in the use of products for which quality, safety and efficacy have not been controlled [133,134].

The Ministry of Health has established a Traditional Medicines Committee but up to now there are no results available [132].

Japan

Traditional medicines have been used effectively in Japanese society for more than a thousand years. Japanese traditional medicine may be divided into folk medicine and Chinese medicine from ancient China, the so-called Kampo medicine. It is not possible to show precisely when and how folk medicine came to gain ground in the life of the Japanese people, but the record shows herbal medicines have been used for the past 1 400 years in Japan. The raw medicinal herbs used as folk medicine are combined with modern preparations in many cases, as are many of the Chinese traditional medicines and medicinal herbs [135].

Market Importance of TCM

Kampo Medicine is extremely popular in Japan, where the per capita consumption of herbal medicine seems to be the highest in the world. The drugs used are known as Kampo drugs. Each Kampo drug is a formula usually consisting of 5-10 different herbs. New features have been introduced into the practice of Kampo. Most of the modern ready-to-use forms of the original formulae are produced in industrialized granular, powdered or other forms based on the classical decoction. Introduced in 1957, it is now estimated that more than 95% of Kampo drugs used in Japan are taken in such a ready-to-use form as ethical drugs. Since 1961, almost 100% of the Japanese population has been covered by the National Health Insurance (NHI). 43 Kampo drugs for ethical use were included in the NHI Drug Price Tariff in 1976, joining a few predecessors. More Kampo drugs were included later, and now 147 Kampo drugs (as formulae) are available as ethical drugs. As these were already registered as drugs by the Ministry of Health and Welfare (MHW), their inclusion might be assumed to have been a matter of course. Their acceptance took place without clinical validation studies [136].

According to a market survey in 1989, among the top 100 items of over-the-counter drugs sold in Japan, 45 items correspond to the raw herb combined preparations which represent 34% in terms of share of sales with considerable economic importance. Chinese medicine shows a steady growth and, in particular, its remarkable expansion in the prescription drugs area indicates that it is highly valued in modern medical practice. In a survey in 1979, 19% of physicians had experience of having prescribed Chinese medicine, but, by 1989, the percentage had increased to 79%. According to another survey, the percentage of physicians usually using Chinese medicine was 28% in 1983, and 69% in 1989. At least 65% of physicians replied that they administered both Chinese and modern medicines to more than 5% of these patients. Physicians generally recognize Chinese medicine as a complement to modern medicine. It is common knowledge in Japanese society that traditional drugs are safe. In fact, according to an in-hospital side effect monitoring report in 1989, Chinese medicines accounted for only 1.3% of all cases. This percentage is quite low as compared to the market share of 2.5% which Chinese medicine occupies [136].

Evaluation of Japanese and Chinese Medicines

The difference between Japanese herbal medicine and Chinese medicine lies in the evaluation methods. Therefore, the applicable approval processes are quite different. The effect of a herbal medicine depends entirely on the sum of the pharmacological actions of the effective ingredients contained in the raw herb. There is no significant difference between the methods of evaluation applicable to herbal medicines and those with chemical substances. With respect to the evaluation of efficacy and safety, those raw herbs which have long been used as folk medicine and also been used for a considerable period as components of an industrial product, are listed in the corresponding monograph. They are freely usable within the range of the monograph. On the other hand, local traditional usage alone is not sufficient for approval as a drug. The claims and rules of combinations are determined on the basis of the pharmacological actions of the ingredients which may be contained in the raw herbs. Usually, the scope of claims is clearly specified in the corresponding monograph. In cases where the monograph is not yet completed, the claims shown in the Japanese Pharmacopoeia are used as a guide [136].

In the evaluation of efficacy of a Chinese medicine, importance is given to the "empirical facts or experience" such as the reference data, clinical test reports, etc., rather than the pharmacological action of each ingredient. In many cases, Chinese medicine is administered in the form of an infusion and/or powders. However, for reasons of convenience or industrialization, raw materials are transformed into extracts and produced and marketed as tablets, granules and powders [135].

Safety and efficacy have been estimated based on general methods employed by modern medical science. In 1972, the MHW designated 210 formulas as over-the-counter drugs. This selection was based mainly on the experience of doctors actually practising Chinese galenic medicine. In 1976, the Ministry specified 146 prescriptions as NHI applicable prescription drugs. In the case of an application for approval of a prescription other than those mentioned, specified data on safety, stability, comparison with other drugs, clinical test

results, etc. are required to be submitted [135].

