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# *FACTORS HAVING A BEARING ON THE INDUSTRIAL UTILIZATION OF MEDICINAL PLANTS FOR THE PRODUCTION OF PLANT-BASED MEDICINES**

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* *The views expressed in this paper are the author's and do not necessarily reflect the views of the Secretariat of UNIDO. Mention of firm names and commercial products does not imply the endorsement of UNIDO. This document has not been edited.*

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## 1. INTRODUCTION

Plants continue to be an important resource material for therapeutic agents both in developed and developing countries.[1-6] There are three major modes in which medicinal plants are used for health care programmes, and these include: (Figure 1)

**(a) Industrial production of phytopharmaceuticals:**

A number of drugs and medicines in the modern system of medicine, and chemical intermediates required for the manufacture of some of them, are obtained from plants, and the industrial production of phytopharmaceuticals constitutes an important segment of the modern pharmaceutical industry. Setting-up of their own phytopharmaceutical production units would be of much economic benefit to the developing countries. Similar modern phyto-pharmaceutical industry units could also be set up for production of traditional medicines needed in large quantities.

**(b) Utilization as traditional medicines:**

These medicines, mainly prepared from plants, are still used by large segments of the population in many developing countries. Their production needs to be modernized and their use integrated with modern medicines into a comprehensive therapeutic framework in each country to meet its specific health care needs. Traditional medicines may also provide remedies for diseases for which modern drugs are inadequate.

**(c) New drug discovery - Lead for new drugs:**

Plants are an important starting point in the discovery of new drugs, through leads provided by the reputed therapeutic activities of traditional remedies or generated by random biological screening of plant extracts or compounds obtained from them. Natural products continue to be a fertile source of novel chemical structures possessing useful pharmacological activities.[7]

The approach, the resources, the expertise and the manpower required for the development of each of the above three areas have to be somewhat different, and so are the social and economic functions which they fulfil. The development of each area has therefore to be linked to the needs, socio-cultural background, the resources available and the technological development status of the country.

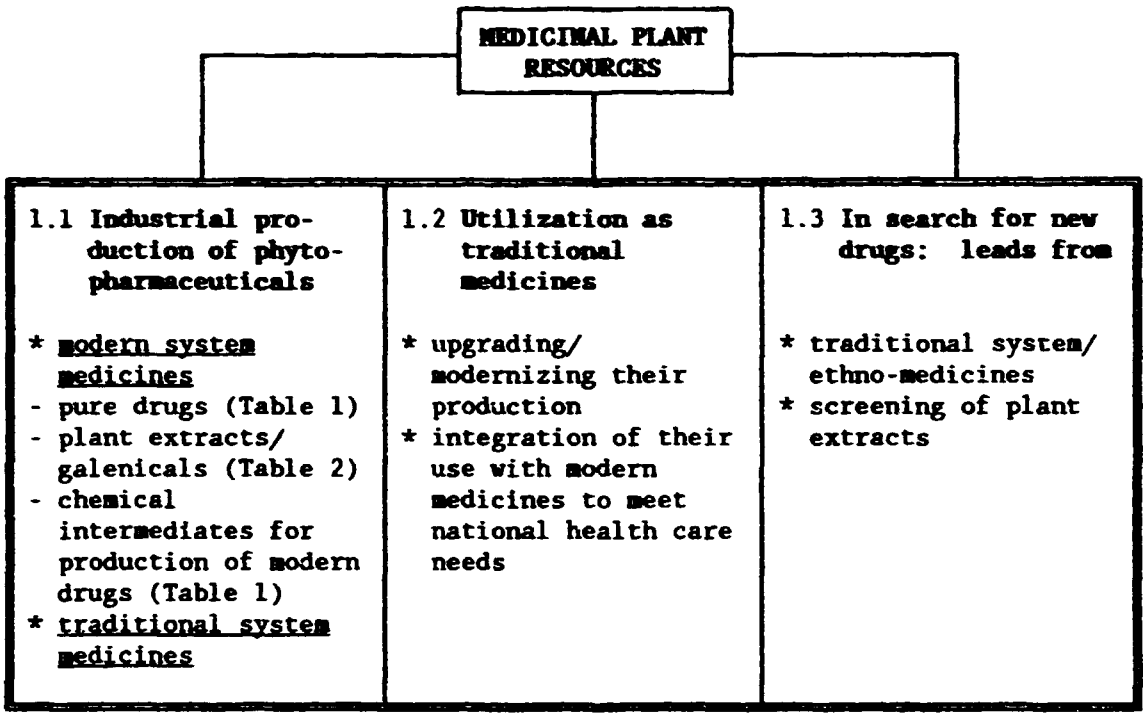


**Figure 1: Medicinal plants: Industrial production and health care**

## 2. *BACKGROUND*

*The importance of medicinal plants as a source of therapeutic agents* and a contributor to health care programmes and economies of both developing and industrialized countries is well established.[3,4,6] The history of the treatment of diseases is intimately woven with that of medicinal plants. Some of the more important facts in this regard are given below:*

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*Various terms are used for the medicines obtained from plants, often as synonyms, and it would be useful to define these terms clearly to avoid misunderstanding. **Traditional medicines** connote products having a 'long' tradition of use and include the following: **folk medicines** are products based on empirical observation or claim of medically useful effect of a plant or its product by even scientifically untrained physicians/persons; **ethnic medicines** refer to folk medicines used by a restricted cultural/regional group; **traditional system medicines** (such as Ayurvedic medicines in India or Traditional Chinese medicines in China) are based on theories, are part of a formally taught system of medicine and have a long history of documentation. **Herbal drug** is a general term for drugs prepared solely from plants and covers both modern/allopathic system drugs and traditional medicines. **Phytopharmaceuticals** is a collective name for the total extract and phytopharmaceutical preparations.

(a) *The earliest medicines used by mankind were obtained from plants, as these were available in the immediate environment. Over the millennia the most effective medicines amongst them got selected and have become part of ethnomedical traditions.*

*In many cultures, such as those of India, China and the Arab world, this experience was systematically recorded and incorporated into the materia-medicas of the organized systems of medicine that evolved in these countries, and are commonly known as Traditional Systems of Medicine.*[6-11] *A significant proportion of the population, particularly in developing countries (estimates vary from 50 to 75%) still uses these traditional medicines - some because of lack of easy access to drugs of the modern system (according to WHO estimates some 1.5 billion people have no access to modern essential drugs), but many by deliberate choice on account of their faith in them. Traditional medicines thus would help to fill the present gap between the availability of and demand for modern medicines.*

(b) *In view of the industrial as well as the health-care importance of medicinal plants, non-governmental organizations and some international organizations like UNIDO,*[3] *UNESCO and WHO,*[4] *have promoted the utilization of medicinal and aromatic plants and supported programmes in consonance with the mandates of their organizations. The thrust of UNIDO programmes in the area, reflecting its mandate to promote and accelerate the industrialization of developing countries, has been on different aspects of the industrial utilization of medicinal and aromatic plants. UNIDO assists in identifying (i) policy, economic, financial and technical obstacles to industrial development in developing countries, and provides guidance in resolving such problems; (ii) methods for the strengthening of existing and the establishment of new forms of North/South and South/South industrial co-operation; (iii) new areas and concepts for UNIDO technical assistance activities, like the development and strengthening of capabilities and capacities in research and development, transfer and development of technology, development of human resources and entrepreneurship to assure sustained growth of the industry.*

(c) *Modern drug research in Europe started in the last century with the analysis of plant-derived drugs. A number of active pure compounds obtained from these plants were accepted in the modern system of medicine; many of them are still largely used (Table 1) and form an important segment of modern pharmacopoeias; commercially feasible synthetic methods are not likely to replace the production of most of these compounds. A number of important chemical intermediates needed for the manufacture of drugs are also obtained from plants, some of which are listed in Table 1.*

**Table 1: Important plant-derived drugs used in modern medicine**

| COMPOUND | PLANT SPECIES |
|---|---|
| Ajmaline | Rauwolfia serpentina |
| Ajmalicine | Catharanthus roseus, Rauwolfia spp. |
| Artemisinine | Artemisia annua |
| Berberine | Berberis spp. |
| Caffeine | Camellia sinensis |
| Codeine | Papaver spp. |
| Colchicine | Colchicum autumnale, Gloriosa superba |
| Digitoxin, Digoxin, Digitoxigenin | Digitalis spp. |
| L-Dopa | Mucuna pruriens |
| Emetine | Cephaelis ipecacuanha |
| Ergometrine, Ergotamine | Claviceps purpureaonrye plants |
| Eugenol | Cinnamomum spp. |
| Glycyrrhizin, Glycyrrhizinic acid | Glycyrrhiza glabra |
| Hyoscyamine | Datura spp., Hyoscyamus spp. |
| Hyoscine | Duboisia spp. |
| Hesperidin | Citrus spp. |
| Menthol | Mentha spp. |
| Morphine | Papaver spp. |
| Papain | Carica papaya |
| Podophyllotoxin | Podophylum emodi |
| Quinine, Quinidine | Cinchona spp. |
| Reserpine & Deserpidine | Rauwolfia serpentina |
| Rutin | Eucalyptus spp., Fagopyrum spp., Sophora japonica |
| Santonin | Artemisia sp. |
| Sennosides A&B | Cassia angustifolia, C. acutifolia |
| Taxol | Taxus baccata |
| Vincaleucoblastine (Vinblastine) | Catharanthus roseus |
| Vincristine (Leurocristine) | Catharanthus roseus |
| Xanthotoxin | Ammi majus, Heracleum candicans |
| **Chemical Intermediates** | |
| Citral | Lemon grass |
| Diosgenin | Dioscorea spp., Costus spp. |
| Phytosterols (stigmasterol and sitosterol | Soya & Calabar beans |
| Solasodine | Solanum spp. |

*(d) The phytopharmaceutical industry uses mainly water and organic solvents for extraction and separation processes which do not cause much environmental pollution. Furthermore, this industry, needing plants as feedstock, promotes farming which not only results in environmental improvement but also in the economic uplift of the farmers.*

*(e) The structures of active constituents obtained from such plants have been an important source of novel leads for drug design; many modern drugs are based on these leads. The study of medicinal plants, therefore, continues to be an important component of modern drug research. This is of particular importance in the search for new drugs for diseases for which modern drugs are inadequate, and there is empirical evidence of efficacy of some traditional medicines/medicinal plants. Furthermore, there is a growing disenchantment with modern drugs on account of their side effects observed in several cases and their greater emphasis on treatment of the specific disease condition rather than of the patient as a whole. Thus, there is a resurgence of interest in traditional systems of medicine which have a more holistic approach to therapeutics.*

