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Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences

General Status on exploitation of medicinal and aromatic plants in China

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Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences

Introduction

Medicinal and aromatic plants (MAP) constitute great social and economic values for China. The annual out put value of medicine in China is around 15 billion (15, 000, 000, 000) US dollars. From which 6 billion is from natural products (mostly MAP), and 9 billion form western medicine. In general, MAP plays almost the same important role in comparison with western medicine.

General Status

The total out put values for natural products in China are shown in Table 1.

Table 1. Annual out put values of natural products in China(unit: millon)

Class	RAM	US$
Crude Drug	10,000	1,250
Chinese Patent medicine	24,000	3,000
Others (healthy foods, spices, raw materials)	14,000	1,750
Total	48,000	6,000

The industrial exploitation of MAP are shown in Table 2.

Table 2. Industrial exploitation of MAP in China

Factories	964
Preparations	4,000
Crude drugs and its preparations in Chinese Pharmacopoeia	920
Out put values of preparations	3 billion US$
Export	0.5 billion US$

Resources of MAP

A latest nation-wide survey of MAP resources showed that there are 11,118 MAP in China (Table 3)

Table 3. MAP resources in China (including 1,208 infrasp. taxa)

Origin	number of MAP
Thallophytes	467
Bryophytes	43
Pteridophytes	455
Gymnosperms	126
Angiosperms	
Dicotyledons	8,598
Monocotyledons	1,429
Total	11,118

The major Chinese MAP are listed in Table 4, 5, 6

Table 4. Major Chinese MAP with annual yields of 10,000--16,000 T

Glycyrrhiza uralensis , G. glabra	rt,rhz
Zingiber officinale	rhz
Dioscorea opposita	rhz
Allium sativum	bulb

Table 5 . Major Chinese MAP with annual yields of 3,000-8,000T

Angelica sinensis	rt
Codonopsis pilosula	rt
Astragalus membranaceus	rt
Panax ginseng	rt
Atractylodes macrocephala	rt
Isatis indigotica	rt,l
Lonicera japonica	fl-bud
Chrysanthemum morifolium	inflo
Salvia miltiorrhiza	rt
Rehmannia glutinosa	rhz
Rheum palmatum	rt,rhz
Polygonum multiflorum	rhz

Table 6. Major Chinese MAP with annual yield of 1,000-3.000 T

Panax noto-ginseng	rt
Ophiopogon japonicus	rt
Aconitum carmichaeli	rt
Aucklandia lappa	rt
Mentha haplocalyx	pl
Eucommia ulmoides	bk
Ligusticum chuanxiong	rhz
Lycium barbarum	fr
Paeonia lactiflora	rt
Pogostemon cablin	rl
Forsythia suspensa	fr
Coptis chinensis	rhz

Strategy of Industrial Exploitation of MAP

A. **Multilevels of development**

Primary development is aimed to enlarge the resources and improve the quality of MAP. ex. Panax quinquefolia, Gastrodia elata.

Secondary development is for the purposes of developing new and improved preparations or products. ex. Hippophae rhamnoides.

Tertiary development is focused on the searching of new drugs. ex. Table 7

Table 7. Examples of new drugs originated form MAP

Name of durg	Clue originated	Indication
Huperzine A	Huperzia serrata (pl)	Improving menory, for myasthesia gravis
Yu-Feng-Ning-Xin Tablet	Pueraria lobata (rt)	Relieving symptoms caused by hyperten-sive disease
Jin-Qiao-Mai Tablet	Fagopyrum dibotrys (rhz)	Antitumor, for pulmonary abcess
Lei-Gong-Teng Tablet	Tripterygium wilfordii (rt)	For rheumatoid arthritis
Shuang-Huang-Lian Powder Injection	Lonicera japonica (fl-bud), Scutellaria baicalensis(rt), Forsythia suspensa(fr)	Various infections
Composite Danshen Tablet	Salvia miltiorrhiza(rt) Panax notoginseng(rt)	For cardiovascular illness

B. **Multidisciplinary Research**

Including botanical, pharmacognostical, chemical, pharmacological and clinical investigations are stressed.

C. **Multilateral Utilization**

MAP are being integrated to the food, cosmetic and agricultural industries as well. They are used as sweetener, bitterness, spices, natural colouring matter, natural insecticides, healthy foods, healthy drinks, cosmetics etc.

New drug development

Criteria of TCD new drugs are divided into five classes:

I New crude drug, new active ingredient
II Injection, new part used, new active fraction
III Composite prescription
IV Improved dosage form
V New usage

From 1987 to 1996, 541 TCD new drugs have been approved, from which I 24, II 25, III 225, IV 265, V 2.

Conclusion remarks

As a trend worldwide today that human-being favours the way of life back to nature, the transition of the medical model from treatment towards prevention of diseases, the prevalence of natural therapy and traditional medicine are becoming more and more predominant. Thus, MAP will play a very important role, and industrial exploitation of MAP will certainly be keeping a key position in this respect.

Quality Assurance of Crude Drugs and Raw Materials

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Institute of Medicinal Plant Development(IMPLAD), Beijing

1. The importance of Quality assurance of crude drugs and raw materials
   . Guarantee the best final pharmaceutical products
   . Environmental protection
   . Sustainable utilization and development of natural resources

2. The criteria of good quality
   . Good efficacy
     high active ingredients
     higher yield
   . Good safety
     less toxicity and side-effects
     minimum pesticide residues
     minimum heavy metals
   . Pure, no contamination
   . Stable

3. Genebank conservation
   . Biodiversity conservation
   . To store plant germplasm for future uses
   . To make germplasm available to create new culti-variety
   . In situ conservation
     Genebanks of medicinal and aromatic plants in Asia
   . In vitro conservation
   . Breeding

4. Biotechnology
   . Plant cell culture
   Digitalis, Cephalotaxus, Salvia miltiorrhiza, Catharanthus
   . Hairy root culture
   More than fourty plants infected by Agrobacterium rhizogenes, such as Lithospermum erythrorrhizon, Panax ginseng, Salvia miltiorrhiza, Glycyrrhiza uralensis, Datura stramoium, Artemisia annua
   Tissue culture
   More than hundred medicinal plants were in vitro culture, such as Aloe,

Crocus sativa, Panax, Mentha etc.

. Genetic engineering

Isolation and purification of an antifungal protein from Phytolacca americana against American ginseng pathogens and synthesis of its gene and expression in E. coli.

5. Suitable growth region

In order to get higher quality of crude drugs and raw materials, select the most suitable growth region for relevant medicinal and aromatic plants is quite important. According to the ecological conditions, flora and other criteria, eight regions for crude drug development have been divided(fig.).

6. Good agrotechnological practices (GAP)

Large scale cultivation of medicinal and aromatic plants relies upon strong and continuing research. The contemporary literature in agrotechnology of several medicinal and aromatic plants demonstrates the fact that plant rarieties with an abundance of desired constitutents can be reproduced, and improved upon under cultivation even in an entirely different area. The cultivation of American ginseng(Panax quinquefolia) in China will be a good example.

---selection of appropriate region based on similar ecological conditions

---introduce a good cultivated variety

---improved yield of the desired secondary metabolite (triterpenoid ginseng saponins)

---reduction of any undesirable constituents

7. Non-polluted cultivation

In order to protect the environment, to sustainably utilize the resources, and to get a good quality of crude drug, non-polluted agrotechnology is rapidly developed in recent years. Those products are commonly called as "Green crude drugs".

---Biological control of insects and pathogens

insects control insects(ex. Scleroderma guani)

nematodes control insects(ex. Steinernema)

fungi control fungi(ex. Trichoderma sp.; Streptomyces spp.)

---Using botanical pesticides

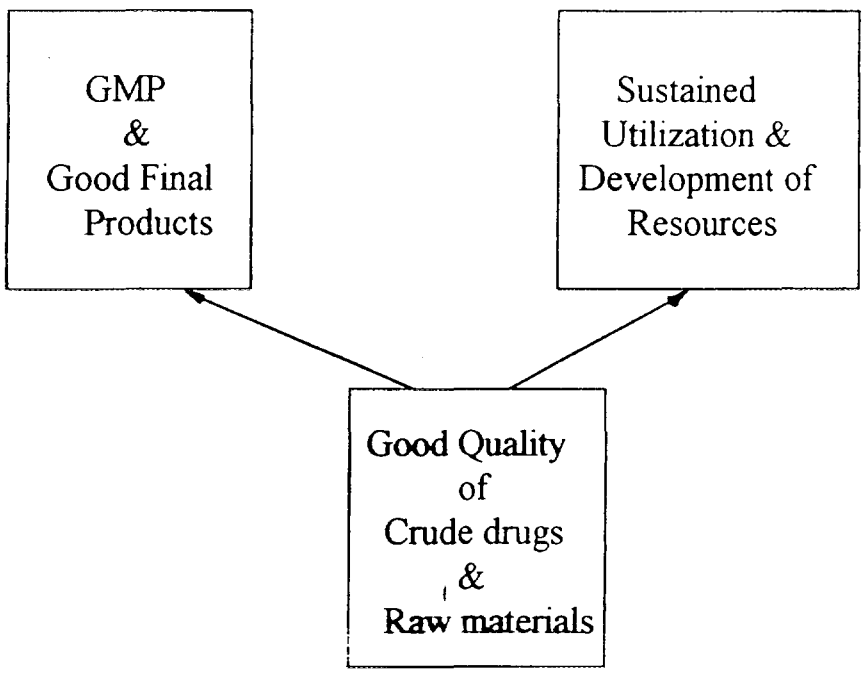
ex. Tripterygium wilfordii, Sophora flavescens, Melia azedarach, etc.

IMPLAD has successfully used comprehensive agrotechnology on Flos lonicerae, Fructur crataegi.

8. Post-harvest

. Right time harvesting
. Good processing
. Good storage
. Extraction or distillation (GMP)
. Quality control

9. Conclusion remarks



Good quality
. Good efficacy
higher active ingredients
higher yield
. Good safety
less toxicity and side-effects
minimum pesticide residues
minimum heavy metals
. Pure (no contamination)
. Stable

Procedure

Pre-harvest Post-harvest

Genetic factors
. Gene bank
conservation
In situ conservation
In vitro conservation
. Breeding
. Biotechnology

. Right time harvesting
. Good processing
. Good storage
. Extraction or distillation(GMP)
. Quality control

Environmental factors
. Suitable growth region
. Non-polluted cultivation (Green crude drugs)
. GAP(Good Agrotechnological Practices)

Gene banks of medicinal and aromatic plants in Asia

country	Institutions	Collection
China	IMPLAD Beijing and its 3 stations	2500 accessions Large collection
India	NBPGR, New Delhi, CIMAP, Lucknow	400 accessions evaluated & characterised
Korea	Economic plants and medicinal plants Gardens	350 accessions 500 accessions
Malaysia	UPM, UM, UKM, USM, MARDI, FRIM, National Research and Kuala Lumpur city council Gardens	450 species
Nepal	Royal Botanic Gardens	339 accessions
Philippines	Herbal Garden, University Garden at Los Banos and other locations	220 accessions
Sri Lanka	Royal Botanic Gardens, Kandy	
Thailand	Several Botanic Gardens	100 accessions

Hairy root culture

Infection of Agrobacterium rhizogenes (more than forty medicinal plants)

Atropa belladonna, Datura stramonium, Astragalus membranaceus, Fagopyrum dibotrys, Artemisia annua, Lithospermum erytherorhizon, Glycyrrhiza rualensis, Salvia miltiorrhiza, Panax ginseng

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The seven tanshinones were found in cultures.

Genetic engineering

An antifungal peptide with 7000Da was isolated and purified from Phytolacca americana (PAFP-S). The gene of PAFP-S was cloned to pGEMT vector and a recombinant pGEMT-210 was formed. A nonfusion prokaryotic expression vector pRSETB-210 for PAFP-S gene were constructed. The result of tricine-SDS-Page revealed that the non-fusion protein of PAFP-S gene was expressed at 0.67% which can be potential application on the disease-resistance breeding of crops.

Several Approaches To The Study of Chinese Traditional And Folk Medicine

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The history of traditional Chinese medicine has a span of over 2,000 years, with a rich accumulation of experience. Traditional Chinese medicine practice and traditional Chinese medicine, along with folk-lore medical herb, have been instrumental in the maintenance of health or Chinese people. Long strides of progress have been made during the past 40 years along the road of integration of traditional and western medical practice. Now I would like to give you some examples of the advances in Chinese herbs research in our institute and my own laboratory.and to illustrate the approaches of the study of Chinese traditional and folk medicine.

1. Researches conducted under the guidance of the theories of the Chinese traditional medicine

The Chinese traditional medicine has formulated theories of a systematic and unique nature and has accumulated plenty of experiences in clinical practice. The researches on Pueraria lobata may be presented as an example for this approach. Pueraria is a Chinese medicine frequently used in therapeutics and Pueraria decoction was used for the treatment of stiffness and soreness in the neck. In conducting a research project on the prevention and treatment of hypertension, the researchers felt uneasy about the fact that while the blood pressure could be reduce to normal or suitable levels, yet many of the hypertensive patients were relieved completely from their stiffness and soreness in the neck persisted. Following the experience recorded in the ancient classic of Chinese traditional medicine, the researchers made a trial on Pueraria to seen if it could relieve the hypertensive patients from the above mentioned symptoms. The results were quite satisfactory. Thereafter, Pueraria was found to be useful in the treatment of angina pectoris, sudden deafness and migraine. The active ingredient of Pueraria was soon identified to be flavones. Four main constituents isolated from

Pueraria lobata are daidzein. Daidzin, puerarin and daidzein 4',7-diglucoside. The last compound is a new structure. The total synthesis of daidzein has been made and is now put into production in large scale. The mechanism by which Pueraria relieves the symptoms of patients suffering from hypertension, migraine, sudden deafness and blindness due basal artery occlusion of eyes might lie in the improvement of the cerebral circulation.

2. The study of plant medicine, taking advantage of the experience of folk medicine

In China, besides traditional medical practice using Chinese medicine that have been recorded in ancient pharmacopoeias and other classics, there are a large amounts of scattered knowledge in folk medicine which utilizes un-recorded medicinal plants of different localities. This offers a good opportunity in the search of new medicaments. Two examples of research on folk medicine are given below.

2.1. Anisodamine and anisodine

In the plateaus of Chinghai and Tibet, the local people have the experience of using Scopolia tangutica Maxi. for the alleviation of pains. Overdosages usually lead to side effect characteristic of atropine-like toxicity. Taking the clue of this finding, two atropine alkaloids, anisodamine and anisodine, from the roots were isolated. Anisodamine differs from hyoscyamine by the presence of one extra hydroxyl group on the tropine heterocycle, while anisodine differs from scopolamine by the presence of one extra hydroxyl group in the tropic acid moiety. Pharmacological studies demonstrated that anisodine is weaker than scopolamine and close to atropine in the effect on the CNS, while anisodamine is still much weaker, about 1/6 to 1/12 of that of atropine. Both alkaloids have spasmolytic activities on the smooth muscles, practically the same as atropine. Anisodine is more marked on the CNS, more effective for the detoxification of organic phosphorus compounds as well as less toxic. Anisodamine, on the other hand, is weaker on the CNS, similar to atropine in s[asmolytic action, with weaker inhibition of nervous system inhibition of salivary secretion and mydriatic activities. Clinical study found that anisodine if effective for the treatment of migraine and diseases if the fundus occuli caused by vascular spasm and also for resuscitation CO intoxication and for the detoxification of organic phosphorus pesticides. Anisodamine is recommended as an emergency

measure for septic shock from toxic bacillary dysentery, fulminate epidemic meningitis and hemorrhage enteritis in combination with other drugs. Animal tests and clinical observations showed that both alkaloids improved disorder of capillary microcirculation. Anisodamine has now been synthesized industrially.

2.2. Rhododendrons in the treatment of chronic bronchitis

There are many species of rhododendron plants occurring in China. A total of 27 constituents was isolated from three species of rhododendrons. Some of the constituents have antitussive activity and some other principles have expectorant action. The expectorant farrerol and the antitussive benzylacetone have been synthesized and found to have identical activities with their natural counterparts in pharmacological tests and clinical trials.

3. Investigations in accordance with leads from clinical practice

In western countries, new drugs used in the clinic generally come from the extrapolation of animal experimental results. In China, however, the study of many herbal drugs follows the lead of clinical practice. After completion of the investigation, a new kind of drug or drugs is obtained which may be used clinically. The study of Fructus Schisandrae will serve as an example. Fructus Schisandrae(FS) is a commonly used as an astringent and tonic in traditional Chinese medicine. In the early 1970's, clinical observation found that the powder or honey pill of FS exhibited therapeutic effects on chronic viral hepatitis, particularly in improving the abnormal liver function such as serum transaminase and symptoms. On the basis of these findings, chemical and pharmacological studies on the chemistry, pharmacology and clinical use were carried out in our institute. The alcoholic extract of the kernel of FS was found to have hepatoprotective action against experimental liver injury and promote protein and glycogen biosynthesis in animals. Based on the results of pharmacological study, more than 20 compounds were isolated from different species of FS. Chemically, these compounds belong to dibenzocyclooctene lignans. Pharmacological study showed that 17 lignans have multiple biological activities such as protective action against hepatotoxins induced liver injury, inducing liver drug metabolizing enzymes, stimulating glycogen and protein biosynthesis, and anti-oxidant activity, and two of the lignans showed inhibitory effect on the CNS.

On the basis of pharmacological and photochemical investigation, we cooperated with a pharmaceutical plant which produces syrups of FS, salvaged the large quantity of residue left by the plant, which contains the sGPT-lowering active principles. The total active principles were extracted, processed into tablets and tried on chronic viral hepatitis patients after safety tests in animals. A total of 107 patients were treated with the tablets of FS, the elevated sGPT levels returned to normal limits accompanied by improvement of symptoms. The use of FS tablets instead of the powder or honey pills of FS reduced the size of the dosage and eliminated the feeling of uncomfortable feeling of the stomach due to the acidity of the preparation.

In order to screen new anti-hepatitis drug, the chemists in our institute attempted to totally synthesized schisandrin C, the most active principle of the lignans isolated from FS for lowering serum sGPT. We screened the intermediates for synthesis of schisandrin. Fortunately, we found that biphenyl dimethyl dicarboxylate(DDB), one of the intermediate, is effective as FS in protection against experimental liver injury and its toxicity is very low , more easier to synthesize. After preclinical study, DDB was recommended to treat chronic viral hepatitis and drug induced liver injury. The results showed that DDB is effective in improving the abnormal liver function. Its efficacy is superior to silymarin(Germany product) and glycyrrhizin(Japanese drug). No side effect was observed. DDB has widely used in China more than 15 years and now exported to Korea and Indonesia. Recent studies demonstrated that DDB has anti-viral and anti-cancer activities.

4. The application of the phytogenetical principle to the search for new remedy from the closely allied plants

It is well known that genetic relationships have been formed during the evolutionary process of the plants. Because of hereditary connections, the closely related species usually revel certain similarity in their phytophysiolgical and biochemical characteristics. By using this correlation, the anti-cancer agent harringtonine was discovered. In 1970 the esters of Cephalotixne alkaloid which were isolated from Cephaphotoxus harringtonia showed anti-cancer activity, thereafter no clinical report has been found beyond China in the available literature. A search for the active principle in the bark of Cephaltoxus hainanesis which is indigenous to Hainan Island in China led to the isolation of 11

alkaloids. Eight of the alkaloids were tested for anti-cancer activity, while four esters of cyphalotoxine: harringtonine, homoharringtonine, isoharringtonine and deoxyharringtonine exhibited various degree of anti-transplantable animal tumors. The clinical trial of harringtonine given as single agent for 66 patients with leukemia showed that 57 patients achieved an objective response in which 21 with complete remission and 36 with partial remission, and the remaining 9 patients failed to response. Harringtonine is especially for treating acute myeocytic leukemia. Now harringtonine is carried out phase III clinical trail in the National Cancer Institute in U.S.A. Similar results like in China were obtained. The research and development of anti-solid tumor drug Taxol is another example. Taxol has been developed by the same way like harringtonine and now sale on the market in China.

5. Application and research on Fungous plant

The Chinese traditional medicine such as Poria, Lasiosphaera, and Ganoderma are all that of dried fungi. Here, Only ganoderma is described briefly. Ganoderma is a mystery and can bee used to treat many kind of different diseases in the folk-lore in China. Since 1970's, the cultivation, chemistry, pharmacology and clinical use of ganoderma have been carried out in China. A number of papers reported that ganoderma has many pharmacological activities such as inhibitory effect on the CNS, stimulating cardio-cerebral circulation, hypocholesterolemia, modulating immune function and anti-aging. Clinical observations found that the injection of the spore of Ganoderma lucidum and the mycelium of G. capense is useful in the treatment of certain diseases such as hair loss, dermato-myocytis and neurasthenia.

Concluding remarks

This is a brief introduction of the route following which we carried out some studies on Chinese traditional and herba drugs. In brief, our subjects of research come from clinical practice, folk medicine and from experiences recorded in traditional Chinese medical classics. Besides, modern scientific knowledge, such as phylogenetical relationships between plants and microbial fermentation, is also applied for the excavation of effective drugs. All of these are integration, promotion or extrapolation of practical experiences,which may afford a better chance to discover new drugs and save money. In some cases, the crude extract of medicinal plants may be used as medicaments. On

the other hand, the isolation and identification the active principles and elucidation of the mechanism of action of a drug is of paramount importance. Work in both mixture of traditional Chinese medicine and single active compounds are very important.

THE STANDARDIZATION AND QUALITY CONTROL OF TRADITIONAL CHINESE MEDICINE

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National Institute for the Control of Pharmaceutical and Biological Products

A. Philosophical basis and historical review

B. Drug quality control and supervision

1. After the founding of new China, the institutions for drug administration and quality control were established to ensure the efficacy and safety of marketed pharmaceutical products and effective use of drugs as well. Since then, many rules and regulations have been formulated. On 20 September of 1984. the Drug Administration Act of the People's Republic of China was promulgated which marked a new stage of which our drug supervision and administration have been governed by means of legislation and also symbolized that China has turned its way from only lab checking to total quality management in administration.

In the last forty odd years, drug administration and drug quality control institutions in China have been expanded rapidly with drug administration agencies and drug quality control institutes setting up under the Ministry of Health and provincial, prefectural and county health bureaus for the law enforcement. supervision, management and quality checking etc. .There are over 3000 personnel engaged in the work of drug administration; 18,000 technical personnel working in more than 2000 drug quality control institutes; and 12,000 drug inspectors in the whole country.

2. All links of total quality control.

The plan for the implementation of GMP was first announced in 1988 and revision was made in 1992 but so far the plan has not yet been fully implemented, only for those newly established pharmaceutical plants that need to be checked before the acceptance according to the GMP standard. Those outmoded pharmaceutical manufacturers should be transformed in line with GMP standard step by step.

Before the products delivering from the pharmaceutical plants, the department of quality control of the factory is responsible for controlling the quality of released products. As for the national control institutions will check the samples randomly collected from the market.

Inspectors are responsible for the supervision of all links of production, circulation, and medical units. In addition, the report system of sub-standard and counterfeit drugs has been set up. The national planned checking program for sampling of all circles are regularly conducted and the results broadcast on TV and published in news daily afterwards.

A network for drug quality information has been established since the April of

1987. The data collected from all provincial Drug Control Institutes, health bureaus, circulation units, manufactures, and hospitals etc.are available through the computer network. The database including drug administration, drug testing results, adverse reaction reporting are analyzed so as to guide the decision-making process.

C. Documentation for the application of new drugs

Pursuant to Articles 21 and 22 of the Drug Administration Law, on 1 July 1985, the Ministry of Health issued and implemented the regulation for the approval of new drugs. The "new drug" is referred to as drugs which have not been produced previously in China, or drugs for which a new indication, a change in the route of administration or a change of dosage form is to be adopted. Any unit or individual engaged in the development, production, distribution, prescription of new drugs must adhere to the provisions of the document. The regulation includes the general principles, classification of new drugs, research on new drugs, clinical trial on new drugs, approval and manufacturing of new drugs and several appendices which provide detailed information on the application form, list of documents required, and technical requirements of toxicological studies, clinical studies for new modern drugs, and new TCM drugs

1. The classification of new TCM

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

2. Documentation to be submitted for new TCM

The data of all research on new medicines should be provided including toxicity, pharmacological properties and clinical research, as well as a detailed documentation on the quality of the medicinal material and the pharmaceutical form. For the above-mentioned five categories, different requirements should be complied with for the medicinal materials as well as for the pharmaceutical preparation.