New Kampo drugs are regulated in essentially the same way as Western drugs in Japan. They are regarded as a form of combined drug, and the same data required for new Western drugs are required for new Kampo drugs in the NDA. The time-consuming and expensive chronic toxicity tests and special toxicity tests such as for mutagenicity, carcinogenicity and teratogenicity depend on the possible length of treatment and indications that apply to them. Data for three-phase clinical trials are also required. For generic Kampo drugs, bioequivalence data are required, which may discourage development, because pharmacokinetic studies of Kampo drugs are difficult to conduct and bioassay methods are quite limited [136].

Re-evaluation Process

Since 1971, the MHW has been running a programme for the re-evaluation of all drugs marketed before 1967. In 1967, the Japanese government instituted a new policy requiring scientific evidence of the efficacy and safety of new drugs. Results of the first re-evaluation of ethical drugs approved prior to 1967 have been made public in several instalments since 1973, and those of the second re-evaluation of ethical drugs approved from October 1967 to March 1980, since 1988. Re-evaluation of more than 99% and 58% of the total number of the products was completed in the first and second re-evaluations respectively. A new system to re-evaluate the efficacy and safety of all ethical drugs every five years was launched in 1988 [136].

For re-evaluation of Chinese medicines, an official notification was issued 1 February 1991. Since the methods of re-evaluation are not always clearly established, a first selection was made of eight prescriptions, the manufacturers being requested to furnish the necessary data to prove their effectiveness and safety [135].

Guidelines on Quality of Kampo Drugs

There was an improvement in the quality control of Kampo drugs in the mid-1980s. After a report on the situation of quality control, the Advisory Committee for Kampo Drugs was established in 1982 in close association with the Pharmaceutical Affairs Bureau of the MHW. A Working Group on the Quality of Kampo Drugs was established and, three years later, a new regulation was issued by the Pharmaceutical Affairs Bureau setting standards for the manufacture and quality control of Kampo drugs. This ensures that the quality of herbs used in each original formula meets precise standards. The regulations also call for quality monitoring of specific ingredients, using at least two different chemical or physical methods to test them [136].

Since October 1986, Good Manufacturing Practice (GMP), a standard required of pharmaceutical drugs issued by MHW in 1976, applies also to Kampo drugs. In addition, in 1988, the Japan Kampo Medicine Manufacturers' Association drew up self-imposed guidelines that take into consideration the unique nature of Kampo drugs [136].

In 1985, guidelines for ethical extract products in oriental medicine formulations were developed, according to which the data from a comparative study of the extract and a standard decoction have to be provided by the manufacturer of an ethical extract product. Besides data on the crude drug and on the standard decoction prepared in accordance with the Chinese traditional medicine prescription, a comparative study has to describe the content of an indicator ingredient in the finished product, which is required to be more than 70% of the content of the indicator ingredient in the standard decoction [137].

Post Marketing Surveillance

The MHW has three major systems for the collection of domestic adverse reaction data. The first is the Adverse Drug Reaction Monitoring System under which 2 915 monitoring hospitals have been designated and requested to report cases of adverse reactions to the MHW. This is a "voluntary" monitoring system, and 1 158 cases of adverse reaction were reported in 1990, of which 15 cases pertained to Kampo drugs.

The second data collection system is the Pharmacy Monitoring System formed by 2 733 pharmacies. This system mainly collects data on cases of adverse reactions to over-the-counter drugs. In recent years, about 400 cases have been reported annually. Among these, reactions caused by Kampo drugs are the most common, though most of these adverse reactions are minor, involving symptoms such as gastric discomfort and skin problems. Fifty cases were reported in 1989.

The third system is Adverse Reaction Reporting from Manufacturers. Several severe cases caused by "Shosikoto", including drug-induced hepatitis and pneumonitis, were documented at medical conferences and in journals and were reported to the MHW by the responsible company in 1990. In addition, since 1988, the

newly drafted Good Post-Marketing Surveillance Practice (GPMS) has been used on a pilot scale for Western drugs dispensed in Japan. When new Kampo drugs are approved and appear on the market, this guideline will also apply to them [136].

Malaysia

The Control of Drugs and Cosmetics Regulation gazetted in June 1984 marked the beginning of systematic regulatory control on pharmaceutical products, including traditional medicines. The registration exercise for traditional medicines began in January 1992 under the third phase of implementation of this legislation. This exercise, it was hoped, would ensure safety, quality and, to a certain extent, efficacy of traditional medicines [127].

The implementation of the registration exercise implies that the Ministry of Health has assumed responsibility for ensuring the safety and quality of imported as well as locally manufactured traditional medicines.