*(f) Plants are a renewable resource. With recent improvement in cultivation practices and application of tissue culture and biotechnology techniques, the yield of active constituents of plants can be greatly upgraded.*

*In view of the wide-ranging importance of medicinal plants (Figure 2), an integrated developmental approach is required to fully exploit the potential of this resource in medicare programmes and for industrial development in developing countries (Figure 3).[3,13] Therefore, the scientific, technological and industrial base of this sector should be strengthened and upgraded.*

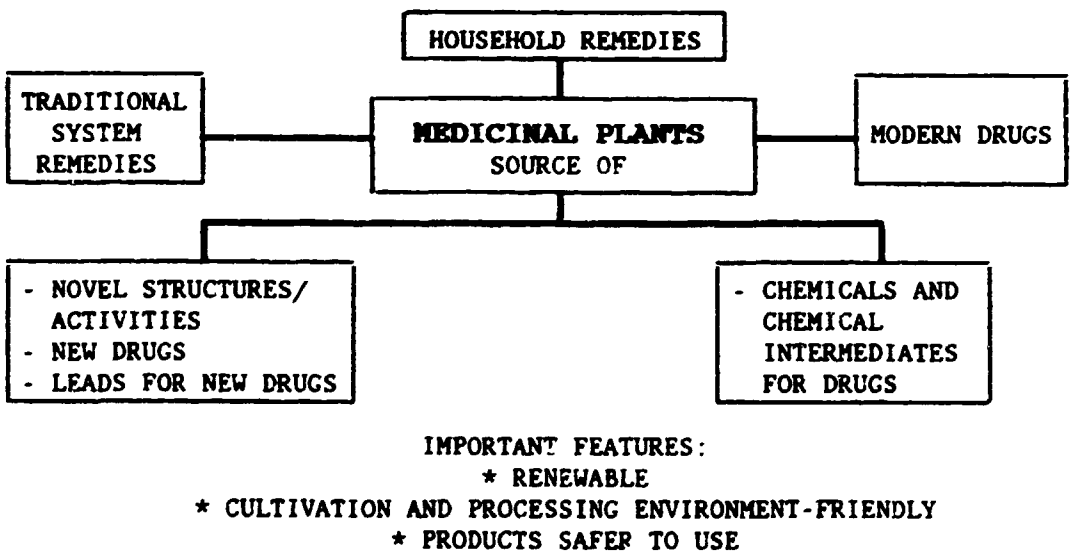


**Figure 2: A composite view of medicinal plant resources**

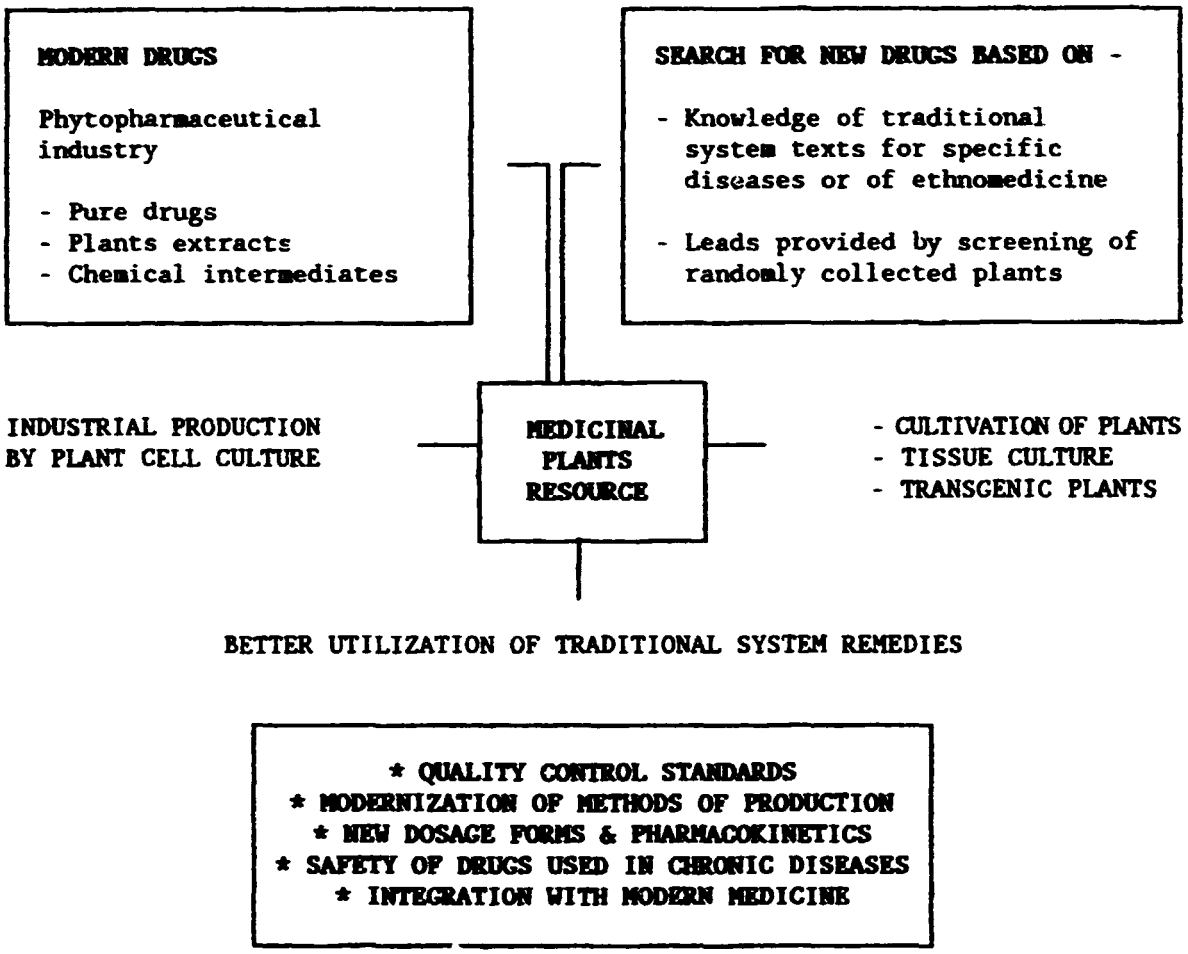


**Figure 3: Drugs from plants: integrated approach to development**

## 3. *NEED AND ROLE OF A NATIONAL POLICY AND PLANNING COMMITTEE*

*Effective exploitation of medicinal plant resources requires co-ordination between a number of sectors and consideration of some basic policy issues. It would be useful for each country to evolve a planned approach to development of this sector for which it is necessary to set up a Policy and Planning Committee. There could be a common committee for the total pharmaceutical sector, with a sub-committee for development of the medicinal plants sector, or a separate committee may be set up for this sector. This committee should have two sectional committees, one dealing with the Phytopharmaceutical Industry and the other dealing with the Development of New Drugs and Traditional Medicines. These two committees will require different expertise; the former would need more plant agronomists and pharmaceutical technologists, while the*

*latter would need medicinal chemists, pharmacists/pharmaceutists and medical scientists. These committees should draw up policy guidelines, particularly on the following issues:*

- *Collection of plants, preservation of germ plasm, and establishment of germ-plasm banks;*
- *Cultivation of medicinal plants vs. agricultural crops;*
- *Promoting the use of traditional medicines along with modern medicines in national health care programmes;*
- *System of registration of traditional medicines and drawing up a traditional drugs pharmacopoeia/formulary;*
- *Centralizing/modernizing production of traditional medicines;*
- *Establishing a phytopharmaceutical industry.*

*Based on these policies, suitable plans would have to be drawn up for collection and cultivation of plants and industrial production of drugs derived from them, taking into consideration local manpower and medicinal plant resources.*

*The Committee should co-ordinate the functioning of different institutions and agencies concerned and monitor progress towards the implementation of the policies in question. The Committee should formulate a short-term and a long-term plan for this sector and set up sub-committees dealing with specific aspects of the sector.*

## *4. TRADITIONAL MEDICINES*

*Traditional medicines and other herbal drugs not only continue to be widely used, but their use is increasing not only in developing but also in developed countries. There are several reasons for this. One of the factors is the lack of easy access to modern medicines in many developing countries, particularly their rural areas, whereas traditional medicines, being locally produced, are readily available. However, many people also use these medicines by deliberate choice on account of faith in them based on tradition and because they are part of their socio-cultural milieu. Furthermore, with political independence, there has been a renewal of interest in many developing countries in their past, including their traditional methods of health care. This almost emotional attachment to traditional medicine is also a part of the national resurgence. The tendency towards the global resurgence of interest in herbal remedies is due partly to a general disenchantment with industrialization which at times poses serious environmental threats (resulting in a movement of going back to nature) and partly to the undercurrent of dissatisfaction with modern drugs on account of the side-effects observed with many of them. Development of stronger tendencies leading towards "naturals" are also gaining ground. A recent study on the use of herbal drugs in EEC countries[4] has concluded "The EEC market for herbal medicines is a buoyant prosperous market that continues to grow at a rapid rate, offering excellent opportunities for investment in both the less developed and the more sophisticated markets". Full*

*exploitation of the opportunities offered by industrial utilization of medicinal plants would provide both therapeutic products for health care and economic benefits at different levels.*

*In view of the resurgence of interest in herbal medicines, some developed countries have even changed their drug registration rules to accommodate quality control standards and criteria which these medicines can fulfil.*

*The herbal traditional medicines which encompass folk-medicines, ethnic medicines and traditional system medicines, fulfil broadly the following functions, depending upon the specific socio-economic - cultural environment:*

- *Provision of essential drugs where modern drugs are not available;*
- *Provision of drugs for primary health care;*
- *Provision of household remedies for self-medication for minor ailments;*
- *Satisfaction of a national resurgence emotion;*
- *Provision of an alternative where modern drugs are inadequate;*
- *Provision of an alternative to modern drugs for people interested in natural products or environment friendly-products (in both developed and developing countries).*

*With this broad spectrum of functions that traditional medicines cover and the wide range of people they cater to, full exploitation of this resource requires a multipronged approach and action. It is necessary to apply the best scientific methods to ensure that their use is safe, effective and economical. The following specific points of action are necessary:*