3. Preclinical studies
   a. Research on pharmacodynamic
   b. Research on general pharmacology
   c. Research on toxicity
   d. Research on quality standards

4. Clinical studies

Here it has to be differentiated between a clinical trial and a clinical verification. Clinical trials shall be conducted for new medicines of categories 1, 2 and 3, while clinical verifications shall be required for new medicines of categories 4 and 5. Clinical trials are divided into three phases while the clinical verification does not have phases. The purpose of a clinical trial phase I is to study the reaction and the tolerability of the human body to the new medicine and to find out the safe dosage. The purpose of phase II of a clinical trial is to get an evaluation of the curative effects of the new medicine

and its safety. The objective of the clinical trial phase III is the further investigation of the safe use or effectiveness of the new medicine on the basis of the second phase.

The clinical verification is applicable for new medicines in categories 4 and 5. The purpose is to observe their curative effects, the contra-indications and the precautions. Different groups for control and for comparison shall be used.

5. Procedure and approval of new medicine

a. Clinical application

Applicants should submit an application for the clinical investigation of a particular new drug to the Bureau of Health of province, autonomous regions or municipalities accompanied with require information and sample.

For new drug of categories 1, 2, and 3 and narcotics, psychotropics, radiopharmaceuticals and contraceptives falling into categories 4 or 5, the Bureau of Health should give their preliminary opinion and submit the entire file to the Ministry of Health for final approval.

An application for clinical investigation of new drugs of class 4 or 5 other than those mentioned above should be approved by the Bureau of Health.

b. Production application

At the end of the clinical investigation of a new drug, the applicants should submit an application for the production of that drug to the Bureau of Health where the applicant is located, accompanied with the requisite information and sample; no objection is raised, the Bureau of Health should present all the data to the Ministry of Health for trial approval.

A new drug certificate and a file number of approval will be issued if the application has been approved.

New drug s of categories 1 and 2 should be produced on an experimental scale for two years immediately offen their approval. The experimental products are restricted to the use by medical units and retailed by provincial, autonomous regional or municipal new drug and especial pharmaceutical shore only.

D. Pharmacopoeia of the People Republic of China.

1. Monographs

The 1995 edition of the pharmacopoeia (Volume I) contained 922 monographs of Chinese Materia Medica, including 522 monographs of crude drugs(including preparations of single ingredient, oils and single processed samples), 16 new admissions compared with 1990 edition, 400 monographs of Chinese patent preparations, 126 new admissions compared with 1990edition, totally amounted to 142

new admissions.

2. Revision Item of Specification

The main revision and addition item of specification of Chinese Materia Medica in the 1995 edition of the pharmacopoeia is microscopically identification, TLC identification and assay. It contained: 537 monographs of drug substances and articles, for the microscopically identification, including 75 new admissions; 401 monographs of drugs substances and articles for the TLC identification, including 240 new admissions; 156 monographs of drug substances and articles for the assay, including 50 new admissions.

3. General monograph in the appendix

The 1995 edition of the pharmacopoeia contained 81 appendices including 21 of general rule of preparation, 3 new admissions of distillate of medicinal herbs, suppositories, tea preparations. Special testing method , reagents, test solutions, totally amount to 60 item, with adding to testing method for ashes, rancidity, time limit for disintegration, time limit for melt, limit of content variation, limit of microbial content. Other general rule for preparations and special testing method were modified.

E. General Guideline for the Standardization of Chinese Materia Medica

1. Quality issue of Chinese crude drug (including processes crud drug)

   The origin of medicinal plant , animal or mineral
   The part used for pharmaceutical purpose
   The appropriate season for collection
   The processing method of crude drugs
   Storage and transportation
2. Description and Action of crude drugs
3. Determination of total ash ,water and Acid-insoluble ash.
4. Determination of ethanol-soluble or ether-soluble extractives
5. Compound and single ingredient identification and determination
   Such as: Volatile oil , Flavonoids , Alkaloids , Saponins etc.
   Methods: HPLC, TLC, GC, etc.
6. Impurities

Pesticide residue Such as: organic chlorine or phosphorus

Test of heavy metal

Such as: Arsenic, Mercury, Plumbum, Cadmium, Cuprum. etc.

Measurement of radioactive substance

Microbiological determination

Such as: Aflatoxin, Bacteria etc.

1.2. The quality issue of Chinese patent preparation

1.2.1. The quality control of material , excipients and additives used in preparation.

1.2.2 the selection of the suitable dosage form and production technology

Such as: Tablets. Capsules. Mixtures. Granules, Injections etc.

Manufacture must be in comply with GMP or GNP (Good Natural Practice)

1.2.3 Test and determination

a. Description

such as: form (appearance or shape) . size , color , odor and taste

b. Identification

Specificity, accuracy and sensitivity must be considered.

(1) Microscopically identification

(2) Chemical method (identification)

(3) Chromatography (TLC, GC, HPLC etc.)

c. Test

(1) Lose on drying, total ash, disintegration test, size of granules, uniformity, dispensability. ethanol content

(2) Toxic component

Such as: brucine, aconitine and heavy metal(such as: As, Hg, Cu, Pb. Cd etc.

(3) Pesticide residue and microbial contamination.

d. Assay

content of active or single representative composition or some chemical composition or total composition

STUDY AND RESEARCH APPROACHES RELATING TO THE USE OF MEDICINAL PLANT

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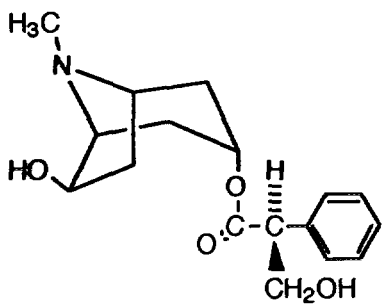
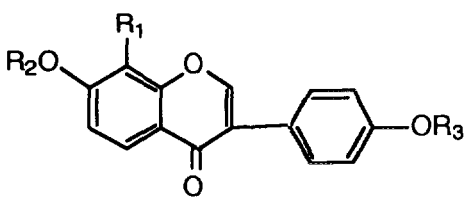
Medicinal plant is a great treasure house for the development of new drugs. Several examples of new drug development from medicinal plant constituents will be discussed.

1. Anisodamine[1~4] from *Anisodus tanguticus* used as an emergency measure for septic shock;



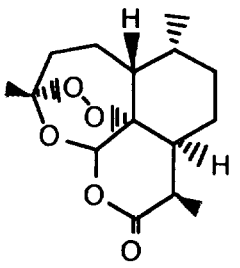
Anisodamine

2. Total isoflavones from *Pueraria lobata* [5~7] for the treatment of hypertension symptoms;

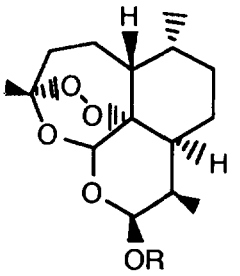


Daidzein	$R_1=R_2=R_3=H$	
Daidzin	$R_1=R_3=H$	R_2=glucopyranose
Puerarin	$R_2=R_3=H$	R_1=glucopyranose
Daidzein-4', 7-diglucoside	$R_1=H$	$R_2=R_3$=glucopyranose

3. New antimalarial drugs developed from Qinghaosu(Artemisinin) [8~9] of *Artemisia annua* Linn.;



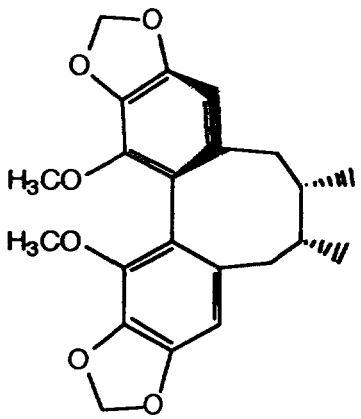
Qinhaosu



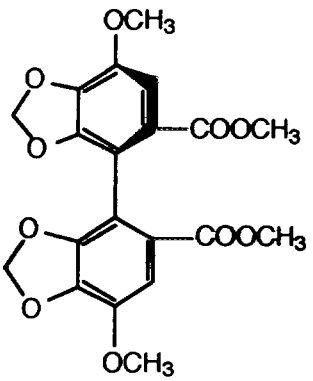
Artemether R=CH_3

Arteether R=C_2H_5

4. DDB(dimethyl dibenzocarboxylate)[10~14] for the treatment of chronic hepatitis developed from Schisandrin C of *Schisandra chinensis* (Turcz.) Baill.

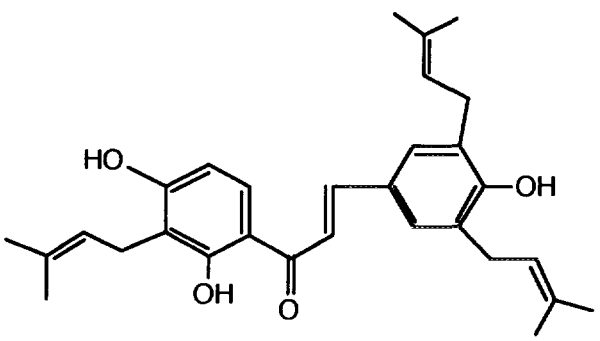


Schisandrin C

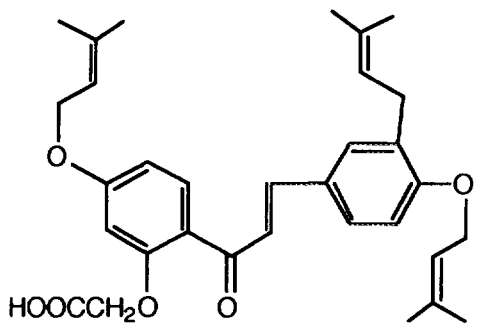


Dimethyl dibenzocarboxylate, DDB

5. Drug for anti-gastric ulcer - a synthetic compound, sopharcone[15~16] developed from sophoradin of *Sophora substrata* ;



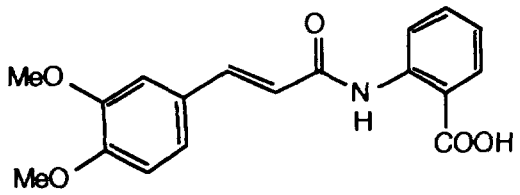
Sophoradin



Sopharcone

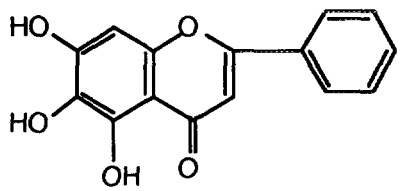
6. Anti-allergy drugs developed from medicinal plant constituents :

(1) Tranilast[17] is a simple derivative of cinnamic acid which is said to be designed from the feruloyl glucose, a constituent of *Nandina domestica* ;

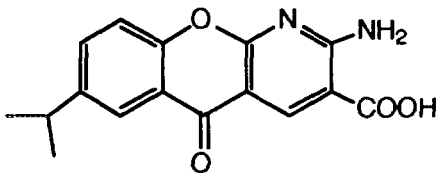


Tranilast

(2) Amlexanox[18~21] is a multi-functional anti-allergy drug which is claimed to be designed from the structure of baicalein, an anti-allergy flavonoid of *Scutellaria baicalensis* used in traditional Chinese medicine;



Baicalein

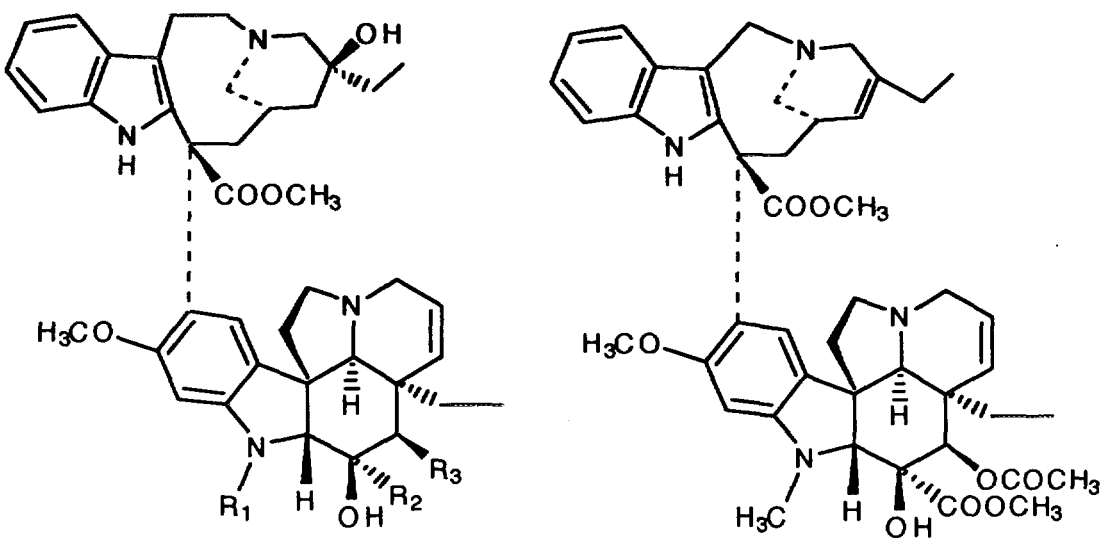


Amlexanox

7. Anti-cancer drugs

The most well known medicinal drug of plant origin used clinically are anti-cancer drugs:

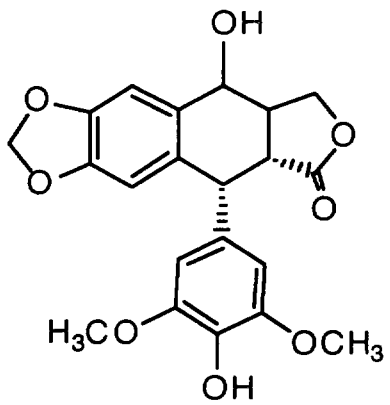
(1) Vinorelbine[22~25] is a semi-synthetic 5'nor-vinca-alkaloid developed from vinca-alkaloid of *Vinca minor* ;



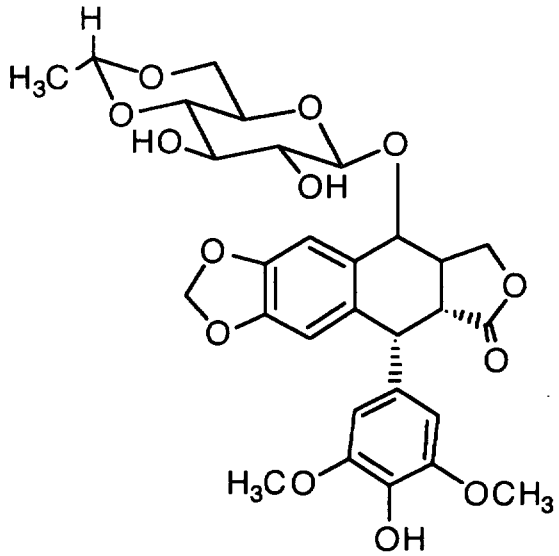
	R_1	R_2	R_3
Vinblastine	CH_3	$COOCH_3$	$OCOCH_3$
Vincristine	CHO	$COOCH_3$	$OCOCH_3$
Vindesine	CH_3	$CONH_2$	OH

Vinorelbine

(2) Etoposide[26~29], a glycoside derivative of podophylotoxin from Podophyllum emodii;

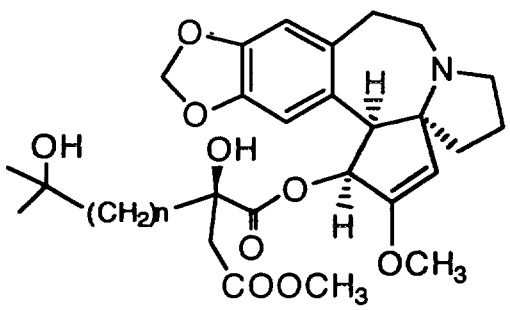


Podophylotoxin



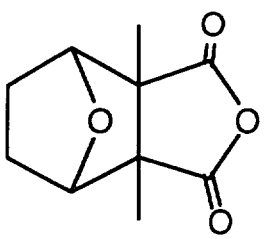
Etoposide

(3) Harringtonine and homoharringtonine[30] from *Cephalotaxus mannii* Hook. f.;

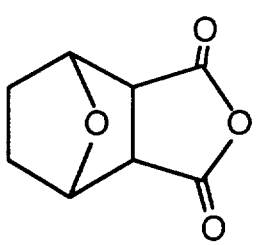


Harringtonine	n=2
Homoharringtonine	n=3

(4)Norcantharidium[31~33], a derivative of cantharidium of *Mylabris phalerata* Pall. It is a medicinal insect used in traditional Chinese medicine;

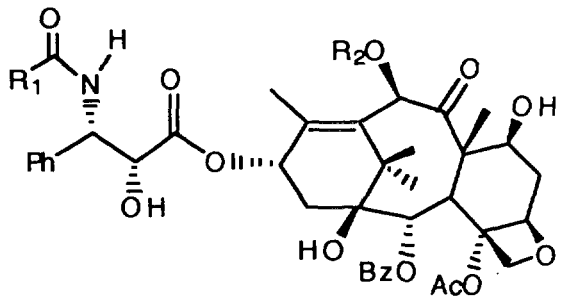


Cantharidium



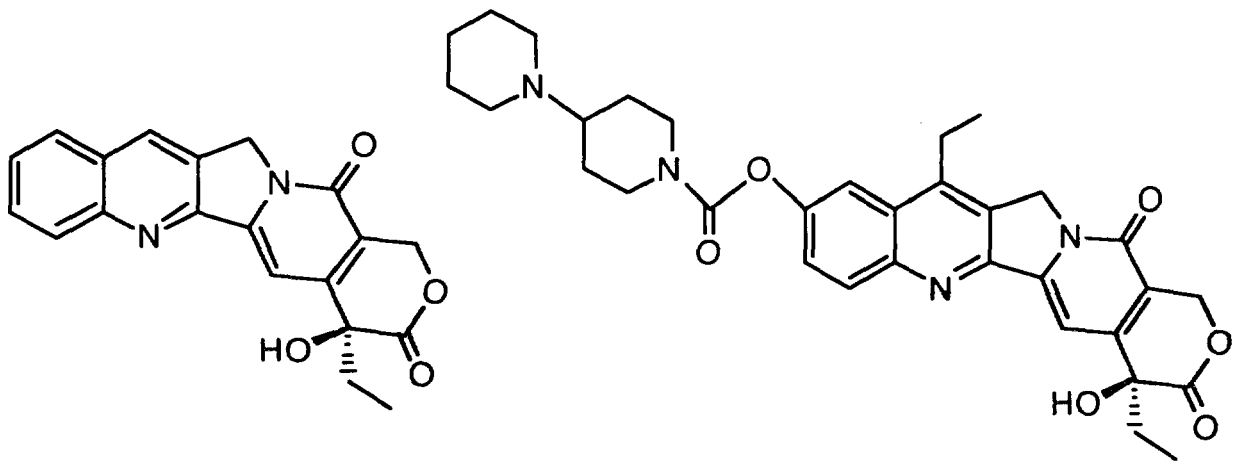
Norcantharidium

(5) Taxol(paclitaxel)[34~35] from *Taxus brevifolia*. is regarded as one of the three main achievements in anticancer drug research in 1990's in the world. Taxotere is a taxol analogue developed by semi-synthetic method;



Taxol	R_1=Ph	R_2=Ac
Taxotere	R_1=t-BuO	R_2=H

(6)Irinoteca[36~37] developed from camptothecin of *Camptotheca acuminata* Decsne..



Camptothecin Irinoteca

In addition, two commonly used methods for the separation of plant constituents " centrifugal thin-layer chromatography and high speed countercurrent chromatography"[38~40], will be introduced.

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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANISATION

INDUSTRIAL UTILISATION OF AROMATIC PLANTS IN DEVELOPING COUNTRIES

TULEY DE SILVA

CHEMICAL INDUSTRIES BRANCH

INDUSTRIAL SECTORS AND ENVIRONMENT DIVISION

INDUSTRIAL UTILIZATION OF AROMATIC PLANTS IN DEVELOPING COUNTRIES

TULEY DE SILVA
Chemical Industries Branch
Industrial Sectors and Environment Division
United Nations Industrial Development Organization

INTRODUCTION

Developing countries are endowed with vast resources of aromatic plants which have been used by the people for centuries as food, health care products, flavours and fragrances. Apart from the traditional ways of using these plants, many are exported to industrialized countries as raw materials for drugs, fragrances and flavours. The value-added products are then imported costing the countries several times more than the original revenue gained from exporting the raw materials. The actual value of these resources has not been retained in many countries for want of know how and trained manpower. Only a few developing countries are producing essential oils and even some of these countries are unable to produce the quality required to be competitive in the world market.Up to now small scale processing of aromatic plants in rural areas whereby more economic benefits could be directed to the rural poor has been neglected for various reasons such as lack of financial resources,entrepreneurial capabilities and the low priority given by the governments.

With a few exceptions, harvesting aromatic plants in developing countries for both local use and export has been from natural wild resources. As a result many plant species have been lost and some are in danger of extinction. It has also caused biodiversity conservation problems. It is therefore vital that systematic cultivation of these plants be introduced in order to conserve biodiversity and protect endangered species.

Systematic cultivation of this type of plants could only be initiated if there is a continuous demand for the raw materials. Hence small scale processing units too have to be established in order the farmer is assured of a market for the raw material. Thus cultivation and processing should be started simultaneously in rural areas.

There is a growing demand in industrialized countries for natural products in place of synthetic compounds not only as food and medicine but for other consumer products as well. Use of essential oils in aromatherapy is increasing, creating a demand for exotic oils. The oils produced from organically grown plants without the use of synthetic fertilizers, pesticides or other chemicals, trade at premium prices sometimes 3 to 5 times the price of conventional oils.

Today the promotion and development of processing of essential oils have gained momentum due to certain ground realities:

- Green consumerism and the current resurgence on the use of "Naturals" in developed countries.
- Free market economy bringing in more openness and expanding markets and demand for new resources, materials and products.
- A growing acceptability of the social responsibility of minimizing socio-economic inequalities in favour of rural people.
- Poor economic conditions in developing countries restricting import thereby placing increasing reliance on substitutes using indigenous plant resources.
- Increasing awareness regarding biodiversity conservation and therefore sustainable and protective use of plant resources.

The development of the essential oils industry is therefore important to many developing countries which have rich resources of raw materials and the climatic conditions for the initiation of

cropwise cultivation programmes. Though a lot of research has gone into synthetic substitutes for essential oils, the demand for natural oils has not declined. Hence the production of essential oils could still be a good source of foreign exchange revenue for developing countries.

Of course the cost of production of the various products will vary according to the raw materials, facilities for processing and labour and energy costs. Their production on a large industrial scale may require significant variations in the technologies used. In case of rural small scale processing these technologies have to be adapted to suit the existing situation at field level.

Synthetic substitutes have been produced from petrochemicals to compete with plant products such as resins, aroma chemicals, phytochemicals, rubber, leather etc. In the case of essential oils and flavours, real substitutes having all aroma characteristics of the natural products have not been fully accomplished. Nevertheless, the low cost of these synthetics and certain improvements on the natural, have affected the production and sale of essential oils. Synthetic chemicals have won a major share of the aroma chemicals market. Back to nature movement has revived the interest on natural products. This trend is good for the developing countries who are endowed with vast resources of aromatic plants.

Although products could be developed, the viability of any industry small, medium or large will depend on the marketability of the products. Information on market prices and demand is difficult to get in view of the protective nature and limitations of the market. Furthermore, the market is characterized by price fluctuations and high competition and substitute synthetic products. As such in the first instance, it may be useful to conduct market studies on local and national demand rather than the export potential. In developing countries, essential oils can be produced for import substitution resulting in saving the much limited foreign exchange. It is also necessary to encourage the development of local secondary processing and user industries.

The lack of information on the social and economic benefits to be derived from the industrial utilization of aromatic plants has been a major factor impeding the development of the essential oils industry in the developing countries. Except for the use of these plants for domestic purposes, not much information was available on the market potential and trading possibilities. As a result, the real potential of these plants was not known to the governments or entrepreneurs.