The term traditional medicine covers any product employed in the practice of indigenous medicines, where the drug used consists only of one or more naturally occurring substances of plant, animal or mineral origin or part thereof, in extracted or non-extracted form and any homoeopathic medicines. All these products are required to be registered with the Drug Control Authority prior to marketing. Only products which meet the required standard are registered by the Drug Control Authority's secretariat, the National Pharmaceutical Control Bureau (NPCB), Ministry of Health, and allowed to be manufactured, imported, supplied or sold. Up to October 1995, more than 15 000 applications were received by the NPCB, 67% of which were for Chinese traditional medicines, and 13% for Malay traditional medicines. Of the remainder, 49% were for Indian products and 51% were for locally manufactured ones. Initial findings show that most local manufacturers of traditional medicines are small-scale and rarely have modern facilities, and that most of them lack know-how on new technologies. The registration exercise can be considered as the starting point of the government's efforts to upgrade the local pharmaceutical industry of traditional medicines.

Traditional medicines must comply with certain basic criteria of acceptable quality to qualify for registration. Quality specifications set by the Drug Control Authority, while safeguarding the public, also allow gradual upgrading of the traditional medicines industry. Local manufacturers and importers are advised to start with some basic quality control parameters even though this requirement is not mandatory. The list of requirements includes visual inspections, and tests for moisture content, uniformity of weight, etc. With effect from September 1993, the Drug Control Authority has imposed parameters for contamination by heavy metals, and microbial contamination to be tested on all traditional preparations, and disintegration tests for tablets and capsules submitted for registration. Local manufacturers are advised to include stability studies as part of the quality control requirements of traditional medicines.

Registrable traditional medicines should be free from dangerous or hazardous ingredients. Incorporation of chemical drugs or scheduled poisons is forbidden. The content of heavy metals such as lead, mercury and arsenic and also pesticides should be below the acceptable limits. Labels for traditional medicines, which are a very important safety/quality feature, must give information adequate and clear enough for the consumers to use the product properly and safely.

As provided in the "Medicines (Advertisement of Sale) Act 1956", traditional medicines and other over-the-counter products are not allowed to claim that they are effective for contraception, for improving kidney function and cardiac function, or for the treatment or diagnosis of 20 major diseases or conditions such as diabetes, epilepsy and asthma [127].

Mongolia

Mongolian traditional medicine has 2 400 years experience and has a close relationship with Chinese, Indian and Tibetan traditional medicine. The current Mongolian Government considers traditional medicine as an important part of medical service to the population, develops it in association with Western medicine, and is investigating the scientific foundation of traditional medicine to identify its optimal applications.

In 1989, a Traditional Medicine Department was established at the Mongolian National Medical University with training courses in traditional Mongolian medicine. There are seven units producing traditional medicine drugs [138].

New Zealand

In New Zealand, herbal medicines are dealt with in two ways according to the Medicines Act of 1981. On the one hand, any herbal remedy may be manufactured and sold if requested for the expressed purpose of treating a particular person. This remedy must not contain a scheduled medicine and must be supplied under a designation that specifies the plant and the process of manufacture of the remedy, without any other name and without any written recommendation as to the use of the remedy. In these cases, no licensing and no assessment is required.

On the other hand, for any herbal medicine not covered by the above-mentioned conditions, marketing approval is required. The assessment of herbal medicines is carried out in the same way as for proprietary medicines by the Therapeutics Assessment and Utilization Section of the Department of Health. The application includes control of active ingredients and excipients, method of manufacture, control tests of the finished product, labelling, stability etc.

The efficacy of herbal medicines is not evaluated critically. Often there are hardly any clinical data for efficacy, since most of these remedies are prescribed on a patient basis. Supporting evidence for efficacy may include references in standard books, unless this information has been superseded by more recent research data. Indication claims are restricted to self-limiting conditions. In some cases, where there is concern about safety, toxicity data have to be provided; if not, a withdrawal from the market may be the consequence [139].

Philippines

Cultivation and use of medicinal plants in the Philippines date back to the pre-Spanish times, and studies began in the 16th century, mostly written by Spanish missionaries. Complete and very useful information on the treatment of diseases is provided by the book of Dr Pardo de Tavera "Plantas Medicinales de Filipinas" published 1892. The first official mandate in recent years that recognized the usefulness of medicinal plants has been the Letter of Instruction issued by the Department of Education in 1973 encouraging public schools to include medicinal plants in health education.

In history, traditional healers (herbolarios) were the first who recommended the use of plant preparations. Now, especially in rural areas where the use of plants for common ailments has never been abandoned, these experiences of community-based health programmes have been very encouraging. It has been shown in several studies that people living in rural areas tend to use more traditional herbal medicines than Western drugs compared to people living in urban areas [140].