### *4.1 Formularies and Pharmacopoeias*

*As a first step to making effective use of this valuable resource it would be necessary for each country to compile a list of all the traditional medicines that are used, their composition with the botanical names of the plants, methods of preparation and uses and to publish it as Traditional Medicines Formulary. In countries where traditional systems of medicine are widely practised it would be useful to compile Pharmacopoeias of Traditional Systems of Medicine, describing methods of standardization and quality control. This will make the products more widely accepted.*

### *4.2 Integrated use with modern medicines to meet national health needs*

*The objective of national health care is to provide effective drugs at an affordable cost to the entire population of the country irrespective of the system or source from which they are derived. It would be useful to identify and demarcate diseases for which modern drugs are more suitable and must be used, such as for acute and life-threatening infectious diseases and those where traditional medicines can provide medical relief and can be safely*

*used. All drugs, from whatever system they are obtained, should be considered for integration into a comprehensive framework to meet health care needs. A group of physicians and pharmacologists may be given the responsibility to recommend a comprehensive list of drugs to be used for different diseases.*

### *4.3 Efficacy testing*

*Though with traditional drugs there is a long-recorded experience of use, it would be useful to check their efficacy applying modern pharmacological and experimental medicine methods and also to establish their position vis-à-vis modern drugs that are available for those diseases. The following points should be observed:*

*(i) In the first instance, plants should be collected and processed in the manner in which they are used in traditional systems. Commonly used animal models may not be adequate in many situations and new experimental models may have to be developed, or straight clinical studies may be initiated after short-term safety studies in experimental animals.*

*(ii) Short-term toxicology studies on animals should be carried out.*

*(iii) If studies (i) and (ii) are satisfactory, clinical trials should be undertaken. Phases (i), (ii), and (iii) should be carried out with properly drawn-up protocols. It would be useful to come to clinical trials as early as possible.*

### *4.4 Standardization and quality control*

*The single most important factor which stands in the way of wider acceptance of traditional medicines is the non-availability or inadequacy of standards for checking their quality by chemical or bioassay methods. This also prevents modernization or modification of the methods of their preparation or production, as there is no way to establish the equivalence of the product made by the modified method with the original product. The main reason advanced for the difficulty in developing quality control standards is that most of these products use whole plants or parts of plants or their total extracts, and in some cases even a mixture of a number of plants. These medicines thus contain quite often a number of chemical constituents and it is challenging to develop suitable standards. However, analytical and bioassay techniques have advanced greatly and it is now possible to develop satisfactory quality control standards even for products containing a number of chemical constituents.*

*The products could be standardized on the basis of one or more of the following criteria:*

A. *Plant material:*

*Each plant used for processing should be properly identified and checked by its pharmacognostic and chemotaxonomic characteristics, description of the place and season of collection, the parts of the plant used and whether used fresh or dried should be recorded.*

B. *Processed Medicines:*

*The method of processing of the plant material and the galenic form prepared should be described.*

*(A) CHEMICAL ASSAY:*

*(i) qualitative and quantitative characterization of the active ingredient, if known;*
*(ii) if, however, the active ingredient is not known with certainty, the percentage of the major chemical constituents could be specified;*
*(iii) if constituents are not known, the mixture may be characterized by an analytical IR, UV, GLC, HPLC, TLC finger print to ensure a reproducible quality of the preparation;*

*(B) BIOASSAY:*

*A bioassay method may also be used wherever possible. For a number of biological activities useful bioassays, which do not take very long and can be used as a routine, are available.*

*(C) STABILITY:*

*Based on (A) and (B) the physical and chemical stability (shelf-life) during storage and transit should be determined and specified.*

*Developing suitable quality control standards is an area of priority for traditional/herbal drugs.*

*4.5 Safety assessment*

*In general, documented clinical experience of long-term use without any evidence of toxicity problems should be adequate for risk assessment. However, documented evidence of long use without associated toxicity should be available. If long-term traditional use cannot be documented, toxicity data should be generated. Moreover, in cases of medicines (a) for chronic diseases; (b) for which some adverse drug reactions have been reported; or (c) which are made from plants known to be toxic, it would be advisable to carry out some minimal animal toxicity testing to ensure safety. A close watch should be kept on possible adverse reactions as it is not safe to rely totally on evidence of prolonged use only. It is advisable to undertake a programme of carrying out toxicity studies in experimental animals of the more widely used traditional medicines.*

*4.6 Modernization of production facilities and development of new dosage forms*

*There have been many advances in process technology for extraction and separation of chemical constituents from plants as well as in pharmaceutical technology for production of new formulations and dosage forms. These advances can be and should be applied in the production of traditional medicines and their dosage forms. Connected with this is the problem of quality control standards and efficacy comparisons to ensure that the products obtained by the traditional method as well as the modified method are equivalent in efficacy, which has been discussed in para. 4.4. Traditionally, the preparation and dispensing of traditional medicines has been carried out by physicians in their dispensaries or hospitals, but that practice requires to be changed. Centralization of production in factories will ensure greater availability of the products with reproducible quality. It is therefore suggested to:*

- *Simplify and modernize methods of production;*
- *Develop appropriate quality control standards;*
- *Set up centralized units/factories for production;*
- *Develop new formulations and dosage forms;*
- *Determine pharmacokinetic, bioavailability and bioequivalence parameters, wherever possible and necessary.*

*Some countries, like India and China, have set up factories in both the public and the private sector and have modernized production technologies and introduced new formulations which have helped to enlarge the use of traditional medicines.*

*4.7 Good manufacturing practices (GMP)*

*In most countries the manufacturing premises of the pharmaceutical industry units are inspected and approved by the Drug Regulatory Authorities before they can commence production and they are also inspected periodically during the course of their operations. This ensures observance of GMP. Wherever production of traditional medicines is undertaken on a large scale in factories, these units should also be subject to the system of inspection and registration (see 5.3.3).*

*Similarly, publication of product information and promotion should be controlled by drug regulatory authorities.*

*4.8 Cost of traditional medicines*

*Keeping the cost of drugs as low as possible so that the largest number of people can use them is a major consideration in rationalization of drug policies. One of the points often cited in favour of traditional medicines is that they are inexpensive, which is not always true any more. It has been observed that some companies in the more developed of the developing countries, taking advantage of the rising popularity of traditional medicines, have started escalating their prices or making new combination medicines of unproven therapeutic value, just to charge high prices. This*

*tendency must be carefully watched by the drug regulatory authorities and kept under check. Otherwise one of the major objectives of promoting the use of traditional medicines will be defeated.*

*While determining the place of traditional medicines in national health programmes, it may be useful to carry out a case by case study of the cost benefit analysis of treatment for different diseases by the modern as well as traditional systems of medicine.*

### *4.9 Registration of phytopharmaceuticals and herbal drugs*

*It is necessary to regulate the use of all herbal drugs, irrespective of the system of medicine/therapy to which they belong or the class of physicians who prescribe them, to ensure their quality, efficacy and safety. This will create confidence in these products amongst both physicians and patients. Such regulation can best be done through a system of registration of the drugs and licensing of their manufacture as is commonly done for medicines of the allopathic (modern) system. Registration of allopathic medicines normally requires submission of a large amount of documented data regarding the product characteristics, their efficacy, safety and quality control, however, as traditional medicines are already in clinical use, submission of such data is often not considered necessary. In view of this, differential consideration has been given to the registration of different types of herbal drugs in some countries.*

*Annex II gives excerpts from Drugs Directorate Guidelines on Traditional Herbal Medicines as issued by the Drugs Directorate, Health Protection Branch, Canada. Reproduction of excerpts from the guidelines is gratefully acknowledged.*

*Phytopharmaceuticals can be broadly classified into two categories:*

*A. <u>Allopathic system (modern) drugs</u>*

*A number of drugs of the allopathic system are of plant origin and are already included in various national or European/ international pharmacopoeias. These drugs include both single compounds and extracts or tinctures. A new candidate drug (under development) is first registered with an Investigational New Drug (IND) application after all the animal biological activity and toxicological data is complete. After all phases of the clinical trials have been successfully carried out the drug is finally registered with a New Drug Approval (NDA). The requirement for data for registration at different stages are now well standardized. An indicative list of the contents for a registration dossier is given below:*

*<u>Summary</u>*

1. *<u>Introduction</u>: a brief introduction of the drug and the therapeutic class to which it belongs.*

2. *Chemical and pharmaceutical information:*
   - *botanical identification and collection;*
   - *method of extraction and composition of product and identification of active ingredients;*
   - *manufacturing process;*
   - *dosage forms and their composition;*
   - *stability;*
   - *method of assay and quality control.*
3. *Animal pharmacology/biological activity:*
   - *specific biological activity;*
   - *general pharmacology;*
   - *pharmacokinetics and metabolism wherever possible.*
4. *Animal toxicity*
   - *acute toxicity;*
   - *sub-acute and chronic toxicity;*
   - *reproductive toxicity;*
   - *mutagenicity and carcinogenicity.*
5. *Human/clinical pharmacology (phase i clinical trial):*
   - *specific and general pharmacological effects with single and multiple dosage;*
   - *pharmacokinetics.*
6. *Phase ii and Phase iii clinical trials*
7. *Regulatory status in other countries*
8. *Marketing information:*
   - *dosage forms and samples;*
   - *proposed product monographs;*
   - *drafts of labels and cartons.*

*For IND application data under points 1 to 4 are required. For NDA, normally all above-referred data are required. But for drugs which are already in use in other countries, if pre-clinical and clinical data from these countries are considered adequate, straight permission for phase III trials is generally granted. In India the registration of new drugs under this category is governed by Schedule Y of Drugs and Cosmetics (Eight Amendment), Rules, 1988, excerpts of which are given as Annex III. Excerpts of Drugs and Cosmetics (Eight Amendment), Rules 1988, relating to (i) data required to be submitted with application for permission to market a new drug and (ii) format for submission of clinical trial reports are given in Annex IV and Annex V, respectively. Reproduction of all these excerpts is gratefully acknowledged.*

## B. *Traditional Medicines*

*These include both traditional system medicines (TSM) and folk/ethnic medicines. TSM are products having a well-documented history of use in traditional systems of therapy which are formally taught, such as Chinese traditional medicine in China, Ayurvedic system in India, Nepal and Sri Lanka and the Unani Tibb system in the Indian sub-continent and in some West Asian countries. The methods of manufacture of these drugs are described in the materia medicas of the respective systems, and their long and continued use over several centuries is sufficient evidence of their efficacy and to some extent of their safety. Registration of such drugs would not pose much of a problem, so long as the identification of the*