The entry into world markets depends not only on the demand but on the competitive price of production, quality and the ability to provide the quantities required by the purchaser. The bottleneck in many developing countries has been the lack of sufficient raw materials to supply the ordered quantities. The expansion of the resource base is therefore essential which may in certain instances mean large scale cultivations.

The sustainable development of industries based on plants requires multi-disciplinary activities and close collaboration between scientists, government officials, NGO's and international organizations. Such efforts have not received much attention resulting in the slow development of the economic uses of the renewable resources. Hence it is important that more action oriented plans are initiated to exploit the full potential of these resources, bearing in mind the conservation issues such that real rural household incomes and national economies could be augmented.

Furthermore inventories on the types of useful plants and their abundance are not available for assessing the possibilities for their industrial utilization. Hence there is an urgent necessity to collate information on resource availability, and process technologies, in order to prepare country specific development programmes.

INPUTS REQUIRED

Inputs for the commercial production of essential oils should include development or transfer of agro-technology, post-harvest technology and process technology, quality assessment, marketing, training and export promotion.

AGROTECHNOLOGY

The demands of the majority of the people in developing countries for essential oils have been met by indiscriminate harvesting of spontaneous flora including those in forests. As a result many plant species have been lost and some are in danger of extinction. It has also caused biodiversity conservation problems.

It is therefore necessary to initiate systematic cultivation of aromatic plants in order to conserve biodiversity and protect endangered species. Systematic cultivation of this type of plants could only be promoted if there is a continuous demand for the raw materials. Hence small scale processing units too have to be established in order the farmer is assured of the sale of raw material. Thus cultivation and processing should be started simultaneously in rural areas.

In order to initiate systematic cultivation of aromatic plants high yielding varieties have to be selected. In the case of wild plants, domestication of them would require careful development work. Sometimes high yielding varieties have also to be developed by selective breeding or clonal micropropagation. The selected propagation materials have to be distributed to the farmers either through seed banks or nurseries. Systematic cultivation of many aromatic plants needs specific cultural practices and agronomical requirements. These are species specific and are not only dependent on soil, water and climatic conditions. Hence research and development work has to be done to formulate Good Agricultural Practices which should include proper cultivation techniques, harvesting methods safe use of fertilisers and pesticides, and waste disposal.

Taking into consideration the requirements of the plants selected, an agrotechnological package has to be developed to suit the infrastructural facilities available.

Research and Development work has also to be carried out in the following areas:

i) Optimization of agronomical conditions for cultivation
ii) Training in safe fertilizer and pesticide use
iii) Development of fast growing varieties
iv) Development of disease-resistant varieties
v) Determination of maturity and time of harvesting
vi) Number of economically viable harvests
vii) Methods of harvesting

Decisions on a limited scale of exploitation of aromatic plants from wild sources have to be based on accurate inventories about the kinds of plant resources, abundance and the feasibility of harvesting without damage to the ecosystem. In case potential candidates identified are not abundantly available, cultivation of them through agroforestry and community forestry programmes will have to be initiated. In this regard, development of industries based on aromatic plants can be included as a priority area as niche markets for these are already available

Good Agricultural Practices (GAP)

Systematic cultivation of many aromatic plants needs specific cultural practices and agronomical requirements. These are species specific and are not only dependent on soil, water and climatic conditions. Hence research and development work has to be done to formulate Good Agricultural Practices which will include proper selection and identification, propagation methods, cultivation techniques including proper and safe use of fertilisers and pesticides, harvesting, step wise quality control of raw material up to processing stage, post harvest treatment, storage and safety. These aspects have to be incorporated into any package for the cultivation of aromatic plants.

Sometimes it is necessary to introduce/promote the cultivation of a mixture of crops so that the farmers can be encouraged to cultivate. The crop mix should contain food and cash crops for short term benefits and trees of economic importance as long term strategies. The cash crops should be carefully

selected on criteria of known demand and possibly be of a non-perishable nature. Trees and undercover species to be selected can be aromatic plants yielding short and long term benefits. But such crops must be supported by creating a demand for the raw materials which means the establishment of small processing units. This will not only win the farmers confidence but result in some gaining entrepreneurship capabilities. Such activities have to be very carefully, planned as pilot projects taking into account many factors such as selection of plants, assessment of economic potential, simple technologies and sustainability. Farmers have to be trained and R & D work has to be carried out to develop the agronomical and technological inputs required.

Organic Farming

Organic farming is another practice that is gaining wide acceptance as world demand particularly in developed countries for organically grown crops is rapidly on the increase. Farmers have to be trained in all aspects of organic farming including obtaining certification from associations that do the monitoring starting from cultivation to final harvesting. As chemicals cannot be used as fertilizers and pest control agents, the cultivations are labour intensive requiring labour for weeding and other farming activities. Hence developing countries which have cheap labour and unpolluted land can opt for organic cultivation. Organic manure has to be prepared which leads to environment friendly methods of organic waste disposal. Organic farming will reduce environment pollution, toxic effects due to use of pesticides and minerals, and problems of biodiversity conservation.

The trend for green products is also increasing and it is expected that some industrialized countries will insist on ecolabelling of products as a condition of import. This will mean that any oils produced have to be certified to ensure that no ecological damage whatsoever has been caused during production.

PROCESS TECHNOLOGY

The products that could be derived and the related processes are depicted in **Figure 1**. The methods used in the production of aromatic plants based products are:

Steam Distillation

Steam distillation is the widely used technique in the extraction of essential oils. In this process steam is passed through the plant material whereby the constituents that are volatile in steam are carried along with the steam. Steam can be generated in a separate boiler or at the bottom of the still by direct heating. The advantage is that the volatile components are distilled at low temperatures than the boiling points of their individual constituents and that on condensing the oils being immiscible in water forms a separate layer thereby easing separation. Though the process sounds simple in theory, there are many variations of the actual commercial processing depending on the characteristics of the raw material and the final product in order to minimise the cost of production and to obtain good quality oils.

Solvent Extraction

Some parts of plants that contain very minute amounts of essential oils such as flowers are extracted using low boiling solvents such as hexane, pentane or petroleum ether. These extracts will contain all material soluble in the solvent including the essential oil compounds. The process of separation of the essential oil needs an additional step of removal of the solvent in separate evaporator.This is an expensive step due to the cost of solvents and the cost of production will depend on the efficiency of the recovery of the solvent for re-use. Hence this process has to be done at a central facility using good manufacturing practices. The scale of production will determine the economy of the process.

In case of many end uses such as for food and aroma therapy, only traces of the solvent could be left behind which necessitates vacuum distillation to remove these last traces, thus adding to the

Processes Used and Products from Aromatic Plants

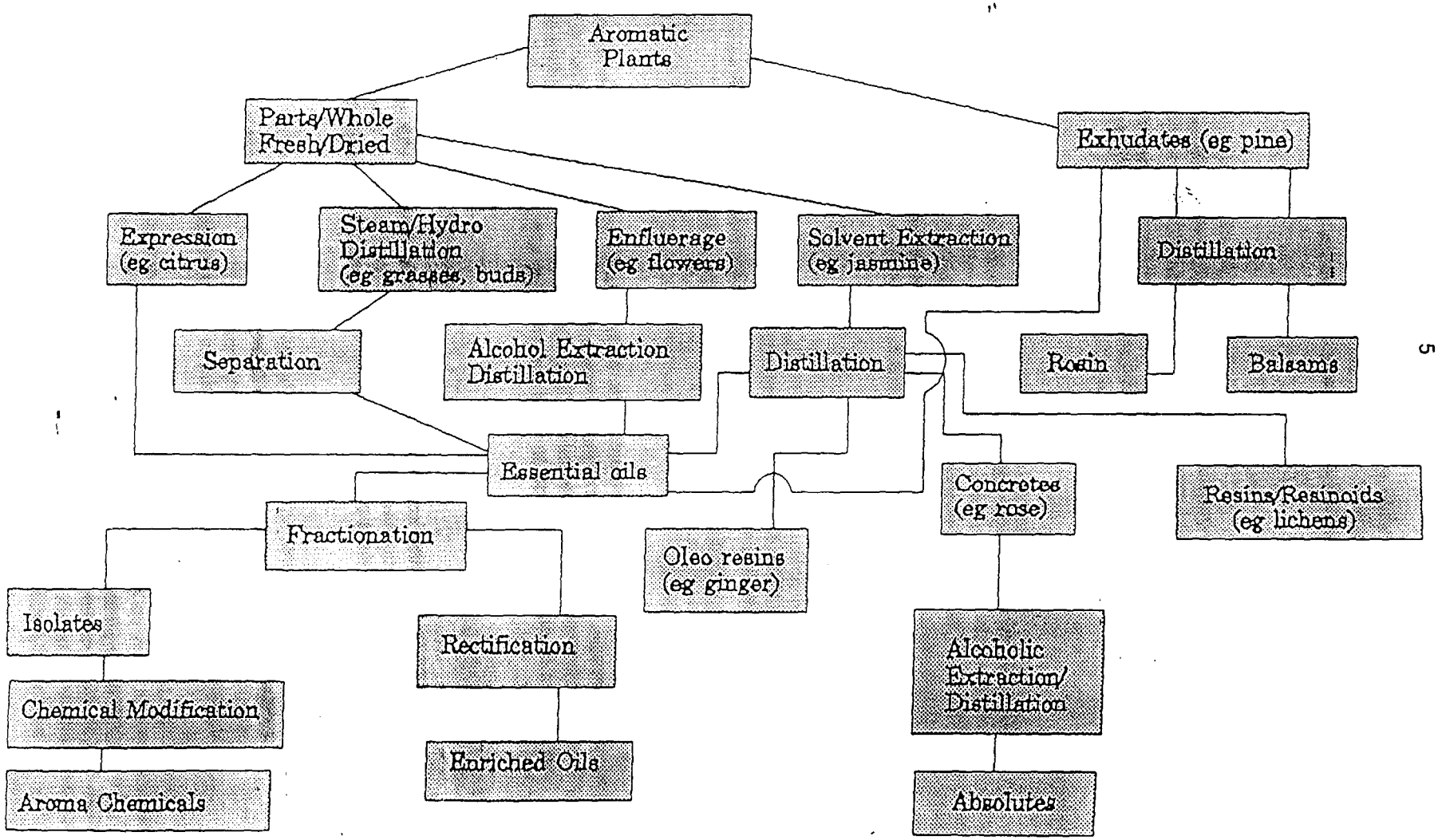


Figure 1

costs. The residue after removal of the solvent is called a "concrete". The process of solvent extraction is therefore expensive and needs additional equipment and safeguards. The concrete contains the essential oils as well as other solvent soluble extractives which together give it a special value in perfumery.

Absolutes

Certain finished perfumery products like colognes use the alcohol soluble fraction of concretes called "Absolutes". The concretes are mixed with alcohol and stirred vigorously to get all alcohol soluble compounds into solution. On cooling the mixture, alcohol insoluble compounds separate out at the bottom. The alcohol extract is filtered and the alcohol is evaporated to yield the absolute. In this case too a primary evaporator and a secondary evaporator are used.

Oleoresins

The extraction of spices such as ginger, pepper, chillie, cardamon using solvents and the removal of these solvents as in the case of concretes yields "oleoresins" which contain not only the essential oil compounds but other flavour principles of the spice such as pungency, waxes and other solvent soluble extractives. Oleoresins therefore are more representative of the spice than the essential oil obtained from it. The extraction process could be a continuous soxhlet extraction process or solvent percolation through a series of extractors.

Expression

Certain oils such as citrus oils can be extracted by simple expression. The technology for this type of extraction has been well developed such that both the juice and the oil could be obtained usin a single machine

Enfleurage

Production of some expensive essential oils from flowers such as jasmine is carried out by a process called Enfluerage. This is a technique by which the raw material is kept in contact with fat in order to get the fat saturated with the essential oil. The adsorbed oil is then extracted from the fat using ethanol. The ethanol is finally distilled off to yield the oil. This will contain all compounds that are adsorbed into the fat.

DOWNSTREAM PROCESSING

Essential oils could be further processed or rectified to add value. Rectification of essential oils is sometimes needed depending on their end uses.The main industrial uses of essential oils are given in **Figure 2**. Rectification usually done by a process of fractionation may consist of one or more of the following:

- removal of moisture, colour and sediment
- removal of some compounds in order to improve the odour characteristics,and stability
- isolation of compounds that are highly valued
- enrichment of the oils by removing some unwanted fractions.

This is done by a process of fractionation which could be carried out in some areas having large scale processing with back up from national research institutions who would carry out the analysis and develop the fractionation parameters. This needs more training and equipment and many not be possible in certain rural communities or with forest dwellers. It would be better to carry out the fractionation of oils at a central facility which can afford to invest the funds and personnel required for this activity. As a result of fractionation, pure isolates of added value such as citronellal and citral could be produced.

Some Industrial Uses of Essential Oils

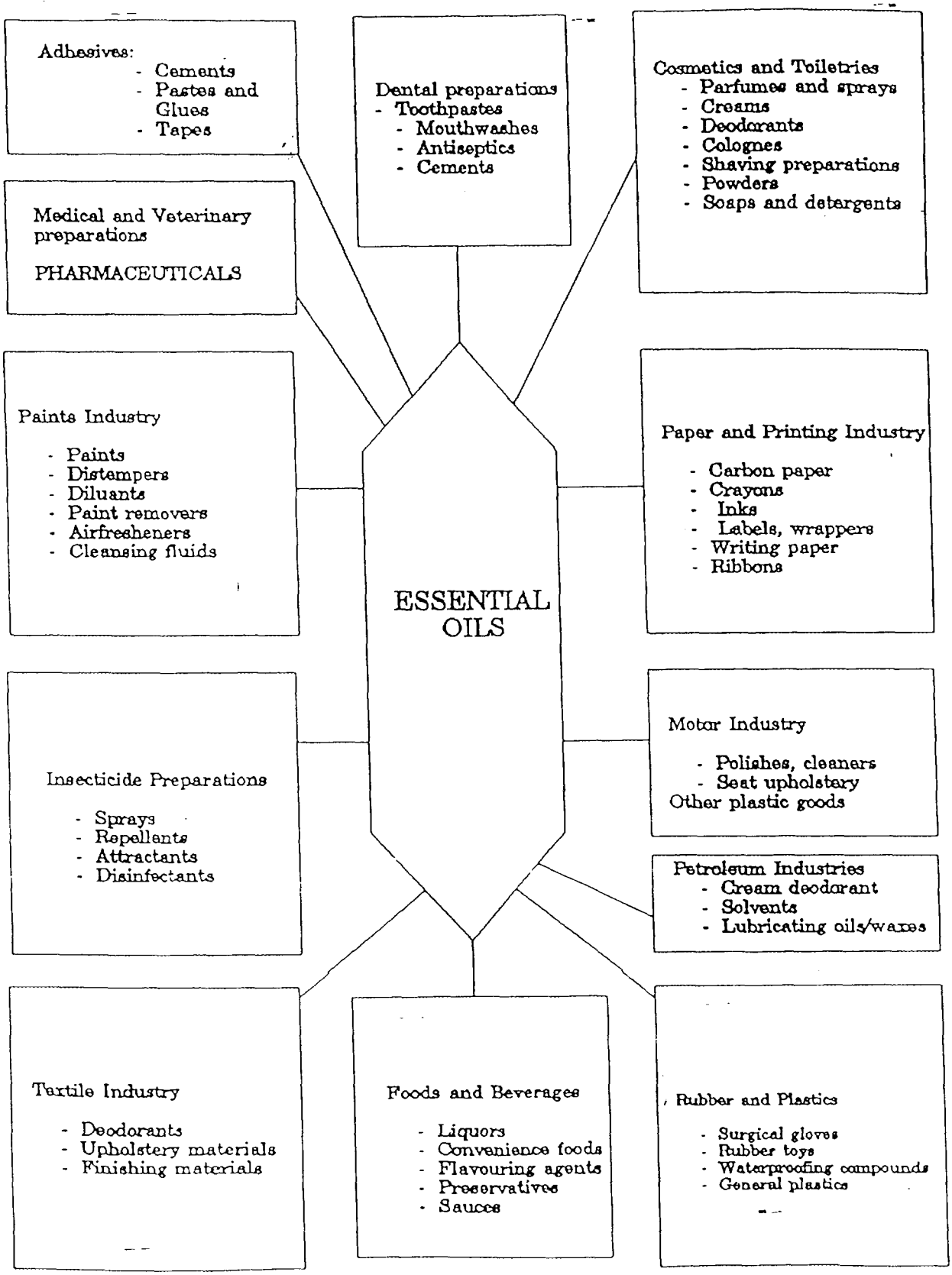


Figure 2

Another stage in the development of the industry is the initiation of downstream processing of the oils to produce isolates which can be chemically modified to produce aroma chemicals. This is possible in countries producing large quantities of oils and where poor and cheap oils could be converted to other value added products. These products could also be used in the development of local perfumery industries. This would require the setting up of laboratories for compounding local perfumery formulations and testing them in various applications in cosmetics and toiletteries. The know how and the techniques for these activities can be transferred to local scientific personnel.

Essential oils are evaluated not only by their chemical and physical characteristics that are measurable but more importantly by their sensory characteristics. Hence the control of the quality of essential oils through sensory evaluation has also to be introduced to developing countries so that they could obtain the correct market prices.

As for the small scale producers in rural areas, integration with central downstream processing factories in the country would be essential to have a regular market for the primary products. These factories will produce requirements for other industries such as cosmetics, detergent, paint, paper and pharmaceuticals and should be encouraged. This link between the downstream processing companies and consumer industries too should be strengthened so as to have a complete chain of operations from the farmer to the consumer as a viable alternative to export.

The production of essential oils too has to be planned depending on the facilities available. The primary processing will require an energy source and a supply of water. Simple field distillation could be introduced in rural areas and the products be sold at the nearby towns or to central collecting stores. Mobile distillation units can be introduced if roads can be built for easy access to these areas.

It is indeed therefore imperative that the industry particularly in the developing countries should be planned, and the technology purpose oriented and designed to suit the requirements. In many respects countries such as India and China have led the way in re-establishing this industry in their countries and also competing with industrialized countries in the processing of downstream products and even formulated fragrances and flavours.

PILOT PLANT FACILITIES

There has been considerable interest and research activity on potentially useful plants endemic to developing countries. Though a lot of time and money has been spent on strengthening institutions and training scientific staff, their work has not contributed much to industrial development. The new products or processes developed by these institutions have not been translated into industrial processes owing to the:

- Lack of team work requiring multidisciplinary cooperation
- Inability to develop process parameters for large scale production and
- Inability to convince entrepreneurs or governments as to the feasibility and cost-effectiveness of production.

This could be remedied by providing pilot plant processing facilities which require the services of many disciplines. Such a pilot plant will enable the R & D work to be upscaled to produce final products which could be market tested. University-industry links have thus to be strengthened. Any institution which wants to initiate downstream processing of medicinal plants should possess facilities for pilot scale production.

The introduction of a polyvalent pilot-plant has been the most significant contribution of UNIDO to the development of the industrial utilization of medicinal and aromatic plants in developing countries. The gap that prevented the transfer of processes and products developed on a laboratory/bench-scale to industry can be bridged by introducing pilot plant processing facilitites and multidisciplinary team work. Many research and development institutions in developing countries lacked the support of their engineering counterparts and most research therefore was confined to academic pursuits. If one is to

undertake commercial production of herbal medicines, the vital role played by chemical engineers in translating bench-scale findings to industrial-scale outputs through pilot-scale process parameter development has to be recognised.

Having recognised the competence and facilities available in some developing countries to fabricate equipment, UNIDO has designed a polyvalent pilot plant incorporating improvements made to existing plants. The design includes all engineering drawings, together with specifications and bills of quantities, so that it can be fabricated in countries where the facilities for stainless steel welding are available. Sometimes the items such as standard pumps, control units and column-packing material have to be procured from outside. The design has just been published with the aim of enhancing self reliance and engineering capabilities in the local fabrication of equipment.

This polyvalent pilot-plant (**Figure 3**) is characterized by simplicity of design, installation, operation, maintenance and repair. Some of its features are:

- Modular construction, wherever possible, so as to permit increase in capacity as well as function by duplicating or adding modules. One can add more unit operations or more sophisticated capabilities later.

- Parts of the plant can be independently operated so that simultaneous processing could be carried out, e.g. extraction at one end, production of solid extracts or oleoresins at the other.

- The pilot plant can be used for aqueous or solvent extraction, continuous extraction, preparation of solid extracts, oleoresins, distillation of essential oils and if needed, fractionation of essential oils and production of absolutes and concretes, and even processing of other economic plant-derived products.

- The scale of operation allows R & D work needed to transfer bench-scale processes to large enough scale to develop process parameters. This was the crucial step hindering the industrialization of research findings.

- It could be used to develop indigenous technologies and to adapt acquired technologies to the requirements of the recipient country.

- It can provide training for local personnel in the processing of medicinal plants, aromatic plants and spices. Other areas of training include plant operation, process control, quality assurance, trouble shooting, maintenance, repair and management.

- Standardized and optimized process control and measuring units, pumps and other ancillaries can be easily replaced.

- All plumbing and electrical wiring are kept simple and easily accessible.

This plant hasto be introduced to R & D institutes if they are to successfully develop products and transfe them to industries. These institutions could also solve any technological problems referred to them by the industries.

New Technologies

Improved methods for processing of aromatic plants and new techniques for quality assessment being developed regularly have to be introduced to developing countries if they are to forge ahead to keep up-with recent developments and new international requirements. One such method of recent development is Supercritical Fluid Extraction of natural products as an alternative for solvent extraction. It is now used both for processing of some pharmaceuticals and essential oils and for the removal of trace amounts of contaminant substances such as pesticides, toxins and surfactents. The use of

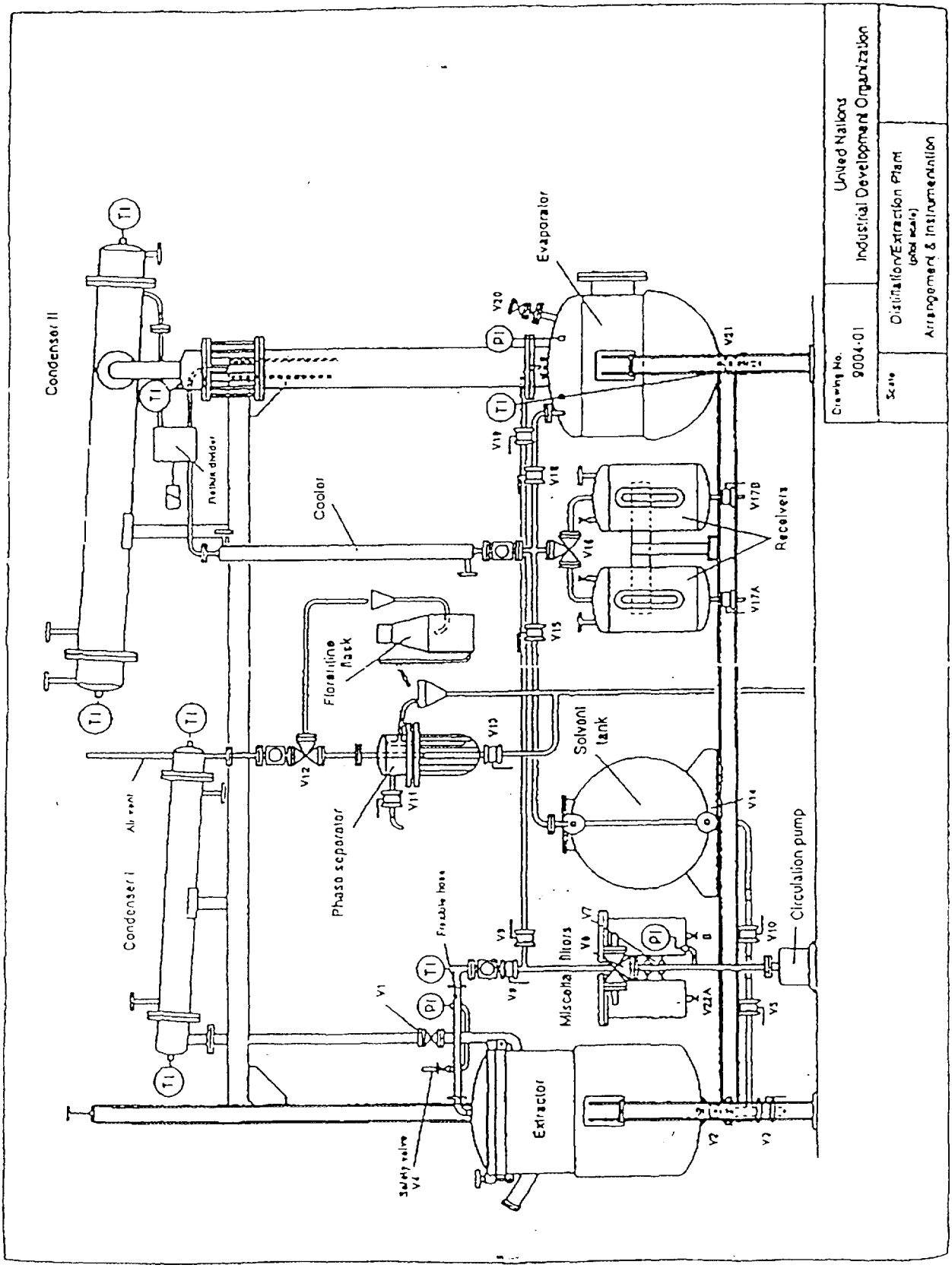

Condensor II
Condensor I
Evaporator
Cooler
Florentine flask
Phase separator
Solvent tank
Receivers
Circulation pump
Extractor
Miscella filters
Drawing No. 9004-01
United Nations Industrial Development Organization
Distillation/Extraction Plant (pilot scale) Arrangement & Instrumentation

Figure 3

Supercritical Fluid Extraction as a means of sample preparation for analysis has received lot of attention during the last few years. Supercritical Fluid Chromatographic technique for analysis has also been developed. These technologies and methods have to be introduced to developing countries having the potential and infrastructure to absorb them.