Legal Status

The regulation and control of herbal products, whether food or medicines, are under the authority of the Bureau of Food and Drugs (BFAD) of the Department of Health. Two administrative orders, issued in 1982 and 1984, require that all traditional drugs both local and imported comply with registration and quality control requirements. An official list of traditional products had to be established according to these orders. Among the quality control requirements are tests for the presence of synthetic drugs (especially analgesics, anabolics, corticosteroids, hormones), heavy metals, alcohol content and impurities. Tests for galenic forms are required as well as microbial tests and stability data.

A monitoring system for import and export of medicinal plant products does not exist. Imported products may be sold in Chinese drug stores. Small community manufacturing of medicinal plants in tea bags, capsules or syrups has proliferated, but no regulation or control has been implemented. It is regarded as very important that the traditional medical system remains distinct from Western medicine, but might complement it. Therefore, the use of safe and effective herbal medicines should be effectively promoted but without false hopes and expectations [140].

In 1987, the National Drug Policy was adopted, emphasizing quality assurance and rational use of drugs. Since then, 10 policies have been adopted of which one dealt with research on traditional healing methods and promotion of the use of medicinal plants [140].

In October 1995, the Department of Health's (DOH) Circular 168-A was signed by the Secretary of Health. This circular lists herbal medicinal plants which are being studied, utilized and promoted by the DOH to serve as safe and effective alternative medicines in the health care delivery system. The list includes 10 scientifically validated medicinal plants and 70 plants which are presently undergoing further studies by government researchers [127].

Republic of Korea

The Republic of Korea has legally adopted two medicare systems, Western medicine and oriental medicine. Traditional medicine in Korea is based on both traditional Chinese medicine and Korean folk medicine. The empirical folk medicine has passed on from generation to generation and is not prescribed by Korean oriental physicians.

Legal Status

The Composite Pharmacy Law governs all activities concerning pharmacies, pharmaceutical industries, and suppliers of medicines including herbal raw materials. The two official drug compendia are the fifth edition of the Korean Pharmacopoeia and the Korean Natural Drug Standards [141].

In 1969, the Ministry of Public Health and Social Affairs published a notification which acknowledged that a herbal preparation could be prepared by a pharmaceutical company without submitting any clinical or toxicological data, provided that the formula is described in the eleven classic books on traditional Korean and Chinese medicines [141].

Since 1983, the government has been working on standardization of 530 medicinal plants, including 145 which were already listed in the Korean Pharmacopoeia. Since 1993, only standardized medicinal plants can legally be distributed. For herbal medicines produced by domestic pharmaceutical companies, the government imposes strict regulations on these companies, so that they follow the GMP standard in manufacturing herbal medicines.

For the production of well controlled herbal raw materials, the Ministry of Public Health and Social Affairs has published a notification under which a new licence will be issued to the manufacturer of standardized herbs. Herbal drugs and preparations thereof have to be standardized and controlled according to the requirements of the Korean Pharmacopoeia, the National Institute of Health and the Ministry of Public Health and Social Affairs. The information required for these products includes taxonomic status, parts of plants, morphology, qualitative examination, purity, content of essential oil or extract, and grade of quality.

A single herb used in traditional medicine may contain hundreds of constituents. In the case of a combination of several herbs, hundreds of natural constituents would have to be assayed in quality control. For this reason the National Institute of Health employs approximate assay methods within which an active natural product or an indicative substance may be analyzed in quality control [141].

The Medical Act and the Drug Administrative Act stipulate that only certified oriental medical doctors or pharmacies with oriental medical doctors' prescriptions can provide patients with any of the herbal medicines listed in the Korean Pharmacopoeia [142].

Market Importance of Oriental Medicine

About 500 doctors a year from 11 schools become oriental medical doctors. At present, registered oriental medical doctors number 5 792, accounting for 12% of all doctors. Among them, 4 208 work in urban areas and 399 in rural areas, with 324 working for general hospitals or oriental medical hospitals, and 4 283 running private clinics. The number of beds in oriental medical facilities is 1 276 or 1.05% of the total number of beds nationwide [141].

Oriental Health Insurance

July 1989 witnessed the establishment of a national health insurance system in the Republic of Korea. Oriental health insurance which was introduced in February 1987, has failed to spread as much as it might because of limited insurance coverage. For example, insurance benefits for these medicines are granted for only 68 single formula extracts out of a total of 530, and for only 56 compound formula medicines out of 250. In 1990, oriental health insurance covered only 1.1% of total treatment cases, and accounted for 0.6% of the total account of benefits. The number of cases treated under oriental health insurance has increased 4.9 times, from 320 770 in 1987 to 1 558 906 in 1990 [141].