*ingredients, individual plants used and the methods of manufacture conform to the classical texts of the relevant system, which can be referred to. As discussed in section 4.4, modern quality control/ assay methods could be added to the documentation to ensure the reproducible quality of the products. These drugs could thus be registered as Traditional Medicines (or under the names used for such medicines in that country such as Traditional Chinese Medicine in China) without requiring submission of freshly generated data on efficacy or safety of such products.*

*In addition, there are recently introduced herbal drugs which are based on the knowledge of the traditional systems of medicine, but deviate to some extent from the documented prescriptions. These, too, may not have been subjected to extensive preclinical toxicology and Phase I-III clinical evaluations. Such drugs cannot be considered strictly as traditional system drugs and certainly not as modern pharmacopoeial drugs. These drugs could also be considered as part of a traditional system of medicine provided there is commonality of the plants used in their preparation with those used for traditional system drugs. Still enough data should be provided to the regulatory/registration authorities on the toxicity and quality control of the products so that their safety can be ensured and the method of manufacture should be reproducible. These could thus also be registered under Traditional Drugs but should have some additional data on safety and quality control.*

*Medicines which are not listed/mentioned in the texts of the traditional systems of therapy, but have a long history of use (at least 50-100 years) with authentic records of safety and efficacy, may also be registered on the basis of this evidence. For all other products, if documented evidence is not available, sufficient data on methods of manufacture, preparation of dosage forms, safety and efficacy should be generated and provided to the registration/regulatory authorities for evaluation before such products can be registered.*

*There are also products like household remedies, not covered by the above categories, which are commonly used for minor ailments such as coughs and colds, as digestives and carminatives or as balms, without consulting a physician. These could be registered as OTC products in the Traditional Medicines category or as Health Foods. It is advisable to limit the number of remedies in this category to the minimum, so as to avoid multiplicity of the products.*

*In view of the great need for employing phytopharmaceuticals to meet the health care needs, particularly in the developing countries, the approach to their registration should be flexible and the regulatory laws fragmatic, so that without compromising with safety, the drugs can be used for the greatest possible benefit of the community. In India, drugs of the traditional systems (Ayurveda, Siddha and Unani), prepared according to specified classical texts of these systems, are registered and licensed for manufacture separately from modern drugs." The resurgence of interest in phytopharmaceuticals in industrialized*

*countries has also prompted many of these countries to have special provisions for registration of herbal preparations, such as in Germany and Canada. They no more insist that a herbal drug should be a pure single compound; a fraction or extract of a plant can be registered as a new drug so long as there is evidence of a therapeutic gain over known drugs and there is enough evidence of safety and the medicine has appropriate quality control standards.*

## 5. *THE PHYTOPHARMACEUTICAL INDUSTRY*

*In modern medicine a number of drugs derived from plants are used mainly as pure compounds and some as standardized extracts or tinctures. Table 1 lists important pure plant products and Table 2 standardized extracts that are currently in therapeutic use in modern medicine. In traditional medicine, however, the whole plant or part of a plant is used as a powder, decoction or extract; a single plant or a mixture of plants may be used. The technology and equipment required for the production of most of these plant products is relatively simple. Most developing countries could set up manufacturing units for the manufacture of these products, which will help both in health care as well as in economic improvement. The specific products to be manufactured and the product mix would depend not only upon the availability of the plants, naturally growing or through cultivation, but also on the prevailing disease patterns in those countries. Depending upon the technological status of the country's industry, the production of standardized extracts could be taken up first, to be followed by that of pure compounds. There is a market for both extracts as well as purified products. The isolation of pure constituents or standardized fractions would of course provide added value and wherever necessary and possible should be carried out. In the case of traditional system remedies it would be useful to modernize their production, develop appropriate formulations and dosage forms and establish quality control standards.*

### *5.1 Criteria for selection of products*

*Some criteria for the selection of products for industrial production based on medicinal plants as raw material are given below:*

- *The medicinal plant required for production should be readily available through spontaneous growth or by cultivation in the country or region.*
- *The drug should be widely accepted and used and/or required to treat diseases prevalent in the country.*
- *The drug derived from the medicinal plant should be safe, approved by the national registration body or its use endorsed by WHO.*
- *Treatment cost with the drug should be competitive with that by synthetic drugs of similar therapeutic category.*

- *Production of the drug should offer some long-term economic benefits such as import substitution or export earning. Technology and/or know-how for its commercial production should be available from indigenous source or on easy terms for import.*

- *Export possibilities of medicinal plants or products derived therefrom to other developing and/or industrialized countries should be an important consideration.*

- *In the case of investigational/candidate drugs, production should be considered only after the clinical efficacy has been established/validated.*

**Table 2: Plants used for production of total or purified standardized extracts for modern medicine**

| PLANT | STANDARD EXTRACT |
|---|---|
| Aloe spp. | Extract containing 20% hydroxy-anthracenones calculated as aloin. |
| Atropa belladonna | Extract containing 1% alkaloids calculated as hyoscyamine. |
| Cassia angustifolia | Extract containing 45% sennosides calculated as sennoside B. |
| Capsicum annum | Oleoresin containing 8-10% capsaiccin. |
| Centella asiatica | Extract containing 70% triterpenic acids. |
| Cephaelis ipecacuanha | Extract containing 6% alkaloids calculated as emetine. |
| Commiphora mukul resin | Standardized ethyl acetate extract containing 5-7% guggulsterones. |
| Digitalis spp. | Digitalis total extract. |
| Glycyrrhiza glabra | Extract, total or purified. |
| Ginko biloba | Teborin for cardiovascular problems. |
| Hyoscyamus niger | Extract containing 1% alkaloids determined as Hyoscyamine. |
| Panax ginseng | Extract containing 10% saponins calculated as ginsenoside Rg 1. |
| Valeriana officinalis<br>Valeriana wallichii | Extract containing 1.3% and 0.75% Valepotriats. |
| Zingiber officinalis | Total extract/oleoresin |

## *5.2 Cultivation of Medicinal Plants"*

*Medicinal plants form the feedstock for both traditional medicines as well as for modern plant-derived drugs. The availability in adequate quantity of medicinal plants of the appropriate quality is very often a limiting factor in the success of a phytochemical industry. Their long-term availability has therefore to be assured. It is emphasized in the texts of traditional systems that the quality of a medicine is determined by the natural environment in which the plant normally grows. It is well established that the chemical constituents of a plant are greatly affected, qualitatively and quantitatively, by its geographical location and season/time of collection. However, no phytochemical industry, whether for modern drugs or for traditional medicines, can be built on naturally growing plants for lack of assured supply and danger of species depletion. Furthermore, no improvement in quality of plant variety would be possible unless cultivation is undertaken. What is, therefore, more pertinent is to fix the criteria for the quality of the plant, and ensure that the cultivated plant meets those standards. A number of plants commonly used in the traditional systems of medicine in India and elsewhere are already on the endangered list. An illustrative list of plants for which cultivation may be required is given in Table 3.*

**Table 3: Plants widely used in modern and traditional medicines which need to be cultivated**

1. Achyranthes aspera
2. Aconitum heterophyllum
3. Acorus calamus
4. Aloe vera
5. Anacyclus pyrethrum
6. Andrographis paniculata
7. Asparagus recemosus
8. Atropa belladona
9. Azadirachta indica
10. Berberis aristata
11. Boswellia serrata
12. Capsicum annuum
13. Cassia spp.
14. Catharanthus roseus
15. Cephaelis ipecacuanha
16. Cinchonna sp.
17. Commiphora wightii (syn.C.mukul)
18. Crocus sativus
19. Datura metel
20. Digitalis lanata
21. Dioscorea spp.
22. Duboisia myoporoides
23. Ephedra gerardiana
24. Gentiana kurroo
25. Gloriosa superba
26. Glycyrrhiza glabra
27. Meusae nagassarium
28. Mucuna pruriens
29. Ocimum spp.
30. Papaver somniferum
31. Phyllanthus amarus
32. Picrorrhiza kurroa
33. Piper longum
34. Plantago ovata
35. Podophyllum hexandrum
36. Rheum emodi
37. Sophoa japonica
38. Swertia chirata
39. Terminalia spp.
40. Valeriana wallichii
41. Withania somnifera
42. Zingiber officinalis

*Connected with availability is also the need for genetic improvement of the species for special characters such as increase in yield of the active constituent. For example, digitalis plants have been selected which yield mainly digoxin or digitoxin and ergot strains yielding mainly ergotamine or ergometrine. The success of the industry based on medicinal plants has depended largely on the development and propagation of special varieties of plants.*

### 5.2.1 Economic Mapping

*It would be desirable to carry out a quantitative survey of the natural availability of selected plants. Such economic mapping would provide useful information needed for setting up production units and also about the availability of the original germ plasms, on which will depend the steps that should be taken to preserve them.*

### 5.2.2 Tissue culture and plant biotechnology for improved cultivation of plants[14,15]

*The recent developments in clonal micropropagation of plants through tissue culture techniques has been of great help in the cultivation of medicinal plants by providing planting material of standard quality. Some of the medicinal plants which have been successfully cultivated through tissue culture techniques are Cephaelis Ipecacuanha, Rauwolfia serpentina, Dioscorea spp., Valerian, Hyoscyamus niger, Duboisia spp., Solanum spp., and Cinchona. Recent advances in biotechnology for producing transgenic plants have added a new dimension to plants as a source of pharmaceutical products. These are some of the priorities of R&D connected with the cultivation and improvement of medicinal plants.*

*The number of medicinal plants of well established economic value required in large quantities is around 50, and priority should be given to the cultivation of these plants to ensure their availability.*

### 5.2.3 Marketing and management

*Successful cultivation of medicinal plants is dependent on a management system for collection, storage and marketing of the plants. A marketing organization should, therefore, be considered to be an integral part of the cultivation of medicinal plants. Moreover, apart from their use as feedstock for local industrial production of phytopharmaceuticals, there is a big world trade in medicinal plants per se, and so export of medicinal plants as such, but preferably of their value added products, can provide much economic benefit to the developing countries.*

### 5.2.4 Plant cell cultures for industrial production of natural products"

*Plant cell culture provides a useful alternative approach/ source for obtaining natural products. Plant cell culture has been used in three principal ways for obtaining natural products:*