QUALITY ASSURANCE

Quality has to be built into the whole process beginning from the selection of propagation material to the final product reaching the consumer. It is therefore a management system where all steps involved in the industrial utilization process have to be properly and strictly controlled to produce the desired quality products. The requirements for ISO 9000 certification have to be introduced and the personnel trained so that enterprises could introduce the proper systems needed for certification.

The control of the quality of the raw materials, finished products and of processes is an absolute necessity, if one is to produce goods for world markets and human use. Monographs have to be prepared for each product to include all specifications developed. Modern analytical techniques have to be extensively used to develop identity and quality parameters. The machinery and processes used in industries have to be validated to comply with International Standards.

It is imperative that the processed products comply with national and/or international specifications. There are International Standard Organisation Specifications (ISO)for most of the essential oils. In addition, countries and buyers can have their own requirements. Hence the products could be tailor made to conform to the buyers requirements. Sometimes the requirements of the buyers are more stringent and specific, demanding the application of good manufacturing procedures.

Associated with quality management is the compliance with current good manufacturing practices. WHO requirements of good manufacturing practices have to be introduced in every project as most developing countries fall very short of GMP. Without GMP products cannot be expected to be of required standards and quality. The concept of safety is almost non-existent in many developing countries. Safety requirements, with respect to buildings, machinery and staff have to be introduced and, ii possible, safety manuals have to be prepared in order to focus the attention of the management and staff on these issues.

Stringent requirements are being introduced presently to safeguard the environment, to reduce pollution caused by use of synthetic chemicals, reduce health risks due to side effects of using synthetic materials and to conserve the biodiversity. Hence eco-audit procedures will be required for safeguarding environmental damage. Organic production will reduce the risks of contamination of products and the environment with synthetic chemicals.In fact ISO 14000 requirements may have to be met in the future if the buyers insist on ecolabelling.

HUMAN RESOURCE DEVELOPMENT

Many developing countries have a core of trained personnel in the fields of chemistry, biology, agriculture, pharmacology and pharmacy: They lack such resources in chemical engineering and technology. This can be considered as a main constraint upon industrial development. Most of the agronomists are involved in the cultivation of cash crops and not of other useful plants.

Human resources required for this specific area of industrial activity can be developed by conducting:

- Training abroad at appropriate institutions
- Training at site by international experts
- In service group training
- Tailor made group training courses on a interregional basis
- Workshops and seminars in specific areas
- Study tours and participation at international seminars/ congresses/ workshops and
- Provision of up-to-date know-how through books and journals

Training programmes have to be conducted to enhance the knowledge of farmers to introduce proper agricultural practices including post harvest treatment. Harvesting methods, protective and sustainable in the case of forest plants should also be introduced during training programmes.

Training of Women

Many para-processing activities relating to industrial utilization of aromatic plants are labour intensive and therefore will generate employment particularly for women in rural areas. In order to seek their active and productive involvement, motivation seminars and training courses must be conducted. Training in entrepreneurship has also to be included to encourage women to participate in such activities.

Management Training

The viability and sustainability of industrial projects depends on good management practices. There is a dearth of resources in this area in developing countries. Furthermore as state and private sector institutions are involved, competitiveness has to be built into marketing strategies. The training in and involvement of management systems have been introduced into all projects.

MARKETING

Marketing is an unsurmountable problem besetting the development of the essential oils industry in developing countries as it is a function of two groups, the rich buyers and the helpless producers. The prices are dictated by the buyers who control the market. The poor producers have been let down many times that some have even given up processing oils in favour of other avenues to make a living. As a result, there could be the eventual disappearance of certain products from the markets. A case in point is the producers of Ylang Ylang oil in the Indian Ocean Region countries who are abandoning this product in favour of other crops because of the unreliability and the low prices of the market.

Marketability will be a crucial factor in determining the failure or success of industries. The market outlets can be for local use and for export. As for local use, some products could reach the consumer directly while others have to be either further processed or used as additives in other industries. Hence user industries have to be promoted so that locally produced essential oils can be used to save foreign exchange needed for importation of such additives. Further processing to yield value added products will be limited by the local demand situation unless they could be produced at prices to be competitive in the world market. Even if the cost of production is low and quality of the products are good, substantial market promotion has to be undertaken in order to penetrate the world market.

Market tie ups with progressive entrepreneurs from the developed world would be a convenient and a realistic option for securing markets for the finished products. Joint ventures or trade agreements could be initiated with companies that are expanding their production to meet the ever increasing demand for green products.

Following activities can be undertaken to improve the market outlets:

- feasibility studies for new ventures in terms of investments, marketability, sustainability and economic viability and explore joint venture activities.

- Increasing awareness of the potential use of essential oils in other industries amongst entrepreneurs through workshops, symposia and exhibitions.

- Trade promotion activities such as visits to brokers/buyers, participation in trade fairs.

RESEARCH AND DEVELOPMENT

Industrial development has to be accompanied if not preceded by research and development. Research and development is a high cost investment that most of the developing countries cannot afford. Nevertheless, research in the area of chemistry and bioactivity of indigenous flora of developing countries has been ongoing for quite sometime. These efforts have been funded through bilateral aid or non-governmental donor organisations. A systematic and a concerted approach to this activity has not been maintained for want of sophisticated equipment and high-cost chemicals. Moreover, these attempts have been mainly academic pursuits. The concept of applied research in the industrial use of plants has not received much attention. In other words, the contribution of this type of industry-related research in their own countries has been negligible.

Many countries have established research centres for the development of many food crops and cash crops but neglected developmental work on useful non-wood forest products such as essential oils. Even scientists have not given much attention to these products of commercial value except for those to be used for curative purposes. Hence most of the R & D work has been concentrated on the development of new drugs which requires large sums of money, long periods of research and sophisticated equipment and facilities, most of which are not available in developing countries.

Already many countries are exporting aromatic plants as raw materials to industrialized countries for processing. The income so obtained is very low and some value addition or even the finished product itself could be made at the local level in order to retain more value of the resources in the countries of origin. The secondary processing activities require a considerable effort in R & D which has to be carried out by already established research institutes and Universities. Sometimes these institutions may have to be strengthened to undertake such R & D work on essential oils. One of the constraints in this regard is the motivation of the scientific personnel who are bent on academic research and publications. Increase of awareness of the usefulness of applied research to the country and some incentives for such work could help in getting the scientists involved in R & D work directed at value addition to raw materials.

Any threat from synthetic products should be taken as a challenge and has to be combatted by vigorous R & D work to improve the economic competitiveness of the product. In the essential oil industry where the survival of many essential oils and flavour industries is largely due to the intensive research on breeding new and better oil yielding varieties, improvements on agrotechnology and post harvest technology, by-product utilization, value added product development, new formulations resulting in improving their competitiveness vis a vis synthetic substitutes.

Research work should encompass all activities ranging from the development of superior propagation materials, agrotechnology, low cost and efficient process technologies to improve quality and yield, quality specifications, new formulation, new products and market strategies.

In the area of essential oils, research has to be focused on quality improvement via secondary processing and on the production of aroma chemicals

Advances in genetic engineering and transgenic manipulations which contribute to development of high yielding and disease resistant clones can be transferred to the developing countries. These could easily be used to produce propagation material leading to improved yields and low costs of production.

INDUSTRIAL INFORMATION

Large volumes of literature are available on the chemistry of aromatic plants in various regions of the world. These focus mainly on research. There is very little authentic information on the extent of their use nor on world market trends. Agronomical data on industrially useful plants are rather scanty as compared to those on other agricultural cash crops. Many developing countries lack the resources to subscribe to research journals or acquire access to data bases. The few data bases which offer a

free service are now finding it difficult to continue the free service. Moreover, the data required by the scientific personnel in developing countries with respect to technologies and methods used for processing and formulation of useful plants are not readily available in the literature nor in the data bases

Having recognized the lack of access to and non-availability of information on industrial use of aromatic plants, UNIDO has played a small but a significant role in trying to fill this gap by publishing a manual on the essential oil industry and some proceedings of workshops so that the know how can be disseminated to a larger clientele. In addition, one can have access to the large number of technical reports submitted by consultants who assisted in the development of activities in very specific areas of the plant based industries.

National data bases

In view of the greater demand for information on traditional uses and proper identification of plants used in developing countries and the tremendous volume of information presently being generated, a user friendly information storage and retrieval system will be of considerable importance.

A national data base should be established to provide:

- list of plants
- distribution and availability
- traditional uses
- information on Research conducted in the country
- bibliographies and research publications
- Research Institutes carrying out projects
- results of scientific researchers including scientific data.
- formulations in use
- users of plant preparations
- trade and marketing aspects

EXPORT PROMOTION

Assistance required to promote the export of aromatic plant based products produced in the developing countries include expert advice on the assessment of market data, demand and supply situation, price trends, most feasible types and qualities of essential oils, that could be marketed, identification of different marketing arrangements and important trading houses, and introduction of short-and long-term strategies for export promotion.

Another approach entails getting the developing country companies to exhibit their products at trade fairs in developed countries in order to negotiate trade agreements and joint venture activities

INTERNATIONAL COOPERATION

Interregional cooperation can be initiated by holding seminars and workshops in developing countries to which participants from developed countries are also invited. These result in an exchange of know-how and the development of collaborative programmes. Some of these institutions provide training for scientists from other developing countries. Interregional activities should be encouraged so as to develop more South-South and North-South cooperation. The establishment of Regional Centres specializing in industrial activities relating to aromatic plants should be initiated.

CONTRIBUTION OF UNIDO

In accordance with its mandate to promote and accelerate the industrialization of developing countries and to increase the share of the developing countries in the total world industrial production, UNIDO pioneered an integrated action oriented programme for the systematic exploitation of medicinal

and aromatic plants resources for the benefit of the populace of developing countries. UNIDO initiated these programmes nearly two decades ago and has since improved and extended its activities in the field.

The main contribution of UNIDO to this process has been to build up technological and scientific personnel capable of sustaining, improving and developing the industrial utilization of medicinal and aromatic plants in the developing countries. Foci for activities in all areas ranging from cultivation to marketing have been created. Interaction and cooperation between research institutes and industry have been initiated, as a result of which research activity has increased as their findings are being translated into practical realities for the benefit of the society at large.

Technical assistance has been provided to rectify one or many of the constraints depending on the country situation and assistance requested. Furthermore, new crops have been introduced as required. As for technology development, UNIDO has secured improvements in distillation methods, including improved stills both for field and centralized processing and given assistance in the fabrication of equipment to suit specific requirements of the oils to be distilled. It has introduced quality assessment of the raw materials, processes and finished products. Fractionation of essential oils has also been introduced using the polyvalent processing plant. UNIDO has also supplied pilot-scale processing equipment, analytical equipment and some agronomical instruments, chemicals and books. Training has been provided to local staff in cultivation, post-harvest treatment, processing, analysis, packing and marketing, both locally and abroad. Reference standards, standard analytical profiles and journals have been provided. Where appropriate, technologies for the production of oleoresins, aroma chemicals and fragrance substances have been provided. Perfume blending has been introduced as a third stage of development.This has resulted in the establishment of local cosmetic industries.

Systematic crop-wise cultivation has led to environmental conservation the and protection of some endangered plant species. Para-processing activities have created employment opportunities for the rural poor, in particular women. Processing using clean and pollution free technologies have been introduced.

Above all, research and development capabilities, including human resources in developing countries have been greatly enhanced so as to ensure the growth of industries based on aromatic plants.

REQUIREMENTS FOR PLANT BASED INDUSTRIES

Major requirements for establishing aromatic plant based industries in developing countries can be listed as follows:

- Availability of natural forest resources capable of being sustainably harvested.
- Initiation of systematic cultivation programmes.
- Selection of plants for processing based on facilities available and the marketability.
- Fabrication or procurement of equipment, provision of required services (water, energy, chemicals etc.) .
- Transfer of know how on agronomical practices, harvesting and post harvest treatment.
- Training in methods of processing and quality control.
- Actual processing with assistance from experts (local or international) and NGO's and international agencies.
- Packaging and storage of finished products.
- Marketing outlets (local or export). International agencies should provide assistance in this area. In some cases the primary processed product could be used as a raw material for downstream processing such as production of aroma chemicals, isolates, flavours, perfumes, extraction of pure chemicals, and other consumer products.

The following aspects have to be taken into consideration in designing country specific programmes for implementation:

- suitability of climatic and soil conditions.
- availability of raw materials.
- economic benefit, if any, from export as well as import substitution.
- factors that hinder systematic cultivation and industrial production.
- appropriate technologies that could be absorbed.
- prospects for regional, interregional and global cooperation.
- inter-agency cooperation and collaboration
- other issues such as conservation, energy, employment generation and involvement of women.

A scheme for the establishment of processing industries based on plants is given in Figure. 4. It must be emphasised that the proper coordination of the multidisciplinary activities needed is vital for the success of industries venturing into this field.

CONCLUSIONS

The development of any industrial processing activity has to be linked to the specific needs, socio-cultural background, resource potential and the technological capabilities of each country. Consequently, any integrated development approach adopted has to exploit the full potential of this resource by providing a proper scientific, technological, economic and an industrial base.

Main factors impeding the development of essential oil industries in developing countries are the lack of:

- Awareness on economic benefits
- Information on resource availability
- Equipment and focused R & D work
- Technology and trained man power
- Recognition by governments
- Financial support, credit facilties and incentives
- Multidisciplinary team work
- Market contacts

Developing countries including those which are producing plant based products have to overcome many constraints to be competitive in the world market. Some of the problems associated with these industries in developing countries are:

- Absence of inventories on the useful plants and their abundance
- Poor agricultural practices
- Poor harvesting (indiscriminate) and post harvest treatment practices
- Lack of research on development of high yielding varieties, domestication etc
- Poor propagation methods
- Inefficient processing techniques leading to low yields and poor quality products
- Poor quality control procedures
- High energy losses during processing
- Lack of current good manufacturing practices
- Lack of R & D on product and process development
- Difficulties in marketing
- Lack of facilities to fabricate equipment locally
- Lack of access to latest technological and market information

Hence they require technical assistance to overcome one or many of the above constraints impeding the development of essential oils and their derivatives. Lack of qualified man power and appropriate technologies can be considered as the major constraints. Besides, concepts of quality

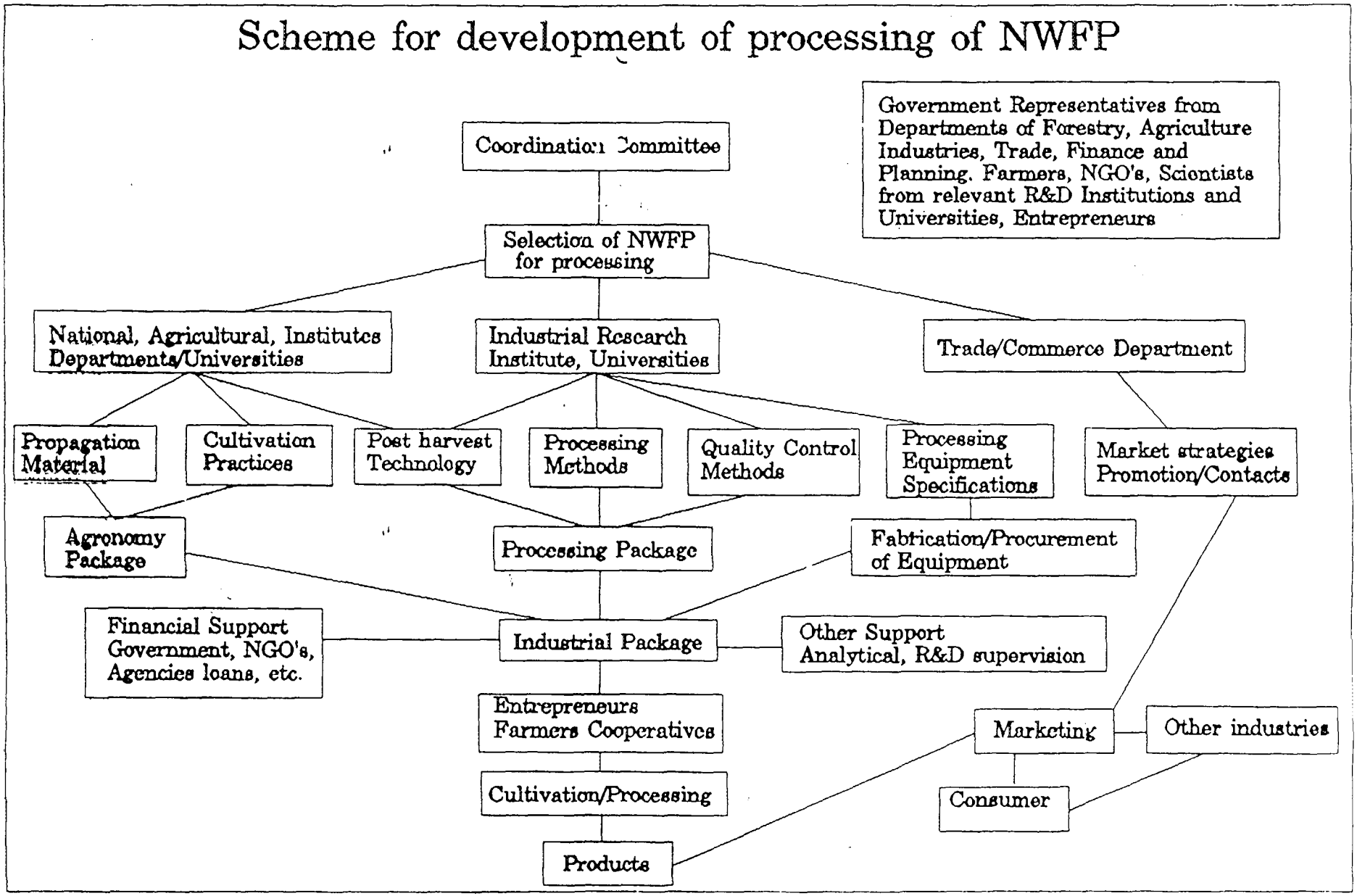

Scheme for development of processing of NWFP
Government Representatives from Departments of Forestry, Agriculture Industries, Trade, Finance and Planning. Farmers, NGO's, Scientists from relevant R&D Institutions and Universities, Entrepreneurs
Coordination Committee
Selection of NWFP for processing
National, Agricultural, Institutes Departments/Universities
Industrial Research Institute, Universities
Trade/Commerce Department
Propagation Material
Cultivation Practices
Post harvest Technology
Processing Methods
Quality Control Methods
Processing Equipment Specifications
Market strategies Promotion/Contacts
Agronomy Package
Processing Package
Fabrication/Procurement of Equipment
Financial Support Government, NGO's, Agencies loans, etc.
Industrial Package
Other Support Analytical, R&D supervision
Entrepreneurs Farmers Cooperatives
Marketing
Other industries
Cultivation/Processing
Consumer
Products

Figure 4

assessment, good manufacturing practices and customer safety concerns have to be introduced. More emphasis has to be laid and opportunities have to be provided for the transfer of research findings to the industry. Strengthening University-Industry links would assist in this regard.

As for the small scale producers of rural areas, integration with central downstream processing factories in the country would be essential to have a regular market for the primary products. These factories will produce requirements for other industries such as cosmetics, detergent, paint, paper and pharmaceuticals and should be encouraged. This link of secondary product produce and consumer industries too should be strengthened so as to have a complete chain of operations from the farmer to the consumer as a viable alternative to export.

Developing countries need to build up the technological and scientific capabilities to develop, and improve the production of essential oils for use in their countries and to conduct R&D to develop products for export thereby enabling countries to supply new markets which are being created as a result of consumer orientation of societies, increasing affluence and demand for green products. Sustainable use of this renewable natural resource will not only contribute to rural industrial development and poverty alleviation but also to biodiversity and forest conservation.

Extract: A concentrate of a dried less volatile aromatic plant part obtained by solvent extraction with a polar solvent.

Infusion: A hot extraction of either a plant part of its exudate with either water or an organic solvent. Infusions are not at all popular because it is difficult to control their chemical composition.

Tincture: An alcoholic or aqueous alcoholic extract of a natural raw material in which the solvent is left in the extract as a diluent. Tinctures are used both in the fragrance and pharmaceutical industries. The amount of alcohol in the tincture, which ranges from 20-95%, is standardized by the manufacturer.

Spice/Herb Oleoresin: A solvent extract of a dried spice or herb which is virtually free from the extracting solvent. It is used exclusively by the food and pharmaceutical industries as a replacement of ground spices and spice tinctures.

Essential Oil: The isolated aromatic portion of a plant that is borne in that plant within distinctive oil cells. In some exceptional cases the essential oil is formed during processing. Most essential oils are isolated by either hydrodistillation or cold pressing.

Extrait: An alcoholic extract of a pommade produced by enfleurage. It is a tincture of a pommade.

Balsam: A natural exudate obtained from a shrub or a tree. It is characterized by being rich in benzoic and cinnamic acids and their corresponding esters.

Gum Resin: A natural exudate obtained from a tree or plant. It is comprised of gums and resins. If the gum resin source also contains an essential oil, it is called an oleo-gum-resin.

Oleoresin: The natural tree trunk or bark exudate which is extremely rich in an essential oil.