Singapore

Although Western medicine is the main form of health care in Singapore, TCM continues to enjoy considerable popularity, but its practice is confined to outpatient care. About 12% of daily outpatient attendance is estimated

to be seen by TCM practitioners. At present, the government imposes minimal control on Chinese medicinal materials (CMM), and registration of herbal products is not required. The situation, however, will change when a system of listing Chinese proprietary medicinal products will be implemented. This control would include the issue of a product licence, an import licence, a wholesalers' licence and a manufacturers' licence including WHO GMP guidelines for herbal products. Legislation is being developed.

In July 1994, the Minister of Health appointed a Committee, headed by the Senior Minister of State for Health and Education, to review the practice of traditional Chinese medicine (TCM) and recommend measures to safeguard patients' interest and safety, and to enhance the standard of training of TCM practitioners. The Committee released its report in September 1995.

The enforcement activities currently carried out are targeted more towards safeguarding the public from toxic substances and the prevention of adulteration and exaggerated claims. As most raw herbs have low toxicity and herbs containing toxic substances are already controlled under the Poisons Act, the control of raw CMM (in terms of import, export, sale and distribution) can be maintained at the present level. For the control of Chinese proprietary medicines (CPM), the Committee recommends:

- Strengthening the control of CPM quality and safety standards. Control measures should be introduced gradually. For a start, a simplified system of product registration, generally referred to as "listing", should be implemented. This will involve the issuing of product licences for individual products and licensing local CPM manufacturers and importers/wholesalers.
- Establishing a CPM Advisory Committee under the Medicines Act to advise the Ministry of Health on the evaluation of CPM products and the granting of licences to manufacturers and importers/wholesalers. The members of the CPM Advisory Committee will be appointed by the Minister of Health and will include CMM experts.
- Setting up a CPM Listing Unit in the Ministry of Health. This unit will be responsible for processing applications for product listing and licensing of local CPM manufacturers, importers and wholesalers [127,143].

Viet Nam

Viet Nam possesses an old system of traditional medicine. Medicinal plants have made a tremendous contribution to the national health, and the Vietnamese people, especially in the countryside and the mountains, have used locally available medicinal plants for medical treatment and certain vegetables and spices as food to protect their health. The government has adopted a policy of integrating modern and traditional systems of medicine and pharmacy. To implement this policy of integration, scientific research on medicinal plants plays an important role [144].

Market Importance of Herbal Medicines

The percentage of herbal medicines prescribed in medical treatment is still increasing. Several places have already succeeded in using 100% plant-based drugs which reduces the burden of the State's subsidy on medicines. Thousands of communes have achieved a certain percentage of herbal drugs to be used in treatment, as set by the Ministry of Health. The successful combination of modern and traditional medicine has given impetus to the gradual modernization of herbal medicine to facilitate handling and promote exports. Medicines are produced from plant extracts and purified products, and they are exported as finished or semi-

finished products. All medicines prepared from medicinal plants can be used in Viet Nam as substitutes for Western drugs and Chinese herbs which, in former times, have been more important [144].

Legal Status

To ensure the quality and therapeutic efficacy of herbal drugs, the Viet Nam Pharmacopoeia, with national standards for 215 plants commonly used in traditional medical practice and 27 indigenous medicines prepared from medicinal plants, has been published by the Viet Nam Committee for the Pharmacopoeia. The monographs on medicinal plants, in addition to protocols for quality control, testing methods and storage, also include regulations on processing and formulation methods, properties, therapeutic efficacy, use, dosage and contra-indications [144].

An inventory has been made of the most important medicinal plants, so as to be able to exploit them rationally and use them properly. The results published so far give information on the remarkable progress that has been made during the past 25 years. From plants commonly used in folk medicine, 1 863 species of 238 plant families have been found. Most of them are wild species, and numerous plants are specific to particular regions and areas of the country [144].

III. CONCLUSION

The growth of the pharmaceutical industry and the unceasing development of new and more effective synthetic and biological medicinal products has not diminished the importance of medicinal plants in many societies. On the contrary, population growth in the developing world and increasing interest in the industrialized nations have greatly expanded the demand for medicinal plants themselves and the products derived from them. Regulations in countries for the assessment of the quality, safety and efficacy of medicinal plants, and the work of WHO in supporting the preparation of model guidelines in this field, have been helpful in strengthening recognition of their role in health care. It is hoped that assessment of these traditional remedies could become the basis for a future classification of herbal medicines, as well as for evaluative studies on their efficacy and safety, and their potential use in national health care systems in different parts of the world.

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