*(1) as an alternative source for established products;*
*(2) as a source of lead compounds;*
*(3) as a biotransformation system for obtaining drugs from precursor molecules.*

*Significant progress has been made in the last decade in plant cell culture technology and a number of plant products have been produced in this way which include: Catharanthus indole alkaloids, shikonin, nicotine, anabasine, L-dopa, valepotriates and berberine; of these perhaps shikonin is the only one which is commercially produced on a large scale by this technique. The main reason for lack of commercialization of this technology is the long process time for plant cell systems and consequently the high labour costs. However, the system in principle is very promising, and should be investigated as a credible alternative both for production of established products as also to provide key biotransformation enzyme systems. Proper economic assessment of the viability of each system has to be carried out.*

### 5.2.5 Research Institute for Introduction of New Medicinal Plants

*The establishment of a phytopharmaceutical industry is thus closely linked with the cultivation and availability of medicinal plants of the right quality which requires many R&D inputs on a continuing basis. As the scientific expertise required for cultivation and related scientific disciplines is different from that required for production, it is suggested that developing countries should consider setting up separate research institutes for work on different aspects of medicinal plants (loc. cit.). Countries such as China and India (e.g. Central Institute for Medicinal and Aromatic Plants, Lucknow, India) have made a considerable contribution to improving existing indigenous plant species and introducing plant varieties in their respective countries and establishment of a phytopharmaceutical industry. The main objectives of such a research institute should be the following:*

- *Economic mapping of important medicinal plants;*
- *Preservation of germ plasm;*
- *Improvement of varieties by (i) classical selection; (ii) clonal propagation; (iii) genetic recombination;*
- *Introduction of new varieties by classical or tissue culture methods;*
- *Use of plant cell cultures for industrial natural products;*
- *Standardization of post-harvest technology for preservation and transport of plants;*
- *Documentation and dissemination of information and liaison with industry.*

## 5.3 Industrial production

Plants are used in medicines mainly in one of the following forms:

(a) Crude drug: Fresh or dried powder as such or formulated;
(b) Extract: Fresh juice, extract or decoction, tincture, galenical, or dried extract formulated as tablets, capsules and syrups both as traditional and modern drugs;
(c) Pure constituent: (a) as drug, mainly in modern system of medicine; (b) as chemical intermediates for semi-synthetic production of drugs.

The industrial production, therefore, covers the following types of products:

(a) Bulk medicinal products:

- Standardized powder of dried whole plants or parts thereof;
- Traditional medicines made from a single plant or mixture of plants according to indigenous pharmacopoeias;
- Extract or galenical forms used as modern drugs;
- Pure compounds for use as modern drugs.

(b) Formulations and dosage forms from bulk medicinal products as described above under (a).

### 5.3.1 Production of bulk medicinal products

The industrial production of bulk medicinal products can be carried out in a multi-purpose plant capable of carrying out a number of unit operations such as the following:

- Comminution of plant material (crushing, pulverizing);
- Aqueous/alcoholic percolation/extraction (batchwise/continuous);
- Concentration and removal of solvent/recovery of solvent;
- Drying of product;
- Steam distillation of volatile constituents;
- Separation of volatile water-immiscible oils;
- Filtration and purification by crystallization;
- Fractional distillation.

It is useful to set up a multi-purpose pilot plant which can carry out all these unit operations. UNIDO has prepared detailed drawings for the fabrication of a versatile distillation cum extraction unit for processing of medicinal and aromatic plants and these engineering drawings could be made available to interested countries.[17] It is expected that such pilot plants would lead to setting-up of industrial units utilizing locally collected/ cultivated plant species. The UNIDO pilot plant is of simple design and construction and can be easily fabricated, installed, operated and maintained. It has been designed as a frame mounted package unit for carrying out various unit operations involved in

*extracting flavour, aroma and medicinal constituents from plant material. An illustrative list of basic equipment for such a pilot plant is given in Annex I.*

*The operations that can be carried out either successively or simultaneously are:*

- *Steam distillation and separation of essential oils;*
- *Fractional distillation of essential oils;*
- *Percolation with a solvent at ambient temperature;*
- *Hot solvent extraction by the soxhlet method;*
- *Extraction by repeated leaching with hot or cold solvent;*
- *Filtration;*
- *Vacuum concentration of the extract;*
- *Solvent distillation and recovery.*

*Production of extracts or steam distillates requires simple technology and can be carried out by a technologist with basic qualifications under the supervision of a chemical engineer. Separation and isolation of pure chemical constituents on a large scale are more sophisticated processes and require a higher level of chemical and engineering skills. In most cases the technology could be developed indigenously, in-house by the industry, if it has a good R&D section, or by referring the problem to academic institutions, chemistry departments of universities, schools of pharmacy or engineering institutions; in some cases it may be advisable to import the technology and then build on it.*

### *5.3.2 Formulations, dosage forms and packaging*

*The formulation unit can be coupled with the bulk production plant or it can operate as a separate unit. It would be more or less like any modern pharmaceutical formulation plant with the only difference that the raw materials used will be bulk medicinal products. The general impression that a formulation unit producing traditional medicines need not be very sophisticated is totally misplaced. Any formulation plant producing drugs for human consumption must follow good manufacturing practices (GMP) to ensure safety of the products. Moreover, formulation of plant extracts poses some special problems, and to make modern formulations from them requires a high level of technology, certainly no less than that required for formulating modern system drugs.*

*Annex I gives an illustrative list of equipment which would be required for a formulation plant making tablets, capsules, syrups and ointments catering to the needs of a population of about 1 million.*

### *5.3.3 Good manufacturing practices (GMP)*[18]

*The quality and safety of pharmaceutical products is ensured by following proper procedures for inspection and checks before, during and after manufacture; these cannot be ensured by mere one-*

*time inspection at the end of processing. This facet is becoming increasingly emphasized and thus some voluntary and some statutory codes have been developed to ensure observance of GMP.*

*Without going into details, some definitions and points which have relevance to good manufacturing practices are listed below for general guidance.*

***Premises:*** *Building should be located in clean/healthy surrounding, and designed, constructed, adapted and maintained to suit the operations carried out therein.*

***Equipment:*** *Equipment, including services and containers, should be designed, constructed, adapted, located and maintained to suit the processes and products for which they are used.*

***Personnel:*** *Staff employed must have the requisite qualifications and training, and must be available in adequate numbers to suit the production processes and products which are produced.*

***Good housekeeping and loss prevention:*** *Facilities, systems and procedures should meet a high standard of safety, orderliness and hygiene and comply with the loss prevention policy of the organization.*

***Production procedures and documentation:*** *Processes and procedures must be clearly described in master documents and kept carefully. Such documents must only be amended on the written instructions of authorized persons. The procedures followed and the results obtained for each manufacturing batch must be immediately recorded in the notebooks provided for this purpose, and should be available for checks and inspection.*

***Quality control:*** *A defined quality control system should exist, comprising checking of all incoming materials and finished products, and independent overseeing of processes and examining of samples of finished products. The person in charge of quality control should be directly responsible only to the top management.*

### *5.3.4 Research and development*

*The pharmaceutical industry is highly research and technology based. It is most important that the pharmaceutical industry units should have adequately equipped research and development laboratories. The investment in R&D would, of course, vary from unit to unit depending on availability of resources, human and financial. It is only then that the indigenous industry can grow properly, solve day-to-day problems, assimilate imported know-how and develop new technology. For this purpose, establishment of separate R&D institutes and linking them to various units of industry would also be of help.*

*The emphasis of R&D should be on the following:*

- *Development of technology for bulk production of medicinal products;*
- *Development of quality control standards for the starting materials as well as for the finished products;*
- *Development of new formulations and dosage forms specially suited to the prevailing climatic conditions and adapted to locally available raw materials;*
- *Assimilation of acquired technology and its continuous improvement to make the products competitive;*
- *Bioequivalence, bioavailability and pharmacokinetic studies on the dosage forms developed;*
- *Search of new plant sources for known drugs and for new drugs from locally available plants.*

*Given the situation in most developing countries, production of standardized plant fraction should have priority over that of pure active substance, because of the simple technology needed and hence lower cost of the product, provided of course the toxicological testing indicates that the product is safe. It would be advisable to find out the chemical composition of the composite fraction and the pharmacological action of each constituent to ensure that they are safe and compatible with each other.*

*In view of the high capital and recurring costs of R&D, collaboration among developing countries and between developed and developing countries is advisable.*

*5.3.5 Human resource development and infrastructural build-up*

*Industrial production and marketing call for a wide range of experience and expertise. The availability of suitably trained personnel is a critical factor in starting and operating pharmaceutical industry units and establishing a marketing organization. Both technologists and management experts are required. It is important for each country to devote attention to human resource development for this purpose. Possibilities of co-operation between developed and developing countries and among developing countries for imparting such training in all principal areas, such as agro-technology, process technology, engineering, quality control, pharmacological testing, etc. at all levels should be explored. In addition, the facilities for training at regional/interregional levels provided by international organizations like UNIDO, WHO, UNESCO and ILO, should be fully used. The facilities provided by these organizations include provision of training fellowships and supporting organization of seminars and workshops to promote a wider use of herbal medicines.*

*Training in conduct of clinical trials could be provided by setting up clinical pharmacology centres in developing countries, jointly by institutions in developing and developed countries, for trial of plant-derived medicines. The approach to human resource development has to be comprehensive and multifaceted and may need to include industrial infrastructure, for which it may be necessary to strengthen existing or establish new industrial and*

*technological institutions. Training of administrative staff in business management and marketing is desirable which could be done through business management schools.*

## *6. MEDICINAL PLANTS IN RESEARCH FOR NEW DRUGS*

*Modern drug research began in the last century with phytopharmacological investigations of plants reputed for their medicinal properties in traditional or folk/ethnic medicine. Pure active constituents were isolated, many of which are still used as drugs in modern medicine. These include codeine, digoxin, emetine, ephedrine, morphine, quinine and quinidine. Structures of the constituents provided the first leads for structure-activity relationship studies and resulted in the synthesis of analogs with greatly improved activity. This indeed set the direction of future drug research which, broadly speaking, is still being followed. It would not be an exaggeration to say that most modern synthetic drugs are in some way based on the structure of active compounds from plants, which still continue to be an important source of leads for drug design. However, in spite of the tremendous advances made in drug research, modern synthetic drugs are still not available or adequately suitable for several conditions such as liver disorders, degenerative diseases, rheumatic conditions, some central nervous system diseases and diseases involving the immune system. The traditional system of medicine seems to have effective drugs in these areas which are useful leads worthy of investigation.*