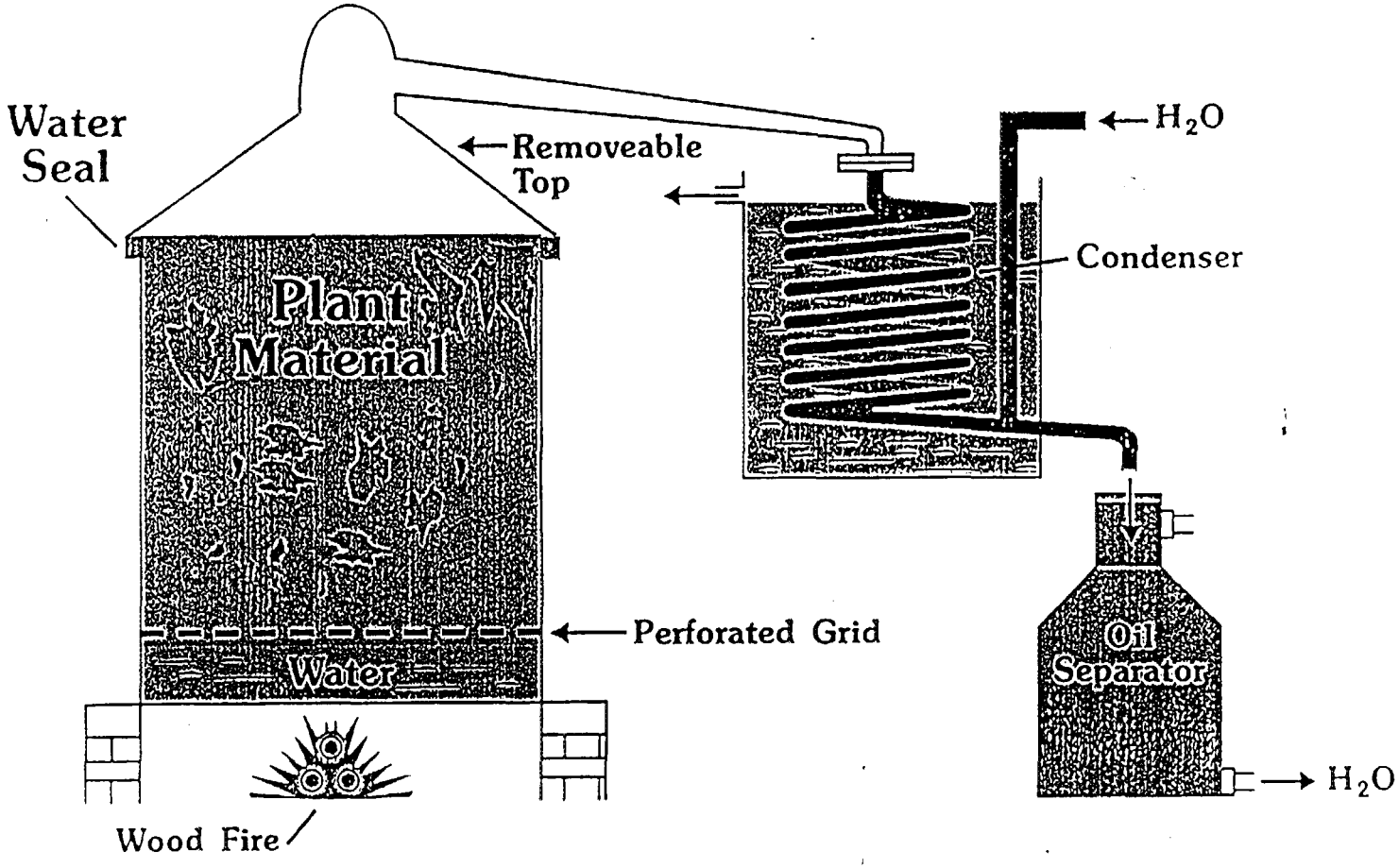
Concrete: An extract of fresh plant parts by the use of a hydrocarbon solvent. It is rich in hydrocarbon soluble material and devoid of water soluble components. It is generally a waxy semi-solid dark colored material free from the original solvent.

Absolute: A highly concentrated alcoholic extract of a concrete which contains only alcohol soluble materials. Its primary use is in alcoholic perfumes. It contains only a very low level of alcohol.

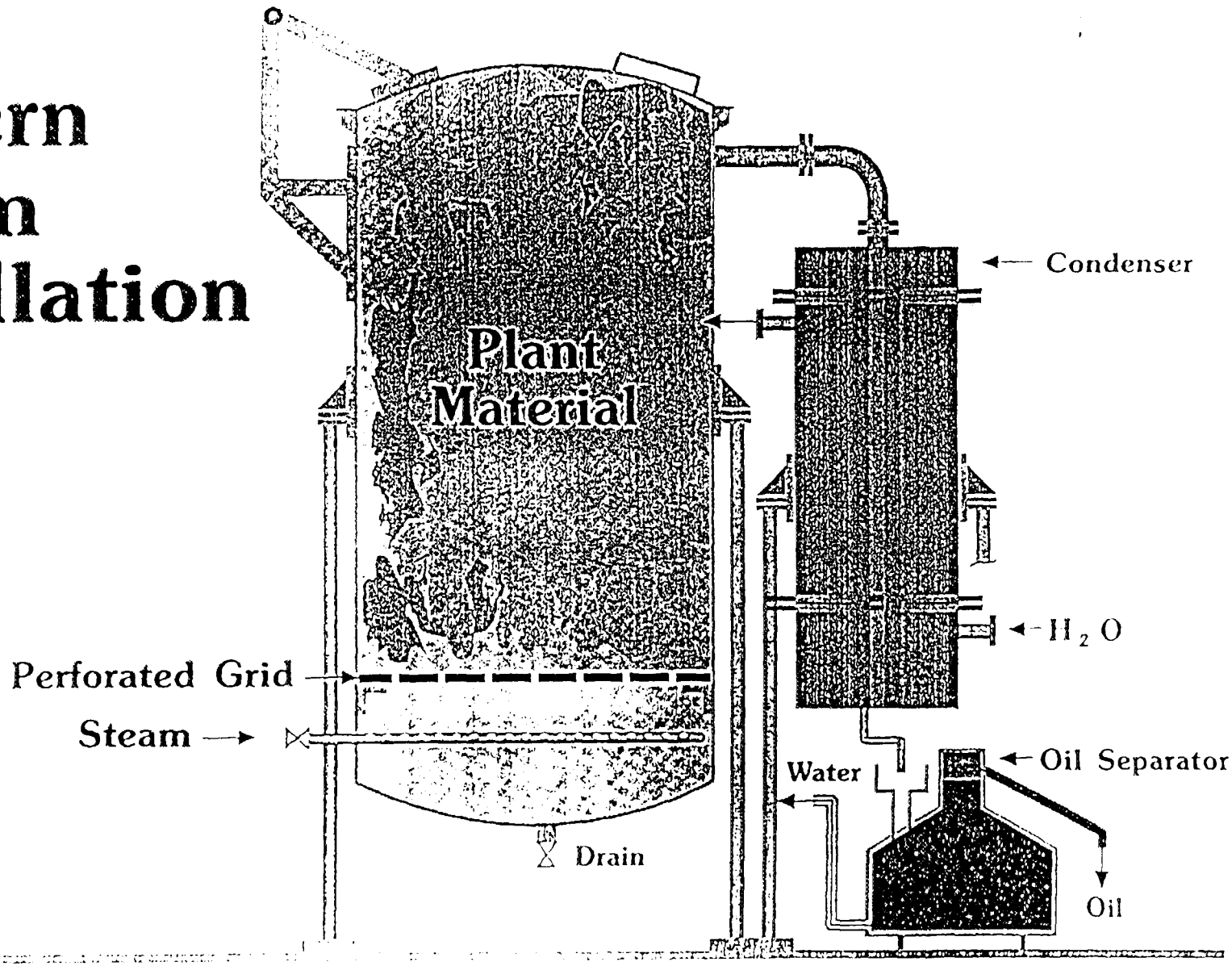
Pommade: The product of the enfleurage fat extraction of fresh flowers.

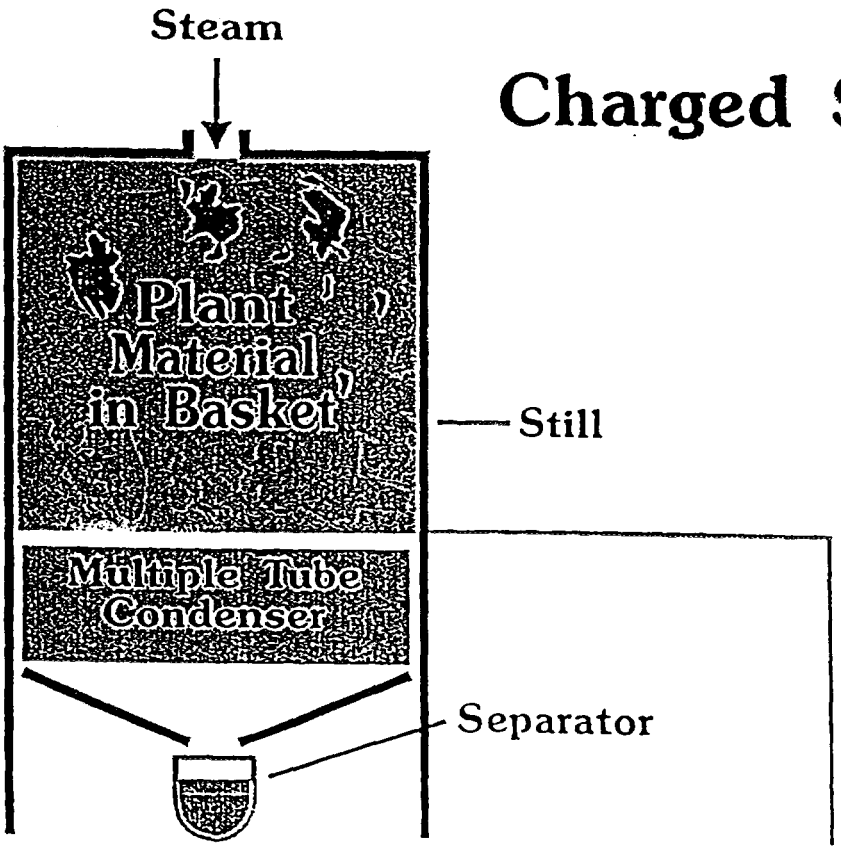
Resinoid: A solvent extract of a resin-rich containing natural exudate or dried plant material with a hydrocarbon solvent. Resinoids are generally viscous to semi-solid mixtures. They can be considered as being concretes of dried materials.

Traditional Steam and Water Distillation Still



Modern Steam Distillation Unit





HYDRODIFFUSION DISTILLATION PROCESS
(DIAGRAMMATIC)

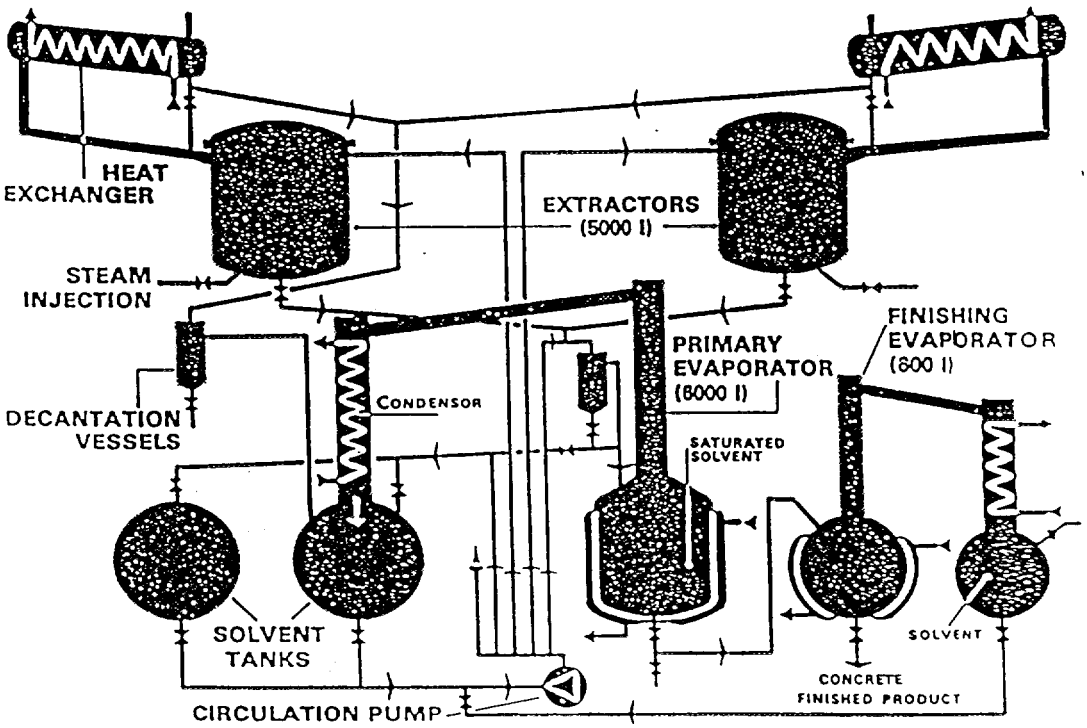


Figure Diagrammatic representation of the concrete extraction process

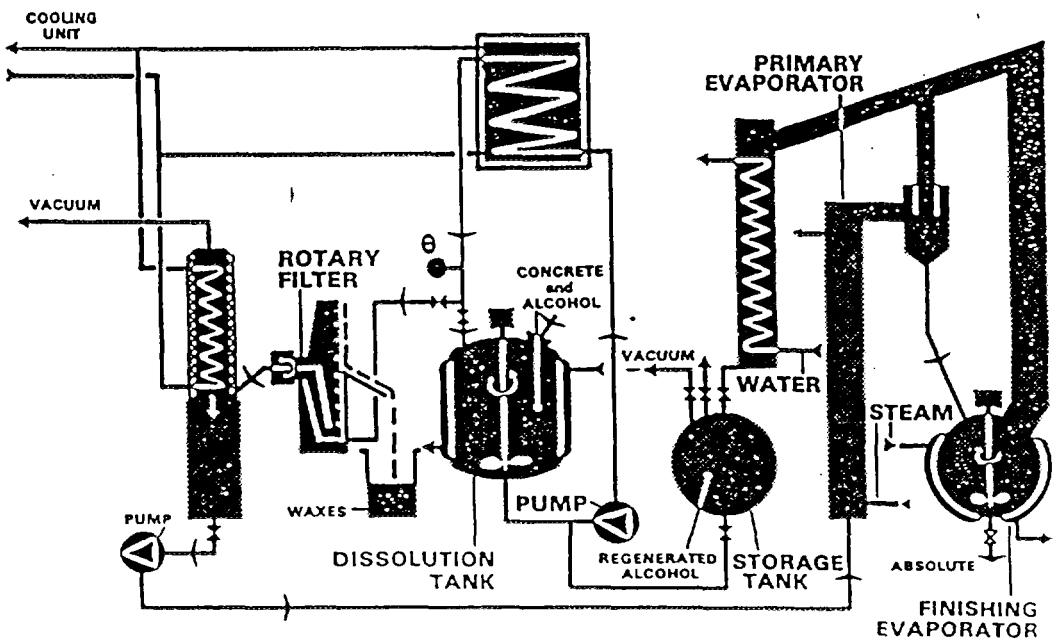
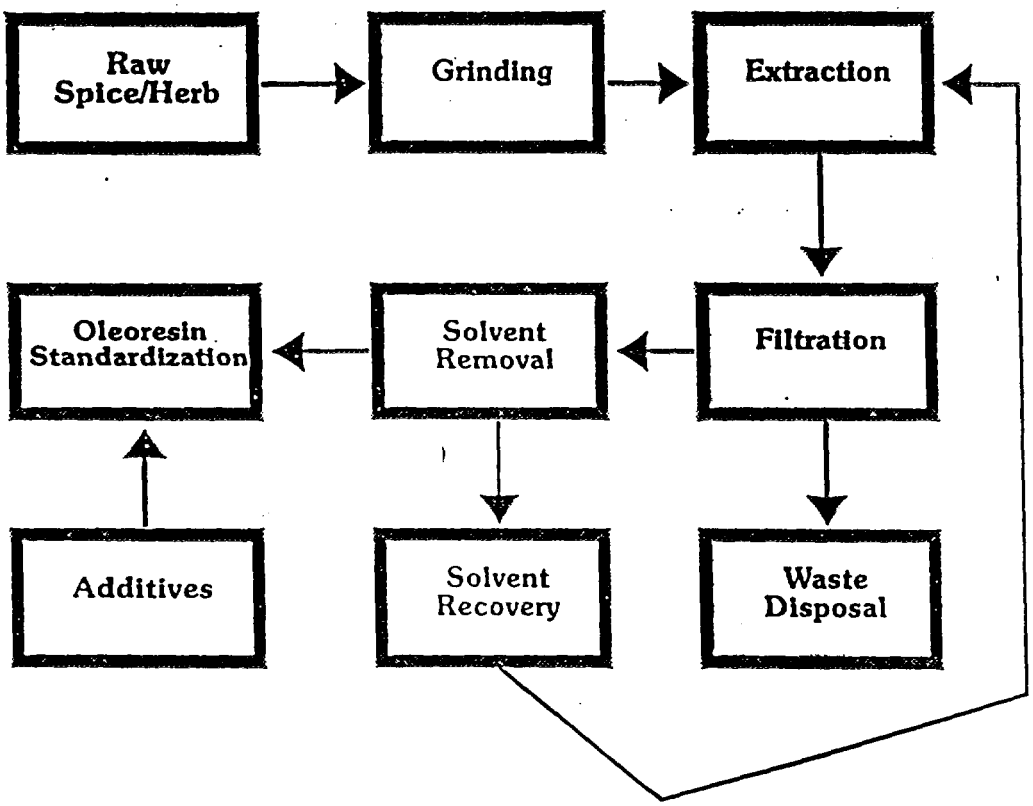


Figure Diagrammatic representation of the process to convert concretes into absolutes



OLEORESIN MANUFACTURING PROCESS
SINGLE STAGE (FLOW DIAGRAM)

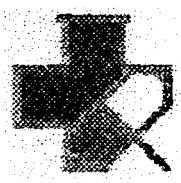
Industrial Exploitation of Indigenous Medicinal

and Aromatic Plants:

Formulation and Industrial Utilization

Dr. Krisana Kraisintu

Research and Development Institute
Government Pharmaceutical Organization
THAILAND



BEIJING, CHINA, 17-27 JUNE 1997

What's in the Name?

- **Herbal medicines**
- **Botanicals**
- **Phytopharmaceuticals**
- **Traditional Chinese medicines (TCM)**
- **Ayurvedics**
- **Complementary Alternative Medicine (CAM)**

Phytopharmaceuticals should always contain the active principles together with coexisting materials from the source plant, these additional materials having a greater or lesser beneficial influence upon the activity of the drug.

Significant Consumer Interest Shift towards Natural Product

Consumer perceive modern health care to be ineffective, expensive, and having undesirable side effects.

People today want to prolong their lives, protect their good health and promote a more active lifestyle.

With more leisure, interests have turned toward health and fitness, preventive instead of cure.

Consumers preferred "natural" products instead of synthetic "chemicals".

Phytopharmaceuticals as "Nutritional Supplements"

- ***Advantage***
  - Easy access for consumers
  - Low cost
- ***Disadvantage***
  - No quality control
  - No proof of safety of efficacy
  - Problems in labeling

Phytopharmaceuticals as "Drugs"

- Research:
  - Evaluation and validation; methodology and outcome measurement
- Quality Assurance:
  - In process monitoring; source material
- Clinical Trials:
  - Requirement and design

Therapeutic Categories

Acne

Alters Vaginal pH

Analgesic

Analgesic & Anesthetic

Analgesic & Anesthetic & Antipruritic

Anorectic

Antacid

Anticholinergic

Antidiarrheal

Antifungal

Antimicrobial

Antipyretic

Antirheumatic

Antiseptic

Antitussive

Aphrodisiac

Astringent

Benign Prostatic Hypertrophy

Boil Treatment

Bronchodilator

Bulk Laxative

Cholecystokinetic

Corn & Callus Remover

Corrective

Counterirritant

Dandruff

Demulcent

Diaper Rash

Digestive Aid

Diuretic

Dysmenorrhea

Emetic

Expectorant

External Analgesic

Fever Blister

Hair Grower

Hyperosmotic Laxative

Ingrown Toenail

Insect Bite & Sting

Menstrual

Minimize inebriation

Minor Irritations

Mucolytic Effects

Nasal Decongestant

Oral Muscosal Protectant

Overindulgence Remedies

Pediculicide

Poison Ivy, Oak & Sumac

Protectant (External)

Protectant (Internal)

Saline Laxative

Skin Protectant

Sleep Aid

Smoking Deterrent

Stimulant

Stimulant Laxative

Sunscreen

Toothache Relief

Wart Remover

Wound Healing

Dosage forms

HERBAL TEAS, HERBAL REMEDIES

Herbal tea or infusion mixtures are mixtures of unground or suitably ground medicinal plants to which drug plant extracts, ethereal oils or medicinal substance can be added.

Drug plants have to be suitably ground to the following particle sizes:

Leaves, flowers and herbs 500 mm

Leaves, flowers and herbs with leaf veins more than 300 mm thick 3150 mm

Fruits, seeds woods, barks, roots and rhizomes 3150 mm

Infusion mixtures should be as homogeneous as possible. If they become slightly inhomogeneous they should be thoroughly mixed again in a suitable manner before being dispatched.

STANDARDIZED DRUG POWDERS

Accurate dosing of potent drugs requires the exact determination of their active substance content. Standardized powders are therefore used for dispensing and in pharmacies.

DRUG EXTRACTS

Drug extracts are preparations obtained by extracting drugs of a certain particle size with suitable extraction agents (menstrua). The extract obtained after separation of the liquid from the drug residue is called a miscella.

It may already represent the final liquid dosage form, e.g. as a so-called fluid extract, or be used as an intermediate product which is to be further processed as quickly as possible.

3.1 Aqueous drug extracts

Depending on the type of plant parts are used for the extract in the following degrees of comminution:

Leaves, flowers and herbs shredded	(4000 mm)
Woods, barks and roots shredded	(2800 mm)
Fruits and seeds	(2000 mm)
Alkaloid-containing drugs powdered	(710 mm)

3.1.1 Decoctions

The drug in the prescribed commimution, is put into water at a temperature above 90°C. The container is suspended in a water-bath and maintained at this temperature for 30 min, with repeated stirring. The mixture is then strained while still hot.

If the prescribed weight of the decoction is not attained after gentle expression of the drug residue, the required quantity of boiling water is poured on to the

residue which is again gently expressed. This second extact is added to the main decoction to give to the prescribed weight.

3.1.2 Infusions

one part of drug in the prescribed comminution is kneaded several times in a mortar with 3-5 parts of water and left to stand for 15 min..

The rest of the boiling water is then poured on to the mixture, which is suspended in a container in a water-bath and kept for 5 min, with repeated stirring, at a temperature above 90°C. The mixture is covered and left to stand until cool.

If the prescribed weight of infusion is not obtained after gentle expression of the drug residue, the required quantity of cold water is poured on to the residue which is gently squeezed out again. This second extract is added to the main infusion to make it up to the prescribed weight.

3.1.3 Macerates

The drug, comminuted as prescribed, is left to stand, with occasional stirring, for 30 min after the required quantity of water has been poured on to it at room temperature. The extract is then strained and made up to the prescribed weight with the rinsings.

3.1.4 Aqueous drug extracts prepared on industrial scale

Water, if necessary mixed with lower alcohols, plays an increasingly important role as menstruum for the technical preparation of drug extracts, especially where the end-product is to be a dried extract wich is to be clearly soluble in water.

Spray-drying has made it possible to obtain powders which are easily soluble in water. Aqueous miscellae (solution containing extracted substance), especially when they are prepared at a low temperature in order to preserve the active substances,

contain numerous microorganisms such as bacteria, fungal moulds and yeasts, which contaminate the plant starting material. The miscellae also act as an excellent nutrient medium for the replication of the microorganism.

3.2 Tinctures

Tinctures are extracts from drug plants prepared with ethanol of varying concentration, ether, or mixtures of these, perhaps with certain additives, in such a way

that 1 part of drug is extracted with more than 2 parts, but at most 10 parts, of extraction liquid.

Solutions of dried extracts in ethanol of suitable concentration are also regarded as tinctures.

3.3 Fluid extracts

Fluid extracts, like tinctures, are liquid preparations, the difference being that they are more concentrated.

3.4 Dry extracts

Dry extracts are usually very hygroscopic, and should therefore be ground and mixed under conditions which exclude moisture as much as possible. intermediate and end-products must also be stored under dry conditions.

Annealing or sealing of the products in suitable moisture tight synthetic foils has proved a good method for this.

Pharmaceutical development

Liquid dose forms

Liquid preparations may be solutions, emulsions or other colloidal preparations , or suspensions , in increasing order of 'particle size', and may be intended for administration parenterally , orally or topically , including administration into body cavities.

Semi-solid dose forms

The physical forms of these products tend to be solutions or dispersions (analogous to liquid suspensions) of an active substance in a vehicle.

Particle size may need particular attention , to ensure correct dispersion properties, as well as to guard against possible mechanical abrasion generated by large 'gritty' particles.