*Research on traditional drugs thus is aimed at: (a) Developing new drugs acceptable to modern physicians, particularly for diseases for which modern drugs are not adequately suitable and available, and (b) Modernizing traditional drugs to increase their acceptance and usefulness. The approaches to the two objectives are somewhat different and are schematically described in Figure 4.*

### *6.1 Traditional medicines as a lead for new drugs*

*It has been the general experience in drug research that the success rate in the discovery of new drugs is greater when research is based on leads provided by the activity of medicines used in traditional systems. It is therefore prudent that authentic literature as well as practitioners of traditional medicines systems should be consulted when choosing medicines which could serve as leads and these medicines should then be investigated keeping in view the following:*

- *In the first testing the medicines as prepared traditionally should be tested;*
- *The fractionation process should be monitored by bioassays;*
- *Generally used pharmacological test systems may not be suitable and new testing models may need to be developed;*

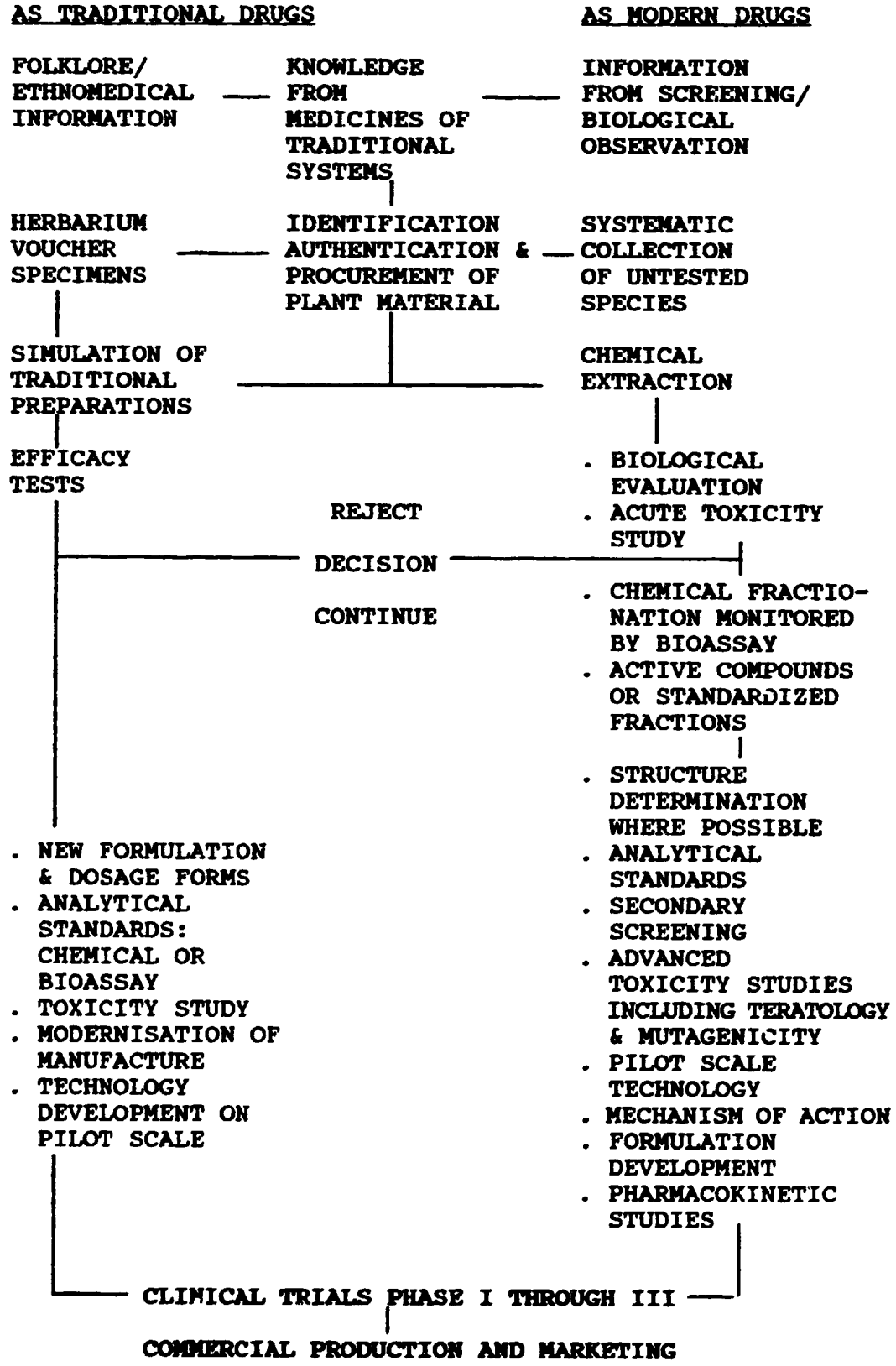


**Figure 4: Stages in drug development from medicinal plants**

- *Undue emphasis on using pure compounds as drugs are unnecessary; standardized fractions could be used, and may even be preferred because of lower processing cost and possible synergistic action of various components as present in the plant; however, all constituents and their physiological actions should be known and the product should have appropriate quality control criteria.*

*An illustrative list of therapeutic categories for which new drugs are needed is given below. The development of these drugs could be based on leads provided by traditional medicines.*

1. *Antimalarials (especially tissues schizontocides for vivax malaria and blood schizontocides for multidrug-resistant falciparum malaria)*
2. *Antifilarials (especially macrofilaricides)*
3. *Antirheumatics*
4. *Immunomodulators*
5. *Antivirals*
6. *Anticancer agents*
7. *Wound-healing agents*
8. *Agents for degenerative conditions and mental retardation.*

*Immunomodulators and hepatoprotectors are of particular importance as traditional systems of medicine give more emphasis to health promoters curative drugs. Certainly not many modern drugs are available in these areas.*

### *6.2 Improvement of traditional drugs*

*There is much scope for improving the method of production and presentation of traditional medicines. The R&D effort for this purpose should be directed, in particular to:*

- *Developing quality control standards;*
- *Modernizing/simplifying methods of manufacture;*
- *Developing better formulations and dosage forms evaluated by bio-equivalence and pharmacokinetic studies;*
- *Generating minimal safety/toxicity and clinical efficacy data.*

*This will greatly widen the acceptance and usefulness of traditional medicines.*

### *6.3 Systematic biological screening of plants for generation of new leads*

*The number of plants used for preparing traditional remedies in various countries or those tested for biological activity constitute only a small fraction of the plant resources of the world. It is estimated that only about 5,000 of the 30,000 plant species known have so far been screened for their biological activity. Moreover, even in the case of plants that have been screened, one has to bear in mind the well-known possibility of variations in the chemical composition of the same plant growing in different soils and climatic regions. It is, therefore, necessary for every country to undertake systematic biological screening of all its plant species from different climatic and soil zones. It*

*must be emphasized that the collection, storage and processing of plants must be done in such a manner that their chemical constituents are not affected. Bioassays and test systems have to be developed so as to measure even weak activities due to minor constituents. The biological test systems employed should be relevant to the disease conditions of special concern to the country and for which satisfactory drugs are not so far available. The above approach is quite different from the classical phytochemical investigation of medicinal plants where the primary objective is the isolation of pure chemical constituents and their characterization and structural elucidation; testing for biological activity of pure constituents is only subsidiary. In contrast, the biological screening approach involves monitoring for biological activity at every step of chemical fractionation/ isolation. The active plant constituents thus obtained may not always possess an acceptable pharmacological/toxicological profile, but their structures could serve as leads for synthesis of new therapeutic agents. Screening of plants has in fact provided many leads in the history of drug research and continues to do so today. Plants are a reservoir of novel chemical structures and a fertile source of bioactive compounds and useful leads for drug design.*

## *7. REGIONAL CO-OPERATION IN MEDICINAL PLANTS RESEARCH CENTRES*

*The overall pharmaceutical industry is highly research-based. Both products and production technology have a high rate of obsolescence. Continuous R&D inputs are the key to the success of the pharmaceutical industry. The industrial units of most developing countries are rather small and do not have the necessary financial resources to set up high-technology R&D laboratories which require high capital and recurring investments. Hence, this is an area in which regional collaboration among developing countries or even between developed and developing countries would be most desirable. Starting with development of process technology, this collaboration could be gradually extended to research in the development of new products. One form of co-operation could be the establishment of regional research institutes. It is important for developing countries to also undertake research for development of new drugs from medicinal plants. This type of research requires a multidisciplinary team of organic chemists, pharmacologists, biochemists, chemical technologists, pharmaceutical scientists, toxicologists, clinical pharmacologists and clinicians working together. Research directed to discovery of new drugs has become highly cost- and time-intensive; on an average, the development of one new drug, whether synthetic or obtained from a plant, costs around US$100 to US$150 million and a time span of 10-12 years. Drug research being so costly, the pharmaceutical companies of the industrialized countries have become highly selective in the choice of their research projects, and carry out practically no research on new drugs for tropical diseases or population control, which are the major problems in developing countries. This underscores the imperative and urgent attention developing countries should give to development of drugs for their specific needs. Not many developing countries have well-trained scientists in all the disciplines mentioned above, or the resources to undertake research to develop*

*new drugs. The only way of doing this successfully would be by active collaboration among the developing countries of a region by establishing regional research institutes. To begin with, an existing laboratory having the core facilities could be identified and a nucleus of this regional centre created in this laboratory with scientists from member countries working together. As the work progresses, this centre could become a separate full-fledged institute.*

*Such a centre should have the following main objectives:*

***Phase 1:***

- *Survey of plant resources of the region and dissemination of this and related information;*
- *Continuous provision of updated information on the methods of production of plant products, such as extracts, powders, tea bags and simple dosage forms;*
- *Drawing-up joint R&D plans for industrial utilization of medicinal plants of the region; development of technology for production of known plant drugs, modern or traditional;*
- *Monitoring the progress of joint R&D programmes;*
- *Developing close links with the industrial units of the region producing plant-based products.*

***Phase 2:***

- *Setting-up experimental farms for cultivation of medicinal plants, and tissue culture centres;*
- *Initiation of development of new drugs from medicinal plants for diseases of particular relevance to the region;*
- *Establishment of a liaison with research laboratories in the region and in particular with international centres for genetic engineering and biotechnology to work on production of plant products through cell culture technologies and to develop improved plant varieties through recombinant DNA techniques.*