Many topical semi-solids are required to be sterile when they are intended for use in critical areas, such as the eye or wounds or large areas of broken skin, especially in immunocompromised patients.

Even non-sterile semi-solids may require the inclusion of an anti -microbial preservative if intended for use on more than one occasion if they are aqueous based and are not self-preserving.

Solid dose forms

Homogeneity of the formulation, however, does become a major consideration in solid dose forms, particularly where the active ingredient is present in lower concentration than the excipients. Powders in dry mixes tend to segregate because of their different surface properties, crystallinity, particle size, etc.

Controlled release preparations

In certain preparations the release of the active substance from the dose has been altered compared with conventional release preparations in order to achieve some particular therapeutic goal.

Such modifications may be carried out for a variety of purposes including prolonged effect, reduced frequency of dosing, reduction in toxic effects, or even a change in indications or an increase in activity.

Solid dose oral preparations

The classic example of such a product is the gastro-resistant (enteric coated) preparation designed not to release the drug until the product has passed through the acid environment of the stomach and reached the small intestine.

In the second case the rate of release of the active substance from the formulation is altered in order to meet the therapeutic target.

Liquid preparations

Liquid formulations for oral use have also been developed based on colloidal or particulate micropheres in an aqueous continuous phase. A number of liquid pharmaceutical formulations have been investigated based on liposomes.

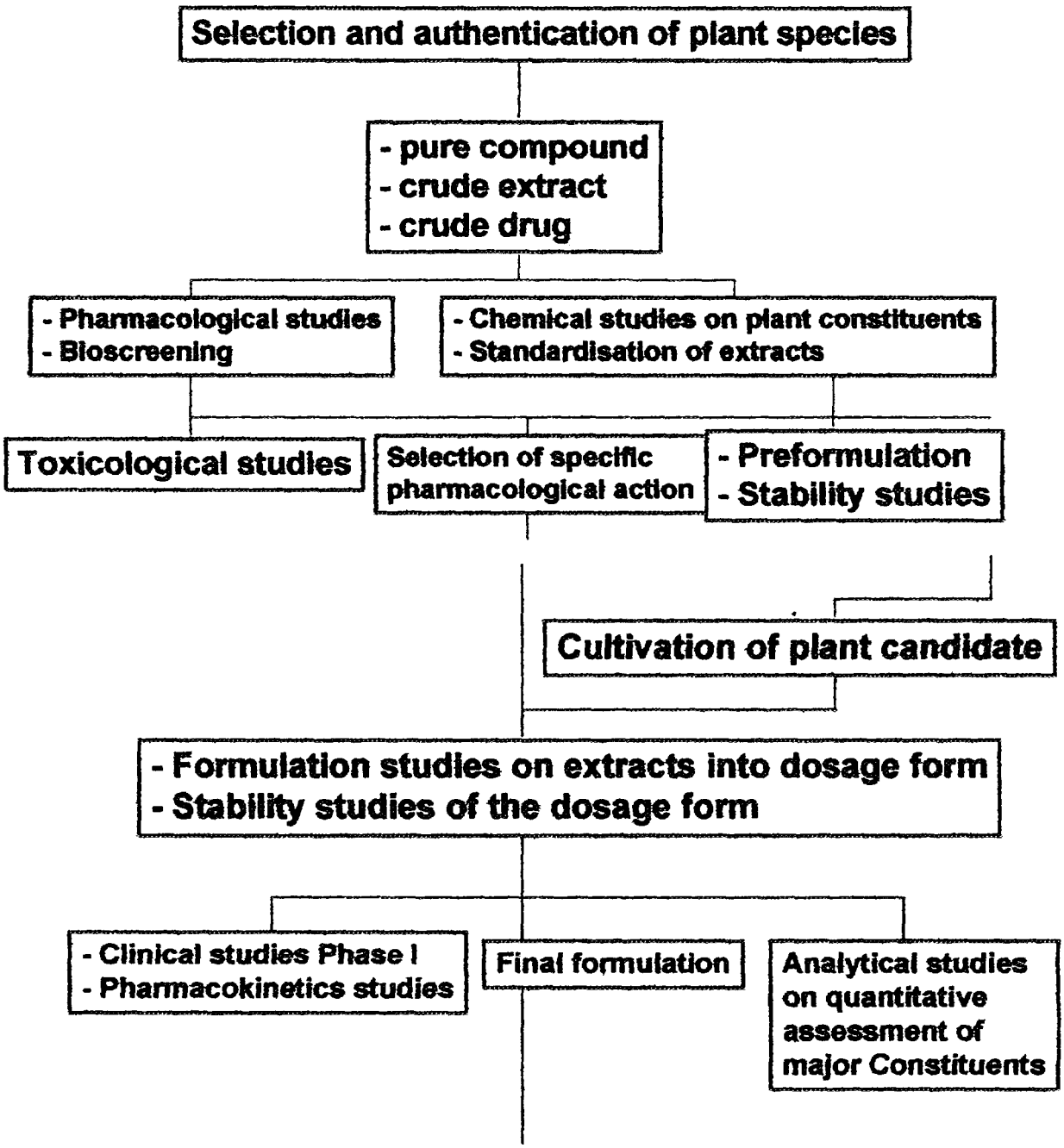
These are microscopic vesicles composed of bi-layered phospholipid membranes enclosing water, which can be used to entrap drug substances.

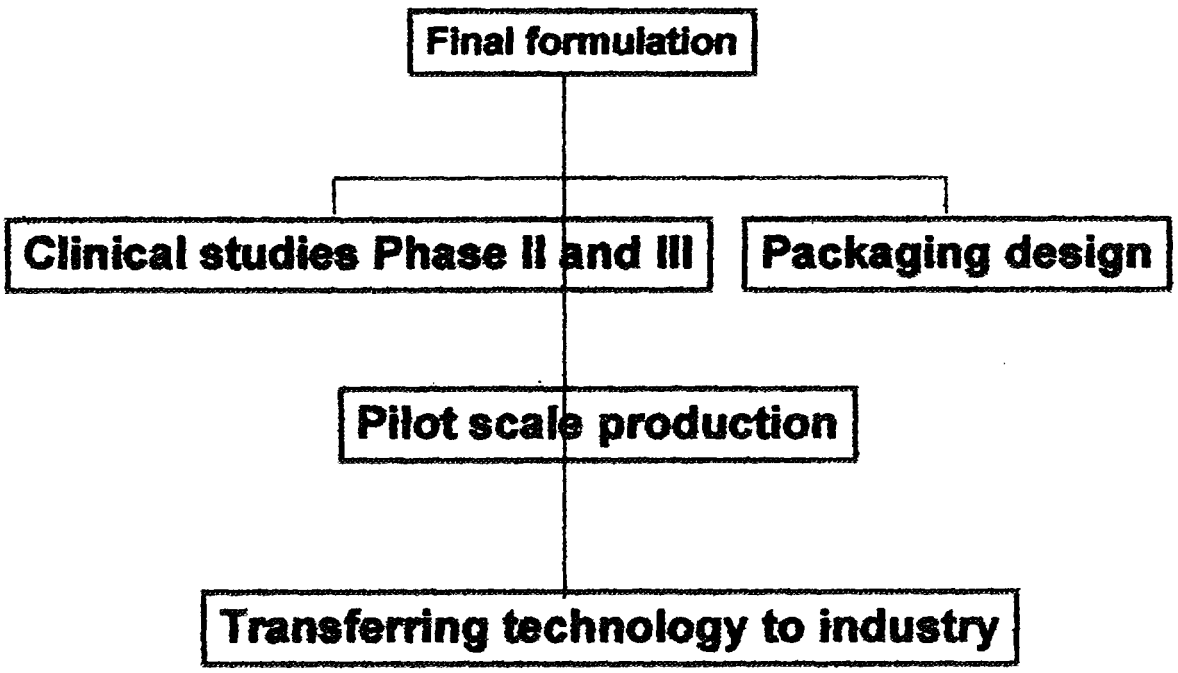
Liposomes used for drug delivery range in diameter from 25 nm to several micrometres, and are usually suspended in an aqueous medium.

Other dose forms

- **Injections and implants**
- **Ocular preparations**
- **Inhalation therapy**
- **Transdermal systems**

Multidisciplinary approach to drug development from medicinal plants





Raw Materials

The most important enzymes which break down substances for the production of drugs are:

- Oxidases and peroxidases, which mainly oxidize phenols, unsaturated fatty acids, terpenes, etc.
- Hydrolases, which cleaves esters and glycosides and break polysaccharides
- Isomerases, which for example isomerize ergot alkaloids or other optically active substances

There are two ways of protecting the drugs from the action of these enzymes:

- Drying as rapidly as possible
- Denaturing the enzymes

Problems in the production of drugs of Pharmacopoeia quality

(1) The drug is not as specified in the Pharmacopoeia because of deliberate or inadvertent substitution or adulteration.

(2) The plant parts do not correspond to those sited in the Pharmacopoeia

(3) The permitted level of "foreign matter" laid down in Pharmacopoeia has been exceeded.

(4) The maximum value of sulphate ash has not been adhered to.

(5) The minimum content requirements for certain constituents either cannot be fulfilled for one year at all or cannot be fulfilled for quantities sufficient to meet demand.

(6) The drug has been rendered unfit for use through infestation or microbial spoilage.

(7) Microorganism contamination is too high.

(8) Pesticide or preservative residues exceed permitted levels.

(9) The quantities of heavy metal residues are in exceed of those laid down for foodstuffs.

(10) Economics and industrial factors, for example standards, or sociologicals problems especially in the countries where the drugs are produced, make it difficult to meet the demands of the Pharmacopoeia, particularly with regard to providing a continuous supply.

(11) Legal regulations, e.g. the law on the import and export of wild animals and plants, caused almost insuperable difficulties when they are brought into force too quickly.

Packaging materials

General properties required for a possible suitable packaging material :

1. Economical or of a suitably low cost;
2. Impermeable - e.g. as glass or metal or of acceptable permeability to moisture, gases, volatile solvents, etc.;
3. Non-reactive - i.e. relatively inert - no extraction, exchange or interaction;
4. Easy to manufacture in a wide range of shapes, preferably by a number of manufacturing processes;
5. Easy to decorate and/or print, again by a range of processes;
6. Good production line efficiency-performance, with the minimum of rejects or

wastage;

7. Effective as a pack (container and closure), i.e. easy to open and reclose and use if multidose; or open if single dose; whilst meeting any special requirements such as child resistance, tamper evidence/resistance, etc.;
8. Easy to produce and maintain clean, etc. (i.e. low in particulates and bioburden);
9. Preferably readily available both in terms of source of supply for raw material (s) and as a converted item component from several suppliers, although 'just in time' (JIT) philosophies have created a trend towards single supply sources;
10. Environmentally friendly or 'environmentally responsible'(very much subject to various interpretations);
11. Able to optimise use of space when stacked (warehoused) or during transportation.

Types of Packaging materials

Glass in packaging

Glass can be found as several variants : (Type I), treated soda glass (Type II) and soda glass (Type III) and non parenteral [NP]).

Metals in packaging

A variety of metals, including tin-plate (tin coated mild steel), tin-free steel, aluminium, aluminium alloys, etc., are widely used in packaging, being found as rigid containers, collapsible containers, aluminium foils (mainly used as a part of combination materials), metallised coatings, etc.

Plastics in packaging

There are five economical materials materials for rigid type containers -i.e. those based on polyethylene (PE), PP, polystyrene (PS), PVC and polyester (polyethylene, PET).

Elastomeric materials (mainly used for closures)

Elastomers can be found as a wide range of basic materials (i.e. natural rubber, synthetic polyisoprene, neoprene, nitrile, butyl, including bromo- and chlorobutyl, ethylene propylene diene modified [EPDM], and silicone elastomers, etc.) which are further extended by specific formulations.

Generalized Production Scheme

Pre-processing

- Washing
- Particle size optimization
- Moisture reduction
- Refinement/concentration

Solubilization

- Insolubles removal
- Product stabilization

Primary extraction

- Primary contamination (s) removal

Purification

- Secondary contamination (s) removal
- Decolorization
- Concentration
- Racemization

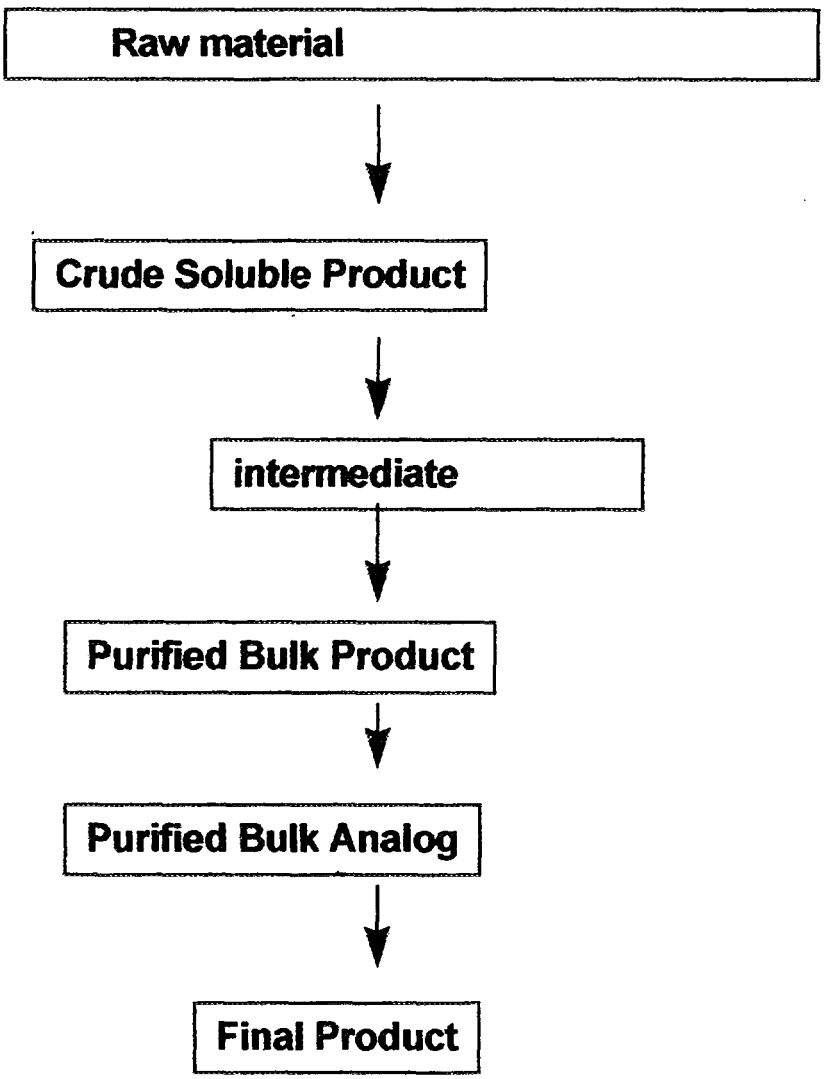
Derivatization (optional)

- Chemical modification

Drying (optional)

- Lyophilization / Spray drying

Generalized Production Scheme



Special Considerations for Manufacturing

Raw material pre-treatment

concentration and availability of actives

Generation of hazardous wastes

wastes with low solvent content

Low number of unit operations

less than 5% yield loss/operations

minimum 60% yield, optimum 85%

Nature of product

thermal and chemical stability

isomeric forms

Worker safety

cytotoxins

allergens

volatile solvents

Manufacturing Efficiency

Process	Yield Loss	
§ Pre-processing	2 - 10 %	
§ Solubilization	5 - 50 %	
§ Primary extraction	5 - 20 %	
§ Purification	2 - 5 %	
§ Drying	1 - 3 %	
TOTAL	15 - 88 %	(40 % average)

Purification Process

Most purification processes use two or more chromatography methods

Column chromatography choices:

§ size exclusion

§ ion exchange

§ affinity interaction

§ hydrophobic interaction

§ reverse phase

Considerations:

§ Temperature

§ Insolubility

§ Chemical stability

§ Rigidity and physical reusability

Major Cost factors in cGMP Manufacture of Plant Medicinals

Raw materials (actives content < 0.1 %)

Capital cost of chromatography equipment

Capital and operational costs

Environmental, Health and Safety

§ Fire control

§ worker exposure

§ HVAC systems

§ Air emissions and wastewater discharge

§ Worker training

§ Hazardous waste disposal

§ cGMP documentation

Quality assessment of botanicals

- Assessment of crude plant material
  - General description of the plant
  - Part used
  - Production of crude drugs
    - Cultivation
    - Harvesting
    - Post-harvest handling
    - Packaging and storage
  - Quality specification
    - Quality specification
    - Chemical/chromatographic identification
    - Foreign organic matter limit
    - Ash content
    - Acid-insoluble ash content
    - Water-soluble extractive

- Alcohol-soluble extractive
- Quality specification
  - Moisture content
  - Main/active constituent content
  - Microbial limit
  - Pesticide residue limit
  - Heavy metal limit
  - Likely contaminants
  - Adulterants

■ Assessment of finished product at intermediate stage of the manufacturing process

Same as described for finished products

■ Assessment of finished product

- For tablets
  - Weight variation
  - Disintegration time (not more than 30 minutes)
  - Identification of preservatives and active ingredients
  - Determination of extractives in various solvents
  - Microbial limit
  - Heavy metals
- For solutions
  - pH
  - Identification of preservatives and active ingredients
  - Alcohol content (not more than 15 percent)
  - Microbial limit
  - Sodium saccharin content (not more than allowable limit)
- For infusion
  - Weight variation
  - Identification of preservatives and active ingredients
  - Determination of extractives in various solvents
  - Microbial limit

- Heavy metals
- Borax

- For sugar coated tablets Similar to tablets except for disintegration time which is not more than 1 hour

Chemical Standardization Methods - Challenges

- Complex and variable mixtures
- Choice of compounds to quantitate
- Difficult sample preparation
- Lack of pure reference standards
- Lack of methods with adequate tolerances by analytical chemistry standards

Chemical Standardization Methods

- TLC/HPTLC
- HPLC
- FTIR

Chemical Markers

- Specifications for raw materials
- Quality assurance in process control
- Standardization of product
- Obtain stability profiles
- Single marker vs. "fingerprint"

Parameters of Assay Validation

- Linearity
- Limits of Quantitation and Detection
- Precision
- Robustness
- Recovery

Limits for microbial contamination

- 6 types of non-sterile pharmaceutical preparations
  - Preparations for burns and severe ulcerations
  - Topical preparations for broken skins, abscess, lesions, and mucous membranes
  - Topical preparations for intact skin
  - Preparations for oral, rectal and transdermal use

Preparations of crude drugs and mixtures of crude drugs for internal use, which will undergo a process for reduction of count before use

- Other internally used preparations which contain whole or ground crude drugs

Stability test

- The stability of the medicinal product should be determined by appropriate fingerprint chromatograms

It must be shown that interactions between the active ingredients and the excipients in the finished product are unlikely to occur

New FDA Policy?

"A long history of safe use might provide sufficient safety information for products that are intended for short-term use. For some thing that's given only briefly.....for short term, you may consider the history of exposure, if it can be documented recently, as relevant safety. However, (it is still) questionable whether a history of safe use would be adequate to support the safety of an ingredient intended for regular, long term use."

"We don't have a rule that people who carry out trials have to be physicians. I don't see why someone with (an herbal) background couldn't carry out the trial. Someone who's experienced in (herbal) use, and believes that certain things are true is probably the best person to help design the trial. You can test Eastern philosophy in a Western controlled trial."

Four FDA Policy Issues (1)

■ Question:

Will HPLC "fingerprints" and markers support composition, uniformity and reproducibility of heterogeneous, multi-component products?

■ Answer:

Yes, technology exists to assure batch to batch consistency with quality control and stability control via HPLC and other analytical techniques.

Four FDA Policy Issues (2)

■ Question:

Would FDA consider the efficacy of multi-component botanicals without requiring studies on the contribution of each ingredient to efficacy?

■ Answer :

Yes, based on the approval of IND's for botanical formulas of heterogeneous multi-component ingredients FDA now appears willing to evaluate these as single therapeutic entities.

Four FDA Policy Issues (3)

■ Question:

Can FDA be convinced to consider "unevenful, long-term usage of botanicals by large numbers of humans" as an adequate predictor of safety in lieu of animal toxicological studies?

■ Answer:

- Are two year studies in 100 animals as predictive of human safety as hundreds of year experience in 1000's of human?

Four FDA Policy Issues (4)

■ Question:

Would FDA consider long-term use combined with pilot clinical trials as sufficient to support the effectiveness of a botanical product?

■ Answer:

A "general consensus" exits in support of the idea that smaller "pilot-type" clinical trials may be acceptable when accompanied by a large body of historical use data.

INTRODUCTION TO THE CHINESE MATERIA MEDICA

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INTRODUCTION TO THE CHINESE MATERIA MEDICA

1. Chinese materia medica - traditional drugs, herbal drugs and minority drugs
2. Books on Chinese materia medica - classical and comtemporary
3. Some basic concepts in classical medical theories - some physiological concepts, standards of value and systems of correspondence
4. The classical pharmacology and pharmacological classification of drugs
5. A comparison with the Occidental materia medica and concepts in classical pharmacology
6. The prospect

Chinese Materia Medica

Chinese materia medica consists of the following component parts:

- Traditional drugs - "Zhong-yao"
  More specifically, the term refers only to those items when used therapeutically according to the guidelines of traditional medicine.
- Herbal drugs - "Cao-yao"
  This is a literal translation. But a more appropriate rendering would be folk drugs and it does not necessarily mean to be drugs of plant origin.

  They are usually more recent recognition, more often used singularly, and more specific to the treatment. They are candidates to the armamentarium of traditional medicine.
- Minority drugs -
  The more important ones are Mongolian and Tibetian drugs.

Chinese Materia Medica

- The Encyclopoedia of Chinese Materia Medica (Zong-yao Da Ci-dian) published in 1977 records 5,767 drugs of plant, animal and mineral origin. It is assumed that more than 80 per cent are derived from plants.
- A recent survey (1) has identified 4,877 plant species with therapeutic value although only about 600 are in common usage.
- The current Chinese Pharmacopoeia (1977 ed.) is published in two volumes. Volume one devotes itself entirely to Chinese materia medica which carries 774 single entities and 270 compound formulations.

Table 1 PLANT SPECIES WITH THERAPEUTIC VALUE

Origin	Number of plant species
Thallophytes	230
Bryophytes	39
Pteridophytes	382
Gymnosperms	55
Angiosperms - Dicotyledones	3,495
Monocotyledones	676
Total	4,877

After Xiao Peigen, in J.L.Beal and E.Reinhard(eds.): Natural Products as Medicinal Agents, p.355

Table 3. cont'd

Title	Author/Compilers (date of work)	Content
(4) Jing Shi Zheng Lei Bei-ji Ben-cao	Tang Shen-wei (Ca.1086-1106 A.D.)	The book was later submitted to the the throne and issued by the state as "Da-guan Ben-cao". A revised edition was issued in 1116 A.D. as "Zhen-he Ben-cao". 32 volumes in all, it describes 1748 items of drugs.
(5) Ben-cao Gang-mu	Li Shi-zhen (1552-1578 A.D.)	Published in 1596 after the death of the author. 52 volumes, describes 1892 drugs, (1094 are plants, 444 animals, and 275 minerals.) The drugs are classified into 16 groups comprising 62 sub-groups. With 11,096 formulations.
(6) Ben-cao Gang-mu Shi Yi	Zhao Xue-min (1765 A.D.)	In 10 volumes, the book describes 716 items which are not included in Ben-cao Gang-mu with further 205 as appendices.

Contemporary Books on Chinese Materia Medica and the Growth in Number of Drugs

- The Chinese Pharmacopoeia: The pharmacopoeia was issued in two volumes in 1977 for the first time. Volume one devotes itself entirely to Chinese materia medica, describing 774 single entities of drugs and 270 compound formulations.
- Zhong-yao Da Ci-dian or Encyclopoedia of Chinese Materia Medica: It is the most comprehensive compilation on Chinese materia medica to date. Published in 1977 in two volumes, it describes 5,767 drugs with drawings.
- Zhong-yao Zhi or the Chinese Materia Medica: It is intended to be a standard handbook. Published from 1959 onwards in four volumes describing 494 drugs in detail. The first volume of a 2nd edition appeared in 1979 and it is to be completed in six volumes.

The growth in number of drugs is momentary since the inception of this century.

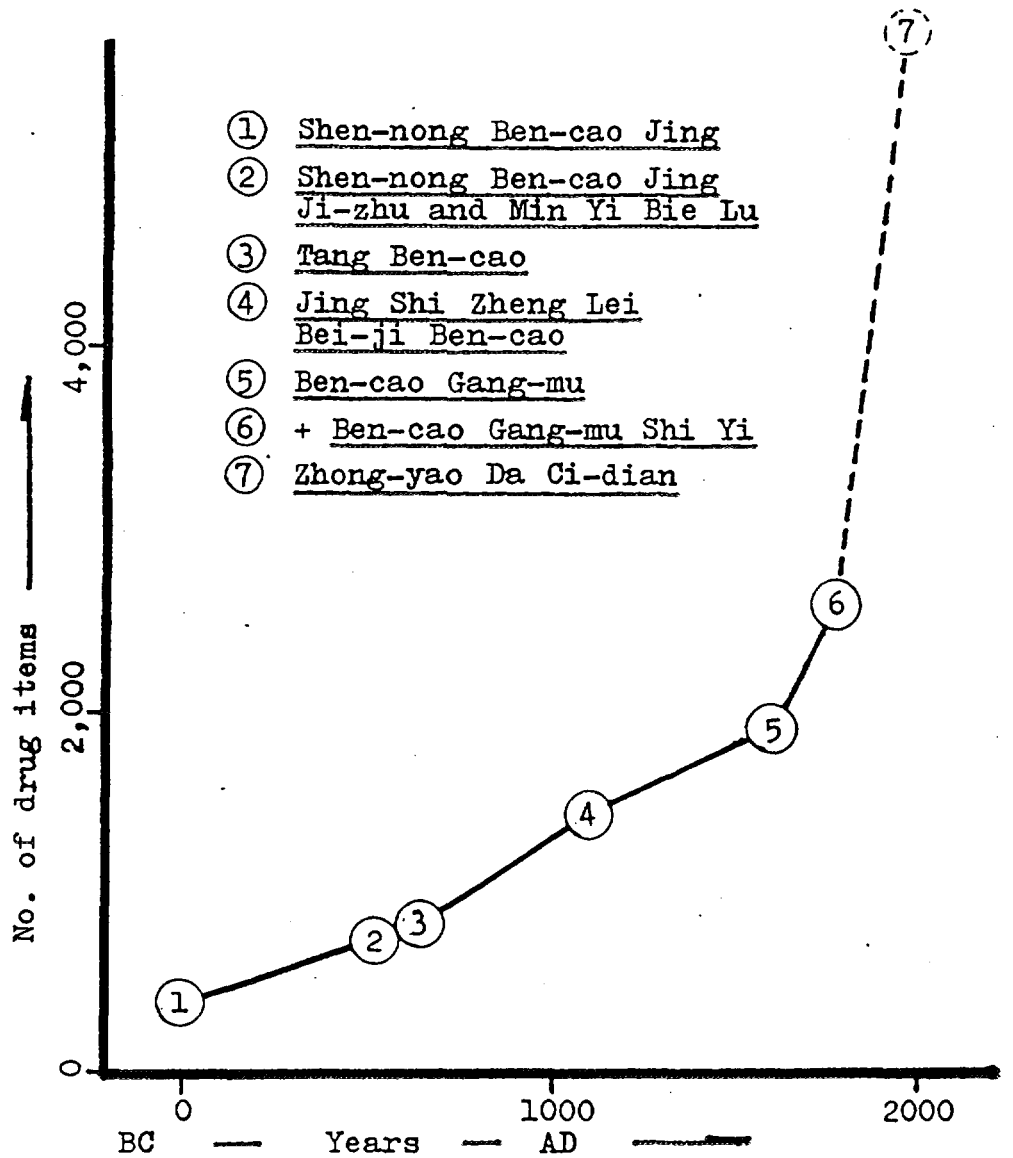

Figure 1. The Growth in No. of Drug Items Recorded in Classical Writings

3. Some basic concepts in classical medical theories

- Basic concepts in Chinese classical medical theories
- Some Physiological concepts
  I. Life constituents
  II. Orbisiconography
  III. The conduits
- Basic standards of value and systems of correspondence
- Homeostasis and drug action

Basic Concepts in Chinese Classical Medical Theories

- The first systematic account of Chinese classical medical theories appears in the Inner Classic of the Yellow Sovereign.
- Early concepts evolved in China bore amazing formal resemblance with those generated in other parts of the historical world.
- However defective in textual transmission, Chinese medical theories were nevertheless further developed in contiguity along the original line.
- What is significant is that the theoretical aspect of Chinese medicine has always been kept in close connection with the clinical aspect such as the observations made during diagnosis and treatment.

Some Physiological Concepts

I. Life Constituents

Probably it is important to point out at the beginning that material terms used in the classics are not just physical entities of anatomy, but rather the substrata or carrier of physiological functions. For example, life constituents are described as: Vital Essence and Spirit, Vital Energy and Blood, Humors and Fluid (Jing, Shen, Qi, Xie, Jing, Yie). It is obvious that they can not be given a mere biochemical definition.

Some Physiological Concepts

II. Orbisiconography

The classical understanding of body's interior -Zhang-xiang, or literally "Internal-organic Pattern", is not the equivalent of anatomy. Likewise, it can only be understood in physiological terms, as the interplay of a number of functional systems. The term "Orbisiconography" has recently been proposed for the purpose (2). According to classical explaination, the Orbs of five viscera are considered to be associated with the storage of life constituents whilst the Orbs of six bowels are with the digestion and transport of nutrients.

Table 4. THE ORBISICONOGRAPHY

The five viscera (Yin Orbs):		
Xin	heart	= the cardial Orb
Gan	liver	= the hepatic Orb
Pi	spleen	= the splenic Orb
Fei	lung	= the pulmonic Orb
Shen	kidney	= the renal Orb
(Xin-bao	pericardium	= the pericardial Orb)
The six bowels (Yang Orbs):		
Dan	gallbladder	= the Orb of gallbladder
Wei	stomach	= the Orb of stomach
Da-chang	large intestine	= the Orb of large intestine
Xiao-chang	small intestine	= the Orb of small intestine
Pang-huang	urinary bladder	= the Orb of urinary bladder
San-jiao	-	= the triple burners

Some Physiological Concepts

III. The Conduits

Jing-luo, often translated as "meridians", is described in Chinese classical medicine as a series of conduits or sinarteries responsible for the distribution of energy throughout the body. Many pharmacological actions are ascribed to act through this functional network of energetic flow. Each conduit is assigned an Orb on the one end to be connected to an extremity of the body on the other.

Table 5. THE TWELVE CONDUIS

1.	The lung Conduit of hand Tai-yin
2.	The large intestine Conduit of hand Yang-ming
3.	The stomach Conduit of foot Yang-ming
4.	The spleen Conduit of foot Tai-yin
5.	The heart Conduit of hand Shao-yin
6.	The small intestine Conduit of hand Tai-yang
7.	The urinary bladder Conduit of foot Tai-yang
8.	The pericardium Conduit of hand Jue-yin
9.	The triple burners Conduit of hand Shao-yang
10.	The kindey Conduit of foot Shao-yin
11.	The gallbladder Conduit of foot Shao-yang
12.	The liver Conduit of foot Jue-yin

Basic Standards of Value and Systems of Correspondence

- Basic standards of value used in common by all Chinese sciences are the polar combination of Ying-Yang, and the cycle of Five Elements.
- It is from these basic standards of value that systems of correspondence are derived.

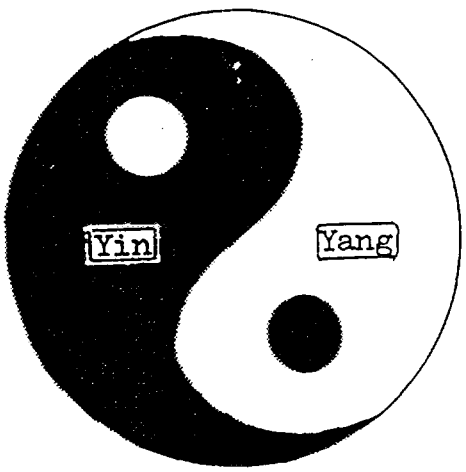

Figure 2. Tai-ji Tu

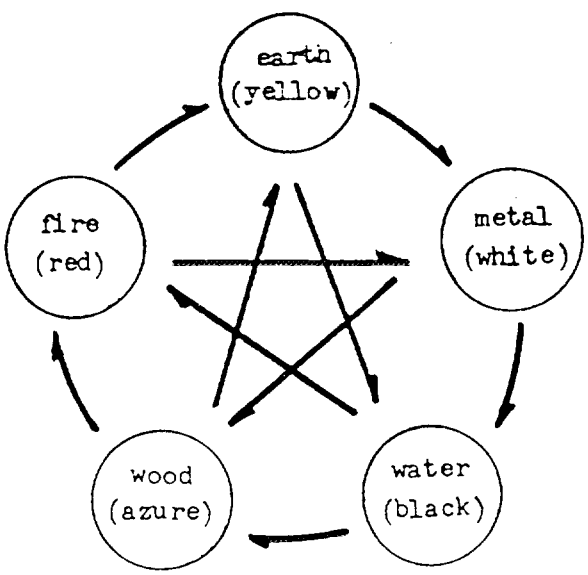

Figure 3. The Cycle of Five Elements

Table 6. A SYSTEM OF CORRESPONDENCE IN FIVES

Elements	Color	Season	Pathogenic factors	Taste	Organs	Viscera & Bowels
Wood	Azure	Spring	Wind	Sour	Eye	Liver, Gallbladder
Fire	Red	Summer	Summer-heat	Bitter	Tongue	Heart, Small intestine
Earth	Yellow	Long-summer	Dampness	Sweet	Mouth	Spleen, Stomach
Metal	White	Autumn	Dryness	Pungent	Nose	Lung, Large intestine
Water	Black	Winter	Cold	Salty	Ear	Kidney, Triple burners

Here, systematic inductive links are established between data defined in accordance with conventional standards of value.

4. *The classical pharmacology and pharmacological* classification of drugs

- Homeostasis and drug action
- The classical pharmacology
- Temperaments and tastes of a drug
- Ascending-descending and floating-sinking
- Pharmacological classification of drugs
- Compounding of drugs
- Seven modes of drug interactions
- Eight therapeutic methods

Homeostasis and Drug Action

- According to basic concepts of Chinese medical theory, it is important to maintain homeostasis in order to achieve well being of a man. Drugs are administered to coordinate Ying-Yang properly and to correct any deficiency or excessiveness in heat or cold. The bias in nature of a drug is utilized to compensate the bias of Ying-Yang in pathological state.

The Classical Pharmacology

- It is the therapeutic effectiveness of a drug that dictates its pharmacological characteristics and not vise versa.
- Pharmacological characteristics of a drug are described in terms of:

  Four temperments
  Five tastes
  Ascending-descending
  Floating-sinking
  Tonic-purgative

  etc.

Temperaments and Tastes of a Drug

Temperaments and tastes are the definitive pharmacological characteristics of a drug. Different combinations of temperament and taste constitute a great variety of drug actions.

- Four temperaments are: cold, hot, warm, cool.

  Cold and cool are Ying in nature;
  hot and warm are Yang in nature.

  Drugs bearing temperaments in between are said to be "moderat".

- Five tastes are: pungent, sour, sweet, bitter, salty.

The Inner Classic states that: pungent resolves, sour consolidates, sweet moderates, bitter hardens, salty softens.

Table 7. TEMPERAMENTS OF DRUGS AND THEIR INDICATIONS EXAMPLIFIED

Temperament	Nature	Drugs cited as examples	Indication
Cold and cool	Yin	Gypsum Fibrosum 石膏 Rhizoma Anemarrhenae 知母 Rhizoma Coptidis 黄连 Radix Scutellariae 黄芩	Heat syndrome indicating excessiveness in Yang: being feverish with reddened eyes, feeling thirsty and uneasy, having full and rapid pulse
Warm and hot	Yang	Radix Aconiti Praeparata 附子 Cortex Cinnamomi 肉桂 Rhizoma Zingiberis 干姜 Fructus Evodiae 吴茱萸	Cold syndrome indicating excessiveness of Yin: pallor, chilliness in extremities, feeling fatigue and sleepy, having weak pulse

Table 8. CORRELATION BETWEEN TASTES AND PHARMACOLOGICAL EFFECTS

Taste	Viscera acted upon	General pharmacology	Drugs cited as example	Therapeutic action
Pungent	Lung	Resolving, invigorating vital energy	1) Rhizoma Zingiberis 生姜 Folium Perillae 紫苏	Resolving, expelling pathogenic factors
			2) Pericarpium Citri Reticulatae 陈皮 Rhizoma Cyperi 香附	Invigorating vital energy, soothing the chest
Sweet	Spleen	Strengthening, moderating	1) Radix Ginseng 人参 Radix Astragali 黄芪	Strengthening Vital energy
			2) Radix Rehmanniae Praeparata 熟地 Radix Ophiopogonis 麦冬	Nourishing the vital essence (Yin)
			3) Radix Glycyrrhizae 甘草 Malt Sugar	Sweetening, moderating and stomachic
Bitter	Heart	Drying dampness purgative	1) Rhizoma Coptidis 黄连 Cortex Phellodendri	Drying dampness, expelling internal heat
			2) Radix et Rhizoma Rhei 大黄	Expelling excessive heat by purgation
			3) Rhizoma Atractylodis 苍术	Drying dampness, improving stomach

Sour	Liver	Astringent, consolidating	1) Fructus Chebulae 诃子 Pericarpium Granati 石榴皮	Antidiarrhetic, checking prolapse of anus
			2) Fructus Corni 吳茱萸 Fructus Schisandrae 五味子	Checking spontaneous sweating, arresting seminal emission
Salty	Kidney	Softening hard masses, moistening bowels	1) Sargassum 海藻 Os Costaziae 海浮石	Resolving phlegm masses and scrofula
			2) Natrii Sulfas 芒硝	Moistening bowels, purgative
Inconspicuous		Promoting excretion and improving resuscitation	Poria 茯苓 Medulla Tetrapanacis 通草 Talcum 滑石	Expelling dampness, and diuretic

Ascending-descending and Floating-sinking

Both characteristics are related to the temperament and taste of a drug.

- Ascending or descending refers to the direction of drug action.
- Floating or sinking refers to the apparent density of a drug.
- Ascending and floating are Yang in nature, drugs of warm and hot temperament, pungent and sweet taste; and also drugs light in weight belong to this category.
- Descending and sinking are Ying in nature, drugs of cold and cool temperament, bitter sour or salty taste; and also drugs dense in weight belong to this category.

Table 9. CORRELATION BETWEEN DIRECTION OF DRUG ACTION AND OTHER PHARMACOLOGICAL CHARACTERISTICS

	Drugs that are ascending and floating	Drugs that are descending and sinking
Nature	Yang	Yin
Direction of action	Upward	Downward
Temperament	Warm and hot	Cool and cold
Taste	Pungent and sweet, such as: Herba Ephedrae, 麻黄 Ramulus Cinnamomi, 桂枝 Radix Aconiti Praeparata 附子 Rhizoma Zingiberis 生姜	Bitter, sour or salty, such as: Radix et Rhizoma Rhei Natrii Sulfas Radix Paeoniae Concha Ostreae
Weight	Light and voluminous, such as: Flos Magnoliae 辛夷 Folium Nelumbinis 荷叶 Radix Platycodi 桔梗 Rhizoma Cimicifugae 升麻	Heavy and dense, such as: Fructus Perillae Fructus Aurantii Immaturus Magnetitum Radix Rehmanniae Praeparata

Table 10. SYNTHESIS AND ANTITHESIS OF PHARMACOLOGICAL CHARACTERISTICS AND ACTIONS

NATURE	TEMPERAMENT	TASTE	DIRECTION OF ACTION
Yang	Warm & hot: Dispelling cold, reinforcing vital function	Pungent: Resolving, invigorating vital energy Sweet: Strengthening, moderating Inconspicuous: Promoting excretion, improving resuscitation	Ascending & floating: Invigorating upwards, expelling upwards
Yin	Cool & cold: Dispelling heat, purging internal fire	Bitter: Drying dampness, purgative Sour: Astringent, consolidating Salty: Softening hard masses, moistening bowels	Descending & sinking: Checking exuberance of vital function, supressing upward flow; consolidating, promoting excretion, expelling heat, purgation

Pharmacological Classification of Drugs

Activities of drugs are deduced mainly through clinical observations during its administration. Thus they are closely related to basic medical theories and treatment principles.

Compounding of Drugs

According to guidelines of formulation, a prescription is composed of four different component parts of ingredients:

- The principal ingredient: provides the principal curative action.
- The adjuvent: helps strengthen the principal action.
- The auxiliary ingredient: relieves secondary symptoms or tempers the action of the principal ingredient.
- The conductant: directs action to the affected conduit or site. It may also be a less significant auxiliary ingredient.

Seven Modes of Drug Interactions

It is learnt from experience that drugs may interact when dispensed together. Modes of drug interactions are:

- Singularly acting (dan-xin)
- Mutual reinforcement (xiang-xu)
- Of assistance (xiang-shi)
- Counteraction (xiang-wei)
- Mutual restraint (xiang-wu)
- Neutralization (xiang-sha)
- Incompetibility (xiang-fan)

Eight Therapeutic Methods

Drugs are compounded to serve the purpose of therapeutics. There are eight therapeutic methods in Chinese traditional medicine:

Diaphoresis (han)
Emesis (tu)
Purgation (xia)
Mediation (he)
Invigoration (wen)
Heat reduction (qin)
Tonification (bu)
Resolution (xiao)

The pharmacological classification of drugs has close association with the therapeutic methods.

Table 11. A SCHEME FOR THE PBARMACOLOGICAL CLASSIFICATION OF DRUGS

1. Drugs for dispelling pathogenic Factors from the exterior of the body (jie-biao yao) - they are essentially diaphoretics
   a) Those with pungent taste and warm temperament (xin wen jie-biao yao)
   b) Those with pungent taste and cool temperament (xin liang jie-biao yao)
2. Antitussives, anti-asthmatics, and drugs for resolving phlegm
   a) Warm drugs for resolving cold phlegm (wen hua han-tang yao)
   b) Cool drugs for resolving heat phlegm (qin hua re-tan yao)
   c) Antitussives (zhi-ke yao)
   d) Anti-asthmatics (pin-chuan yao)
3. Drugs for clearing internal heat (qin-re yao) - essentially antipyretics
   a) Drugs for clearing up and purging intense internal heat (qin-re xie-huo yao)
   b) Drugs for clearing up heat and cooling the blood (qin-re liang-xie yao)
   c) Drugs for clearing up heat and dampness (qin-re zao-shi yao)
   d) Drugs for clearing up heat and pathogens (qin-re jie-du yao)
4. Drugs for dispelling internal wind and dampness (qie-fong-shi yao) - essentially anti-rheumatics
5. Warm drugs for dispelling internal cold (wen - han yao)
6. Aromatic drugs for resolving dampness (fang-xiang hua shi yao)

to be cont'd on next page

14. Drugs arresting discharges (gu-se yao) - including astringents and hemostatics

15. Digestives and evacuants (xiao-dao yao)

16. Purgatives and laxatives (xie-xia yao)

17. Anthelmintics (qu-chong yao)

18. Drugs for external use (wai-yong yao)

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7. Diruetics and hydrogogues (li-niao zhu-shui yao)
   a) Diuretics and mild hydrogogues (li-niao sen-shi yao)
   b) Hydrogogues or drastic purgatives (zhu-shui yao)
8. Drugs for regulating the flow of vital energy (li-qi yao)
9. Drugs for regulating blood conditions and circulation (li-xie yao)
   a) Hemostatics (zhi-xie yao)
   b) Drugs invigorating blood circulation and resolving stasis (huo-xie hua-yu yao)
10. Aromatic drugs for stimulation and causing resuscitation (fang-xiang kai-qiao yao)
11. Drugs stabilizing the spirit (an-shen yao) - essentially sedatives and tranquilizers
12. Drugs for subduing hyperactivity of hepatic orb and the endogenous wind (pin-gan xi-fong yao)
13. Drugs reinforcing vital function (bu-yang yao) - tonics and aphrodisiacs
    a) Drugs for the replenishment of vital energy (bu-qi yao)
    b) Drugs for nourishing the blood (bu-xie yao)
    c) Drugs for replenishment of vital essence (bu-yin yao)
    d) Drugs for reinforcing the vital function (bu-yang yao)

to be cont'd on next page

5. A comparison with Occidental classical pharmacology

- The Graeco-Roman pharmacology

  I. Four elements, four qualities, humors

  II. Bodily constituents

  III. Drug therapy

  IV. Four temperaments and seven tastes

- The concept of the organism as a whole

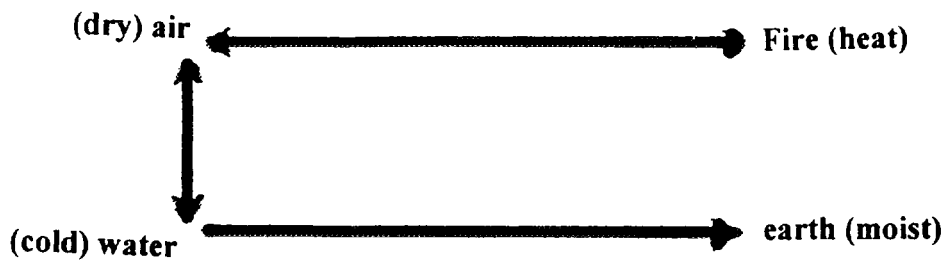
- The modern age

The Graeco-Roman Pharmacology

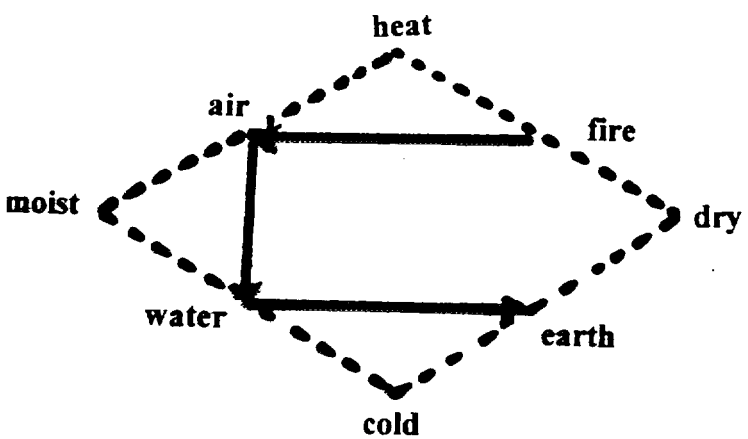
1. Four elements, four qualities, humors

- Throughout the Graeco-Roman period (6th century B.C.- 2nd century A.D.), there were developed the theories of four elements, four qualities, and humors. It was postulated that all matters are composed of fire, air, water and earth; and that they are inter-convertable.

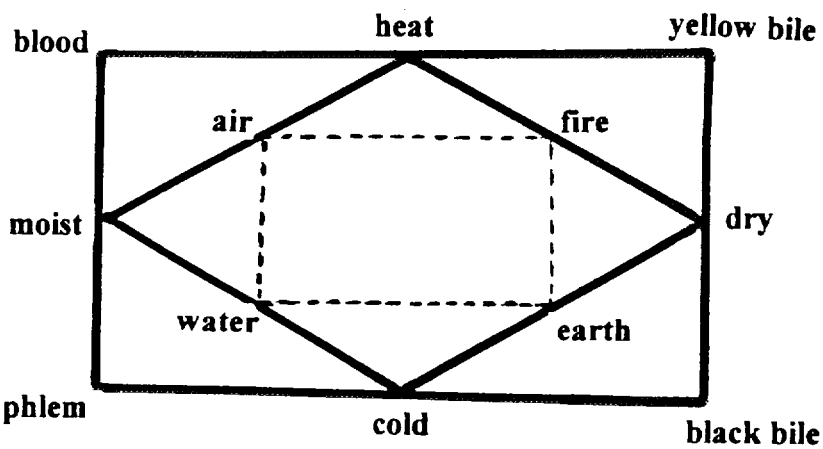
- It was Hippokrates (5th-4th century B.C.) who advanced the humoral concept. By Galen's time (2nd century A.D.) this biological theory became merged with the physical theory of four elements etc..