*Such regional R&D centres could have the following scientific sections:*

- *Phytochemistry*
- *Molecular Biology*
- *Parasitology*
- *Pharmaceutics*
- *Economic Botany*
- *Toxicology*
- *Clinical Pharmacology*
- *Process Development*
- *Pilot Plant and Project Engineering*
- *Farm & Tissue Culture Laboratory.*

## 8. CONCLUSIONS AND RECOMMENDATIONS

*Medicinal plants continue to provide valuable therapeutic agents, used both in modern medicine and in traditional systems of medicine, and also offer good prospects of discovering new drugs. Establishment of a phytopharmaceutical industry manufacturing these therapeutic agents will not only lead to their greater availability for health care programmes but also result in economic growth. The following steps are therefore recommended:*

*(a) Cultivation of medicinal plants needed for processing, and their genetic improvement;*
*(b) Modernization of manufacture of traditional remedies by promoting their production in factories, with proper quality control standards, and integrating the use of these standardized remedies with modern system drugs in national health-care programmes;*
*(c) Establishment of a phytopharmaceutical industry to manufacture standardized plant extracts and pure active compounds used in modern medicine;*
*(d) Promoting R&D for the development of technology for production of medicinal plant products of established therapeutic value and also for discovering new therapeutic agents based on leads provided by traditional system remedies, and systematic broad spectrum biological screening of the flora of the country; and to this end foster co-operation between academic institutions and R&D laboratories within each country and of the region;*
*(e) Promoting the establishment of a co-operative Regional Medicinal Plants Research Centre to provide a backup for the above activities.*

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**ANNEX I**

## Equipment for phytochemical units for processing about 500 tons plant material per annum

Land: 2 acres
Building: 10,000 sq. ft.

**EQUIPMENT**

| Item for Utilities | Capacity | No. |
|---|---|---|
| Boiler | 500 kg | One |
| Compressor | 5 HP | Two |
| Industrial vacuum | 760 mm | Two |
| Chilled water supply | 50 tons | One |
| Misc.: laboratory services and workshop | - | |
| Plant washing machine | - | One |
| Crusher/cutter | - | One |
| Drying machine | - | One |
| Micropulverizer hammer type | - | One |
| S.S. extractor, with stirrer, condenser, storage tank, concentrator | 1000 lit. | One |
| S.S. soxhlet, with condenser and stirrer | 100 lit. | One |
| Vacuum still for concentration, etc. | 20 lit. | One |
| Spray drier | - | One |
| Electrically heated shelf, drier, 12 trays | - | One |
| S.S. vacuum drier 12"x16" | - | One |
| Centrifuge, basket type | - | One |
| Jacketed glass lined | 250 lit. | One |
| Reactor with a stirrer | 100 lit. | Each |
| Glass lined open pans for crystallization | 200 lit. | Two |
| Misc.: glass apparatus, chromatography columns instruments, storage tanks for solvents, storage bins for plant materials, percolators | | |

ANNEX II

## Excerpts from Drugs Directorate Guidelines Traditional Herbal Medicines*

### 1. Introduction

The term "Traditional Herbal Medicine" refers to herbal medicinal products that have received relatively little attention in world scientific literature, but for which supporting references have been found acceptable by the Health Protection Branch (HPB).

The purpose of this guideline is to assist manufacturers in completing an application for a Drug Identification Number (DIN) and in labelling products that fall within the category of Traditional Herbal Medicine (THM).

Before a DIN is assigned to a drug, a proposed label should be submitted, together with a completed DIN application. The information provided in Section 2 can be used in preparing both the application and the label.

#### 1.1 Obtaining an Application for a Drug Identification Number (DIN)

The manufacturer must submit a DIN application form in order for a DIN to be issued.

DINS and Drug Notifications are recorded and used to keep current information on drugs sold.

#### 1.2 Submitting the Information

On the basis of the information contained in and submitted with the manufacturer's application for a DIN, a determination on the status of the THM product will be made by HPB. The manufacturer will be advised by letter of the outcome of the review. The Directorate tries to evaluate submissions within 90 days of the date that the DIN application is received.

### 2. DIN Application and Labelling

The information in this section is provided to facilitate the review and processing of applications for DINs, as well as to assist in the preparation of a draft label. Failure to provide the appropriate information and sufficient detail for either the DIN application or the label could result in processing delays and additional correspondence.

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* Published by the Health Protection Branch, Health and Welfare, Canada, 1990.

*2.1 Identifying the Ingredients*

*Each herbal ingredient should be identified by*

*a) giving both its common and botanical (Latin) name;*
*b) specifying the part of the plant used (e.g. leaf, root, berry, bark), as the pharmacological properties of different parts of plants vary and the appropriate dosage may differ;*
*c) specifying the form in which the plant is present (e.g. powdered extract, fluid extract, tincture, dried leaf).*

*2.2 Medicinal and Non-Medicinal Ingredients*

*Where appropriate, the list of ingredients should be divided into medicinal and non-medicinal ingredients. Medicinal ingredients may be herbal or chemical in origin; they represent the active pharmacological principles responsible for the action of the product. Non-medicinal ingredients include excipients, fillers, flavours, and so on.*

*2.3 References*

*The references used to support the use of each herb in the formulation and that herb's recommended dosage should be provided with the application.*

*2.4 Quantitative Declaration of Ingredients*

*The manufacturer should provide a quantitative listing of medicinal and non-medicinal ingredients per dosage unit. The actions of similarly acting herbs (e.g. diuretics) are often additive in nature, and some herbs, although individually present in small amounts, may be considered medicinal ingredients if they contribute to the overall effect of the herbal drug.*

*For both the DIN application form and the label, the method of declaring the quantity of each ingredient should be the same and should take one of the following forms:*

*a) In the case of solids (powder), give the weight of each herb per gram and per dosage unit.*

*b) In the case of teas, give the weight of each herb per gram and per dosage unit (e.g. teaspoon or teabag).*

*c) In the case of liquids for oral use, give the weight of each herb per millilitre and per dosage unit.*

*d) In the case of drops, give the weight of each herb per millilitre. Also give the number of drops per millilitre, because this number will vary with the dropper size and the viscosity of the liquid.*

*e) In the case of capsules, tablets, or other discrete dosage forms, give the weight of each herb per dosage unit.*

*When the concentration of each ingredient is written as a percentage, the label and the application should also specify whether the figure refers to weight/volume (w/v), volume/volume (v/v), or weight/weight (w/w).*

*2.5 Quantitative Declaration of Extracts or Tinctures*

*When declaring quantities of extracts or tinctures on the DIN application form and label, the manufacturer may display the information as described below:*

*a) LIQUID EXTRACTS OR TINCTURES*

*For a liquid extract or tincture, the notation "1:1", "1:5", "1:10", and so on means that 1 g of crude herb was used to prepare 1 ml, 5 ml, 10 ml, and so on, of the liquid extract or tincture.*

*The declaration of crude, dried herb should be made in grams per basic unit (e.g. ml) of the finished product.*

*b) SOLID OR POWDERED EXTRACTS*

*For a solid or powdered extract, the notation "1:2", "1:3", and so on means that 1 g of the extract was derived from 2 g, 3 g, and so on of the crude, dried herb.*

*The declaration of crude, dried herb should be made in grams per basic unit (e.g. tablet, capsule, teaspoon) of the finished product.*

*2.6 Indications and Claims*

*A clear claim or indication for the use of the THM should be presented on the draft version of the label. The claim should be supported by the references quoted in the DIN application. If a standardized drug monograph (herbal) is available, and if the proposed claims are within the scope of the monograph, a statement to this effect is an acceptable replacement for other references.*

*Claims and indications should*

*a) describe specific symptoms likely to be relieved - for example "expectorant, for the relief of productive cough", rather than "for the relief of cold symptoms".*

*b) be based on modern concepts of therapy. Terms such as "tonic", "supplement", "purifier", "depurative", and other, similar words are not acceptable. Illogical combinations of herbs - that is, combinations that would be expected to exert several effects (including those of diuretics and laxatives) or contradictory effects (laxatives and astringents) - are also questionable.*

*c) comply with existing prohibitions regarding the prevention or treatment of diseases listed in Schedule A of the Food and Drugs Act and of diseases that are inappropriate for self-diagnosis and self-treatment.*

### *2.6.1 Dosages for Children Under Twelve and for Pregnant and Lactating Women*

*Traditional herbal medicines, in doses that are both safe and effective for children under 12 and for pregnant and lactating women, are not considered acceptable for these groups in most cases, because their use in these groups lacks research support.*

*When administration of herbal medicines to the above groups is proposed, the DIN application should include appropriate information supporting the safe and effective use of the herbal product. Where reference to a publication is made to substantiate a claim or to provide evidence of safety, the publication should be clearly identified to facilitate retrieval.*

## *2.7 Label Presentation*

*Labels that accompany herbal medicines should enable the consumer to judge the purpose of the product and to use the product wisely. Consequently, indications, claims, dosage instructions, cautions, and modes of preparation should be clear, specific, and expressed in lay terms.*

*The manufacturer's presentation of a traditional herbal medicine and its packaging should lead to self-medication practices that are consistent with sound therapeutic and pharmaceutical principles. THM products should be clearly and immediately identified as medicines, and should discourage a public attitude that they are foods or that they are innocuous because of their herbal source.*

***ANNEX III***

## *Excerpts from "Drugs and Cosmetics" (Eight Amendment), Rules 1988**

### *Schedule Y*
### *Requirement and Guidelines on Clinical Trials for Import and Manufacture of New Drugs*

*1. Clinical trials*

*1.1 Nature of trials: The clinical trials required to be carried out in the country before a new drug is approved for marketing depend on the status of the drugs in other countries. If the drug is already approved/marketed, phase III trials (see para.7) usually are required. If the drug is not approved/marketed, trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.*

*For new drug substances discovered in other countries, phase I trials (see para.5) are not usually allowed to be initiated unless phase I data from other countries are available. However, such trials may be permitted even in the absence of Phase I data from other countries if the drug is of special relevance to the health problem of the country.*

*For new drug substances discovered locally, clinical trials are required to be carried out right from phase I through phase III. Permission to carry out these trials is generally given in stages, considering the data emerging from the earlier phase.*

*1.2 Permission for trials: Permission to initiate clinical trials with a new drug may be obtained by applying for a test licence (TL) to import or manufacture the drug under the Rules. Data appropriate for the various phases of clinical trials to be carried out should accompany the application. In addition, the protocol for proposed trials, case report forms to be used, and the names of investigators and institutions should also be submitted for approval. The investigators selected should possess appropriate qualifications and experience and should have such investigational facilities as are germane to the proposed trials protocol.*

*Permission to carry out clinical trials with a new drug is issued along with a test licence.*

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* *Published by the New Drugs Division, Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi-110011.*

*It is desirable that a protocol for clinical trials be reviewed and approved by the institutions' ethical committee. Since such committees at present do not exist in all institutions the approval granted to a protocol by the ethical committee of one institution will be applicable to the use of that protocol in another institution which does not have an ethical committee. In case none of the trial centres/institutions has an ethical committee the acceptance of the protocol by the investigator and its approval by the Drugs Controller or any officer as authorized by him will be adequate to initiate the trials.*

*For new drugs having a potential for use in children, permission for clinical trials in the paediatric age group is normally given after phase III trials in adults are completed. However, if the drug is of value primarily in a disease of children, early trials in the paediatric age group may be allowed.*

*1.3 Responsibilities of a sponsor/investigator: Sponsors are required to submit to the licensing authority an annual status report on each clinical trial, namely ongoing, completed, or terminated. In case a trial is terminated, the reason for this should be stated. Any unusual, unexpected or serious adverse drug reaction (ADR) detected during a trial should be promptly communicated by the sponsor to the licensing authority and the other investigators.*

*In all trials an informed, written consent is required to be obtained from each volunteer/patient in the prescribed forms which must be signed by the patient/volunteer and the chief investigator.*

*2. Chemical and pharmaceutical information*

*Most of the data under this heading are required with the application for marketing permission. They comprise:*

*2.1 Chemical name: code name or number, if any; non-proprietary or generic name, if any; structure; physiochemical proportion.*
*2.2 Dosage form and its composition.*
*2.3 Specifications of the active and inactive ingredients.*
*2.4 Tests for identification of the active ingredient and method of its assay.*
*2.5 Outline of the method of manufacture of the active ingredient.*
*2.6 Stability data.*

*When the application is for clinical trials only, information covered in items 2.1 to 2.3 will usually suffice.*

*3. Animal toxicology*

*3.1 Acute toxicology: Acute toxicity studies should be carried out in at least two species, usually mice and rats, using the same route as intended for humans. In addition, at least one more route should be used to ensure systemic absorption of the drug; this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. Symptoms, signs and mode of*

*death should be reported, with appropriate macroscopic and microscopic findings where necessary. L.D. 50s should be reported, preferably with 95 per cent confidence limits; if L.D.50s cannot be determined, reasons for this should be stated.*

*3.2 Long-term toxicity: Long-term toxicity studies should be carried out in at least two mammalian species of which one should be a non-rodent. The duration of study will depend on whether the application is for marketing permission or for clinical trials, and in the latter case, on the phase of trials. If a species is known to metabolize the drug in the same way as humans, it should be preferred.*

*In long-term toxicity studies the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e. the minimum number on which data should be available, are laid down separately.*

*A control group of animals given the vehicle alone should always be included and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it, e.g. 2.5, to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.*

*The variables to be monitored and recorded in long-term toxicity studies should include behaviourial, physiological, biochemical, and microscopic observations.*

*3.3 <u>Reproduction studies</u>: Reproduction studies need to be carried out only if the new drug is proposed to be studied or used in women of child-bearing age. Two species should generally be used, one of them being a non-rodent, if possible.*

*(a) Fertility studies: The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy. The highest dose should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans. The control and the treated group should be of similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.*

*(b) Teratogenicity studies: The drugs should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as for human therapeutic use. The control*

*and the treated groups should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites; resorptions, if any, and the number of foetuses with their sexes, weights and malformations, if any.*

*(c) Perinatal studies: The drug should be administered throughout the last third of pregnancy and then through lactation to weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observation should include macroscopic, autopsy and where necessary histopathology.*

*3.4 Local toxicity: These studies are required when the new drug is proposed to be used topically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.*

*3.5 Mutagenicity and carcinogenicity: These studies are required to be carried out if the drug or its metabolite is related to a known carcinogen or when the nature and action of the drug is such as to suggest a mutagenic/carcinogenic potential. For carcinogenicity studies at least two species should be used. These species should not have a high incidence of spontaneous tumours and should preferably be known to metabolize the drug in the same manner as humans. At least three dose levels should be used; the highest dose should be sublethal but cause observable toxicity; the lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 25 x 1 to make the intermediate dose to be placed logarithmically between the other two doses. A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Observations should include macroscopic changes observed at autopsy and detailed histopathology.*

## *4. Animal pharmacology*

*Specific pharmacological actions are those with therapeutic potential for humans. These should be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s should be given. Special studies to elucidate mode of action may also be described.*

*General pharmacological actions are effects on other organs and systems, especially cardiovascular, respiratory and central nervous systems.*

*Pharmacokinetic data help relate drug effect to plasma concentration and should be given to the extent available.*

5. ***Human/clinical pharmacology (Phase I)***

*The objective of phase I of trials is to determine the maximum tolerated dose in humans; pharmacodynamic effects; adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviour of the drug as far as possible. These studies are carried out in healthy adult males, using clinical, physiological and biochemical observation. At least 2 subjects should be used on each dose.*

*Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centres.*

6. ***Exploratory trials (Phase II)***

*In phase II of trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centres and are carried out by clinicians specialized in the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.*

7. ***Confirmatory trials (Phase III)***

*The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug in patients when used as recommended in the product monograph for the claims made.*

*If the drug is a new drug substance discovered, and not marketed in any other country, phase III data should be obtained on at least 500 patients distributed over 10-15 centres. In addition, data on adverse drug reactions observed during clinical use of the drug should be collected in 1000-2000 patients; such data may be collected through clinicians who give written consent to use the drug as recommended and to provide a report on its efficacy and adverse drug reactions in the treated patients. The selection of clinicians for such monitoring, and supply of drug to them will need approval of the licensing authority.*

8. ***Special studies***

*A. These include studies on solid oral dosage forms, such as bioavailability and dissolutions studies. These are required to be submitted on the formulations manufactured in the country.*

*B. These include studies to explore additional aspects of the drug, e.g. use in elderly patients or patients with renal failure, secondary or ancillary effects, interactions, etc.*

*9. Submission of reports*

*The reports of completed clinical trials shall be submitted by the applicant duly signed by the investigator within a stipulated period of time. The applicant should do so even if he is no longer interested to market the drug in the country unless there are sufficient reasons for not doing so.*

*10. Regulatory status in other countries*

*It is important to state if any restrictions have been placed on the use of the drug in any other country, e.g. dosage limits, exclusion of certain age groups, warnings about adverse drug reactions, etc. Likewise if the drug has been withdrawn from any other country, especially by regulatory authorities, such information should be furnished along with reason and their relevance to other countries' concerned regulatory authorities.*

*11. Marketing information*

*The product monograph should comprise the full prescribing information necessary to enable a physician to use the drug properly. It should include description, actions, indications, dosage precaution, drug interactions, warnings and adverse reactions.*

*The drafts of label and carton texts should comply with the rules.*

**ANNEX IV**

## *Excerpts from "Drugs and Cosmetics" (Eight Amendment), Rules 1988*

### Appendix I - Data required to be submitted with application for permission to market a New Drug

**1. INTRODUCTION**

A brief description of the drug and the therapeutic class to which it belongs.

**2. CHEMICAL AND PHARMACEUTICAL INFORMATION**

2.1 Chemical name: code name or number, if any; non-proprietary or generic name, if any; structure; physiochemical proportion.
2.2 Dosage form and its composition.
2.3 Specifications of the active and inactive ingredients.
2.4 Tests for identification of the active ingredient and method of its assay.
2.5 Outline of the method of manufacture of the active ingredient.
2.6 Stability data.

**3. ANIMAL PHARMACOLOGY**

3.1 Summary.
3.2 Specific pharmacological actions.
3.3 General pharmacological actions.
3.4 Pharmacokinetcis; absorption; distribution; metabolism; excretion.

**4. ANIMAL TOXICOLOGY**

4.1 Summary.
4.2 Acute Toxicity.
4.3 Long Term Toxicity.
4.4 Reproduction Studies.
4.5 Local Toxicity.
4.6 Mutagenicity and Carcinogenicity.

**5. HUMAN/CLINICAL PHARMACOLOGY (PHASE I)**

5.1 Summary.
5.2 Specific Pharmacological effects.
5.3 General Pharmacological effects.
5.4 Pharmacokinetics, absorption; distribution; metabolism; excretion.

**6. EXPLORATORY CLINICAL TRIALS (PHASE II)**

6.1 Summary.
6.2 Investigatorwise reports.

## 7. CONFIRMATORY CLINICAL TRIALS (PHASE III)

7.1 Summary.
7.2 Investigatorwise reports.

## 8. SPECIAL STUDIES

8.1 Summary.
8.2 Bioavailability and Dissolution studies.
8.3 Investigatorwise reports.

## 9. REGULATORY STATUS IN OTHER COUNTRIES

9.1 Countries where:-
(a) Marketed;
(b) Approved;
(c) Under trial, with phase;
(d) Withdrawn, if any, with reasons.
9.2 Restrictions on use, if any, in countries where marketed/approved.
9.3 Free sale certificate from country of origin.

## 10. MARKETING INFORMATION

10.1 Proposed product monograph.
10.2 Drafts of labels and cartons.
10.3 Sample of pure drug substance, with testing protocol.

**ANNEX V**

## Excerpts from "Drugs and Cosmetics" (Eight Amendment), Rules 1988*

### Appendix II - Format for submission of Clinical Trial Reports

- Title of the trial.
- Name of investigator and institution.
- Objectives of the trial.
- Design of study: Open, single-blind or double-blind; non-comparative or comparative; parallel group or crossover.
- Number of patients, with criteria for selection and exclusion; whether written, informed consent, was obtained.
- Treatments given-drugs and dosage forms; dosage regimens; method of allocation of patients to the treatments; method of verifying compliance, if any.
- Observations made before, during and at the end of treatment, for efficacy and safety, with methods used.

  Results: exclusions and dropouts if any, with reasons; description of patients with initial comparability of groups where appropriate; clinical and laboratory observations on efficacy and safety; adverse drug reactions.
- Discussion of results: relevance to objectives, correlation with other reports data, if any; guidance for further study, if necessary.
- Summary and conclusion.