5th century B.C.



3rd century B.C.



Medieval

THE EVOLUTION OF GREEK-ROMAN CONCEPT OF NATURE

The Graeco-Roman Pharmacology

II. Bodily constituents

Life itself was considered by the Greeks to depend upon the "Pneuma" which was inspired from the air. The "Pneuma" made its way into the blood and was then responsible for the phenomenon of neural conduction.

The Graeco-Roman Pharmacology

III. Drug therapy

Galen maintained that: "It is the business of pharmacology to combine drugs in such a manner - according to their elementary qualities of heat, cold, moisture and dryness - as shall render them effective in combating or overcoming the conditions which exist in the disease." (re-quoted from C.C.Mettler: History of Medicine. Blakiston, 1947)

The Graeco-Roman Pharmacology

IV. Four temperaments and seven tastes

According to Paul of Aegina (625-690 A.D.), a Byzantine compiler:

- Four temperaments of drugs are: drying, moistening, cooling and heating.
- Seven tastes are:
  - A) Astringent - contract, obstruct, condense, dispel and incrassate; they are cold and desiccative in nature.
  - B) Acid - cuts, divides, attenuates, removes obstructions and cleanses without heating; being cold.
  - C) Acrid - resembles acid in being attenuant and purging, but differs from it in being hot.
  - D) Bitter - cleanses the pores, is detergent and attenuant, cuts the [illegible]ors without sensible heat. What is watery is cold ...
  - E) Salty - [illegible], braces, preserves, dries, without decidedly heat or cold.
  - F) Sweet - relaxes, concocts, softens, and rarefies
  - G) Oily - humectates, softens, and relaxes.

The Concept of the Organism as a Whole

Alconaen (ca. 6th century B.C.) says that health is the equipoise, and disease the maladjustment of such forces as heat, cold, dryness, moisture. Hippokrates treatment of a disease is: removal of deteriorated humors of the body with sweating, diarrhea, and emesis. How similar they are to the Chinese therapeutic methods!

6. Prospect

—— Modern medical sciences and modern materia medica

—— Shortcomings

—— What is expected of Chinese materia medica

The Modern Age

Claude Bernarde	(1813-1878)
Rudolf Virchow	(1821-1902)
Louise Pasteur	(1822-1895)
Robert Koch	(1843-1910)
Paul Ehrlich	(1954-1915)

What Is To Be Expected Of

Chinese Materia Medica

- Chinese materia medica are for the most part easily accessible healing materials to people living in rural areas.
- There is a great wealth of clinical experiences in the application of Chinese materia medica. Appropriate screening programs may give rise to the isolation of active principles. The latter may serve as lead compound in new drug research.
- Studies may lead to simplification of a complex formulation.
- Many of the treatment principles used in traditional medicine may prove to be invaluable or at least complementary to modern therapy.

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Biodiversity prospecting an activity for sustainable industrial development.
Some ideas for guidelines to develop pilot projects and decison support systems

First draft mainly extracted from the final report of the Scientific Planning and Co-ordination Meeting on Biodiversity Prospecting and Business Creation
(Trieste 21-23 October 1996)
by
Enrico Feoli, International Centre for Science and High Technology, ICS-UNIDO, Trieste, Italy

1. Introduction

Biodiversity prospecting (or bioprospecting) integrates the systematic research of new sources of economically valuable products such as chemical compounds, genes from micro-and macro-organisms, with biotechnology issues. It has the two fundamental goals of making sustainable the use of genetic resources and their conservation, and helping the socio-economic development for biodiversity rich countries (Sittenfeld and Villers, 1993).

An important aspect that bioprospecting, as a new recognized activity within all the activities addressed to sustainable development, has to take always present is the maximisation of reinvestement into acquiring new knowledge and improving biological resource management. As a consequence, wildland biodiversity prospecting has to be developed as part of the national economy. This at the same time has to develop the capacity to preserve biodiversity and the bioindustrial-business relationships.

The combined market worldwide for pharmaceuticals, agrochemicals and seeds is over $250 billion annually, and genetic resources provide the starting material for a significant portion of this market (Putterman, 1995).
Up till now, the primary beneficiaries of bioprospecting have been the pharmaceutical, and agricultural industries. Still today, it is estimated that the returns from potential new drugs developed from the biodiversity found in tropical forests is estimated to exceed US $100 billion in value to society as a whole (Mendelsohn and Balick, 1995). Gene technology promises an even brighter future for biodiversity prospecting. New pharmaceutically-active peptides and proteins from wildlife are already on the market or undergoing preclinical and clinical trials. Natural attack and defence mechanisms of microorganisms, plants and animals are used in agricultural biotechnology to create pest resistance. and include the expression of insecticidal proteins and peptides from bacteria and spider venom in genetically engineered plants

2. Challenge for success

The real challenge for bioprospecting activities is to find ways to capture part of the financial revenues for the source country. Bioprospecting requires that the source country should
1) create regulations on access to genetic together with an infrastructure guaranteeing a reliable natural products supply (including correct taxonomic identification. quality control. full support and approval from government and adherence to national or local regulations on access to resources);

2) acquire technology that adds value to genetic resources wherever possible (from extracts, partially purified or pure compounds to gene sequences or recombinant plants);
3) take advantage of local capabilities using all types of organisms as biological resources attractive to industry (from plants and microbial resources, marine or aquatic life forms to arthropods);
4) develop a reputation as a reliable business partner over time; and
5) reinvest part of the revenues in improving biodiversity management and conservation (Putterman, 1995).

In exchange for access to genetic resources, the industrial partner must agree to the fair and equitable sharing of benefits, both in intellectual and monetary terms; implementation of collection and production methods with minimum effects on biodiversity; and the use of equitable bioprospecting practices for further research on diseases and problems specifically associated with agriculture and health in developing countries.

3. Implementing bioprospecting frameworks

It is necessary for rich biodiversity countries to implement bioprospecting frameworks on the basis of negotiating agreements with scientific research centres, universities and private enterprises, locally and internationally. For instance these pioneering agreements provide significant returns to Costa Rica while simultaneously assigning economic value to natural resources, and providing a new source of income to support the maintenace and development of the country Conservation Areas (Sittenfeld and Lovejoy, 1996).

The fundamental point of departure for a biodiversity prospecting framework is macro-policy, the set of governmental and international regulations, laws and economic incentives that determine land use patterns, access to and control of biological resources, intellectual property rights regimes, technology promotion, and industrial development. Macro-policies are formed on the international, national and social levels. On the international level, agreements, conventions and other mechanisms establish the relationships and protocols for sharing biological resources between countries. Relevant agreements include among others, the Biodiversity Convention, the Trade Related Intellectual Property Rights (TRIP'S) of the General Agreement on Trade and Tariffs (GATT), the Draft Declaration on Indigenous Rights of the United Nations Working Group on Indigenous Populations and sub-regional agreements, such as the North American Free Trade Agreement (NAFTA), the Amazonian Treaty, and the Pacto Andino are considered important documents that provide the guidelines and regulations for genetic resource use

Bioprospecting research within each country is itself an important step towards national economic development, but will only be attractive to the industrial counterpart if results can be patented. In this context policy should :
1) promote soft loans for biodiversity based industries,
2) support for research focused on links between taxonomy, ecology and biotechnology,
3) regulate the import and export barriers,
4) expanding or contracting intellectual property rights protection, and
5) promote other measures that can create an environment that nurtures local industrial development

Supporting the early development of biodiversity industries through tying research activities to public or private universities and research centers can provide the impetus for successful biodiversity industry development

When supported by a favourable international and national macro-policy, three basic elements guide the rational and productive use of genetic resources in prospecting agreements: 1) biodiversity inventories and information management systems 2) business development, and 3) technology transfer.

- *Biodiversity inventories and information management systems*

Biodiversity prospecting begins by searching for chemicals or genes in living organisms but it must be keeped in mind that this will only be successful through the development and management of biological, ecological, taxonomic, and related systematic information on living species and systems. Even with this data, further information is required for the more systematic screening approach used in gene technology. For example, biochemical data must be evaluated, e.g. the occurrence of certain biopolymers, metabolic pathways, enzymes and defence or attack mechanisms (Tamayo, Sittenfeld and Nader, 1996). Biodiversity inventories dealing with catalogues of available resources and their location may prevent damage to ecosystems, areas, species and populations by indicating what resources are available, and where they can be collected without damaging the environment (Raven and Wilson, 1992). However the inventory on which to base decisions should be organized according the local knowledge and uses. Local knowledge should be codified and make available for scientific research. An information management system on which to base decision for industrial exploitation of biodiversity should be based on the following considerations:

- The information necessary to support decisions for industrial exploitation of biodiversity has to come out from the two systems that are involved, namely: the resource system and the exploitation system. Both systems have equal importance to offer the immense information that has to be organized in order to help the sustainable industrial exploitation of biodiversity
- The resource sytem is the result of the long interaction between the biological genetic pool and the environment. Throughout history this interaction has produced the vegetation system (vegetation) that makes green our planet. Vegetation (terrestrial and marine) beside sustaining the botanic diversity is sustaining all the animal diversity. The vegetation system is organized in plant communities, this allows to distinguish vegetation types and to map them. Vegetation maps are useful tools to know plant distribution and to define the environment where plants are living. Plant communities are hosting and patterning all the other living organisms, they depend strictly on self-sustainability of vegetation systems. The knowledge about the ecology and the physiological requirements of the living organism is the essential basis for planning their breeding in the most suitable environment. This will prevent failures and wastage of time and money.
- The exploitation system is based on the local knowledge that is conditioning and defining all the uses of the living organisms. There are many expoitation systems at different levels, from the village level, to national, regional until the global level. The use of medicinal and aromatic plants, for example, produces markets at different levels also. Markets at high level require standards and therefore taxonomy for plant identification, chemistry for chemical analysis and clinical tests are automatically involved in the picture. As a consequence of market requirements improvements in cultivation techniques and chemical techniques for industrial extraction of useful compounds, or for genetic engineering are becoming urgent matters

Following this an information system that integrates the information on species such as taxonomy and ecology with the information on the use of the species and their treatment (industrial treatment when possible) is more and more needed.

There are only few data bases that are specific for biodiversity prospecting. Many of them are commercial and deal only with bibliographic data (references). There are data bases on plant and animal distributions that are mainly reproducing books with wonderful pictures and recipies for preparing the medication and with the chemical formulas of the active principles. What is actually missing is a data base on industrial exploitation of biodiversity (inventories of uses, of distribution of pilot projects, of technologies for cultivation and extraction, of exploitation projects, of markets, of clinical tests, biosafety tests, etc.) that can be used as a decision support system for improving the production and for creating new products. This can be developed and has to be developed on the basis of the already existing data bases: by integrating them in a system able to networking them.

The system on which to base decisons must give the information on taxonomy, ecology, geographic distribution, uses, cultivation techniques and where the species are cultivated, industrial factories exploiting the species, economic results, on markets, etc. The system should be able to compare the different phytoproducts and drugs according to their biological properties, chemical composition, preparation techniques and effects. The system should use artificial intelligence techniques in order to suggest new bioproducts or predict their economic and environmental impact.

- *Business development*

Building upon inventory-generated knowledge, business development defines markets, market needs, major actors, national capacities in science and technology as well as institutional or community strategies and goals. Important requirements include knowledge of one's assets and debilities, market surveys and evaluation of conservation needs.

Using market surveys to identify potential economic users and elaborate research collaborations increases the in-country partner's awareness of private enterprise, academic and scientific research characteristics and needs.

The key to business development is interacting with national and international industry in order to approach the market in a realistic and practical way. Because bioprospecting should promote source-country economic development, business development must encourage the sustainable use of biodiversity by local entrepreneurs. However, this is a definitive challenge for developing countries where industry normally can not take the financial risk of applying innovative technologies.

At the end of any business development negotiation process, contractual agreements must be established to ensure through legal documents (or MTAs) that bioprospecting efforts meet the highest standars of fairness for all participants and stakeholders (Gollin, 1995, Putterman, 1996)

- *Technology transfer*

One of the major issues discussed in the Convention on Biodiversity refers to technology transfer allowing source countries to convert raw biological materials into products of greater value in exchange for access biodiversity. This issue gains tremendous importance,

particularly in a decade of patentable genes. In the near future, genes isolated from tropical biodiversity may provide developed-country farmers with advantages over those of the source countries (Shand, 1993). In light of this, technology transfer in this field may enable source countries to keep pace with the developed countries, and avoid being left out of important agricultural developments. This scenario is realistic because gene technology, in contrast to natural compound chemistry, does not particularly rely on expensive investments in laboratory equipment, and would therefore be easier to implement (Tamayo, Sittenfeld and Nader, 1996).

4. Guidelines for pilot projects

Based on the bioprospecting frameworks here described, developing countries must take an important step and initiate biodiversity prospecting pilot projects. Guidance in this process is expected to come from a series of workshops training courses, study tours and fellowships, supported by ICS-UNIDO. Such projects will test the feasibility and capability of biodiversity prospecting ventures, and will provide the opportunity for 'learning by doing'. This process is intended to facilitate larger initiatives and will depend first and foremost on inventory generated information (development and management of biological, ecological, taxonomic and related systematic information on living species and systems). Information derived from reviewing in-country capacities and technological capabilities, in addition to market needs and realities, will form the criteria for developing the pilot projects. Ultimately selecting and designing them will need to consider current national and international macro-policies regarding biological resource access and utilization.
Designing and implementing pilot projects will allow developing countries to compare alternative scenarios and approaches to bioprospecting according to national realities. This will help establish effective long-term management policies and practices for all sectors involved in the bioprospecting process. Proposers of pilot projects should carefully consider to satisfy the following priorities in order to design a project suiting the needs of a particular country:

1) Market driven inventory by taxa selection vs. all taxa inventory. This will give the better overview of the uses of products and a basis on the possible choices to begin with.
2) Science and technology intensive efforts vs. less intensive efforts that provide more rapid access to market and short-term benefits to local communities.
3) Projects based on existing information or research near to final product development vs. newly generated information.
4) Industrial relationships established very early in the process vs. providing products to industry in the late phases of research.
5) Products for the local market vs. products for international markets for better evaluation and control of their performance and for having an easy feedback from the consumers.

5 Conclusions

The Biodiversity Convention envisions harmonious links between conservation, intellectual property, environmental protection, research and development and economic advancement for developing countries. This is a complex and long-term undertaking by any standard.
Three points remain domain of discussion:
1) What are the factors that govern the selection of candidate material for development as a good bioproduct? Not always a good material from a scientific point of view becomes a

bioproduct commercially successflul. In most real situations the decision is based mainly on corporate strategic interestor commercial concerns.
2) How to deal with policy issues of the interface between ownership and access of genetic materials and how to manage an equitable distribution of benefits arising from commercialization of genetic resources?
3) What is the necessary background to enter into or to create strategic alliances with scientific institutions and private and commercial organizations for mutually beneficial programmes for the commercialization of bioproduct?
Supportive macro-policies, tied to an integrated program for biological research, business development and technology transfer, can provide the backdrop for linking biodiversity and biological resource users in bioprospecting programs that yield short and long-term benefits for conservation in developed and developing countries as a whole. The most fundamental element, however, is the recognition and understanding that this new breed of bioprospecting program ultimately depends on multisectoral collaborations. The largest challenge, however, is the need for local, national and global communities to acknowledge that protected wildlands must become a sustainable generator of economic and intellectual benefits if they are to survive.

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Quality Control of Traditional Chinese Medicine and Some Usage of HPLC in Studying Folk Medicine

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Section I

Quality Control Standard of the Infusion (medicinal granules) of Qingyan Zhike.

The infusion of Qingyan Zhike is a Chinese traditional medicine for cough without sputum. The prescription of Qingyan Zhike infusion is composed of Arctium lappa L. , Glycyrrhiza uralensis Fisch, Platycodon grandiflorum (Jacq.) A. DC., Prunus armeniaea L. var. ansu Maxim., Polyala tenuifoia willd, Bupleurum Chinese DC., Citrus aurantinm L., Paeonialactiflora Pall., et al.. The main medicinal materials of the prescription, such as Citrus aurantium L., Glycyrrhiza uralensis, Paeonialactiflora Pall et al. are identified by HPTLC and HPLC. The content of Paeoniflorin in the infusion is determined by HPLC, the total content of saponins in the infusion is determined by chemical colorimetric method. The total content of heavy metal in the infusion is also determined, according to the method of Chinese Pharmacopoeia(Vol. I, Appendix ix p50).

I. Identification of the main crude drugs in the infusion

1. Identification of Paeonialactiflora Pall

1-1. Preparation of test solution

A sack powder of the infusion is weighed and placed in a continuous extractor, refluxed with 50 ml of methanol. The extract is concentrated to 5ml which is used as test solution of the sample.

1-2. Preparation of blank reference solution.

Except Paeonialactiflora Pall. each of crude is weighed according to a half quantity of the prescription. On the basis of the method of the technological requirements, extraction plaster is prepared. 2.6g of extracts are weighed and blank reference solution is prepared as above 1-1 mothod.

1-3. Preparation of the reference solution of control crude.

10g of crude powders of Paeonialactiflora Pall are weighed, extract is taken on the basis of the technological method. 0.17g of the extraction plasters are weighed. According to preparation of 1-1 item, the solution of contrast crude is obtained.

1-4. Preparation of the solution of semi-finished products(plasters)

3g of semi-finished products (plasters) are weighed. and the solution of semi-finished products is operated on the basis of 1-1 item.

1-5. Preparation of the control solution.

Suitable amount of Paeoniflorin is weighed and dissolved with methanol (2.5mg/ml)

1-6. Identification of TLC

On a HPTLC (silica gel) plate are respectively spotted 2ul of each of the test, the references and the control solutions. The plate is developed with chloroform-ethyl acetate-methanol-formic acid (40:5:10:0.2). After the solvent is evaporated to dryness, the plate is sprayed with 5% vanillin solution in sulfuric acid, colored under heat air steam . The color and position of the corresponding spot due to paeoniflorin in the chromatogram obtained with the test and reference solution of sample, control crude and semi-finished products should be identical except blank reference solution..

2. Identification of Citrus aurantium L.

2-1. Preparation of test solution of the infusion

A sack powder of the infusion is weighed and placed in a soxhlet's extractor, refluxed to colorless with methanol. The extraction is concentrated to suitable volume and added into a column of pretreated macroporous resin D101, eluted successively with ca. 100 ml of waters and ca. 100ml of methanol. The methanol elute is collected and concentrated to dryness under reduced pressure. The residue is dissolved in 2ml of methanol, which is used as test solution

2-2. Preparation of blank reference solution

Except Citrus aurantium L., each of crude is weighed in according with a half quantity of the prescription. On the basis of the method of technological requirements, extraction plaster is obtained, but Citrus anrantium L. is not contained in the plaster. 2.87g of the plasters are weighed and operated as the method of 2-1 item. The blank reference solution is obtained.

2-3.Preparation of the reference solution of control crude

20g of crude powder of citus aurantium L. are taken to prepare the extract on the basis of the technological method. 0.17g of the extract are weighed. In accordance with the method of 2-1 item, the reference solution of control crude is prepared.

2-4. Preparation of the solution of semi-finished products (plasters)

13g of semi-finished products are weighed. and the solution of semi-finished products is

prepared on the basis of the operation of 2-1 item.

2-5. Identification of TLC

Apply separately to the plate coated with silica gel G 2ul of each of the test solution, the reference solution of blank citrus aurantium L., crude and semi-finished products, using a mixture of ethyl acetate-methyl ethyl ketone-formic acid -water (5:3:1:1) as the mobile phase. After developing and removal of the plate, allow it to dry in air. Spray with 2% KBH4 in isopropanol solution, then the plate is fumigated by concentrated hydrochloric acid.

3. Identification of Arctium lappa L. etc.

Arctium lappa L, Glycy rrhiza uralensis Fisch, Prunus armeniaca etc. are identified by similar method.

II. Determination of Paeoniflorin in the infusion by HPLC

1. HPLC data

Apparatus: Waters 510 pump, Waters 490E UV/VIS detector, Waters 810 chromatographic data station

Column: Resolve C18 (15um) 4×250mm

Solvent system: 0.0567M H_3PO_4-Water-Methanol-Isopropanol(2.4:76.6:19:2)

Detection: 230nm

Flow:1.0ml/min

Sensitivity:0.08AuFs

Number of theoretical plates:>4000(for paeoniflorin)

2. Preparation of the reference solution

Weigh accurately 5.05mg of paeoniflorin (dried at 80 to constant weight) into a 50ml volumetric flask, add methanol to volume and shake thoroughly to produce a solution containing 0.101ug/ul.

3.Preparation of the test solution

Weigh accurately 12g of powders of the infusion into a flask. Reflux successively three times with 100, 50 and 50ml of methanol for respectively 2, 1 and 1 hours. Collect the extract and filter. The filtrate is concentrated to 150ml.

4. Calibration curve:

When the content of Paeoniflorin is in 0.1-1.0 ug region, the relation between the content and peak area is linear correlation.

Paeoniflorin content (ug)=0.05946A-0.00296

r=0.9998, A: peak area

Precision: RSD%=0.57 (n=5)

Recovery: 87.2-99.9%(added 0.15-0.20ug)

III. Determination of total saponins in the infusion

1. Calibration curve

10mg of Glycyrrhizic acid are accurately weighed, dissolved and diluted to 25ml in a volumetric flask with methanol . The Portions of 50,100,150,200 and 250ul of the reference solution are measured accurately into each of five 10ml stoppered test tubes, evaporated in a water bath to remove methanol and allowed it to cool. To each tube, 0.5ml of 4.5% vanillin in 80% ethanol and 5ml of 78% sulfuric acid are added accurately, shake and stopper the test tube, and heated on the water bath at 60 for 20min. The test tubes are removed and cooled to room temperature. The absorbance at the wavelength of 544nm was determinated(reagents as blank).The linear regression equation is obtained.

Total saponins (ug)=309.3A+5.404.

r=0.9958 A: peak area

2. Preparation of the test solution

12g of powders of the infusion are weighed accurately into a flask. It is refluxed with 50ml of methanol in water bath for 2 hours, filtered and the residue is subsequently refluxed with 25ml and 25ml of methanol for 1 hour and 0.5 hour. Three times filtrate are collected, adjusted to 100ml in a volumetric flask with ethanol. 50ml of the solution is measured accurately, evaporated to dryness and residue is dissolved with 20ml of water. The aquous solution is extracted with 4× 10ml of n-butanol (saturated with water), butanol extract is collected and concentrated to dryness, dissolved with methanol to 5ml as the test solution of the infusion. 50ul of the test solutions are measured accurately into a stoppered test tube, in accordance with the operation of calibration curve, the content of total sapons is measured and counted .

The precision (RSD%) of the colourimetric determination is 0.018.

IV. Determination of the total content of heavy metal (expressed as Pb) in the infusion.

The determination is conducted in accordance with the procedure given in the Chinese Pharmacopoeia (Vol.1 Appendix p46, method 2 .

V. Determination of Pesticide Residues

Our laboratory established determination methods of some pesticide residues in Traditional Chinese Medicine and herbed drugs by GC and HPLC, such as BHC and DDT(contain their isomer), Aldrin, Heptachlo. Chlorothalonil, Parathion, methyl-Parathion, carbendazim, Endrin, fenpropathion. carbaryl. carbofura. Isoprocarb. methomyl. Aldicarb. etc.

Section II

HPLC-Analysis of Saponin from Clinopodium Linn.

1 Introduction:

Clinopodium polycephalum and Clinopodium chinense are called 'Duan Xieliu' in Chinese that is used in folk medicine for the treatment of haemorrhagia disease. With bioassay directed, we found saponins and flavones to be the active compositions. In order to utilize and develop the natural resources, we detected one saponin and five flavones on 10 samples from 9 Clinopodium species by means of HPLC.

2. Apparatus:

The HPLC system consisted of a Waters 600 pumping system and a 996-PDA Detector.

3.Chemicals:

Redistilled water and Redistilled methanol of AR grade were used. Clinopodiside A (represententive saponin) was prepared from Clinopodium polycephalum.

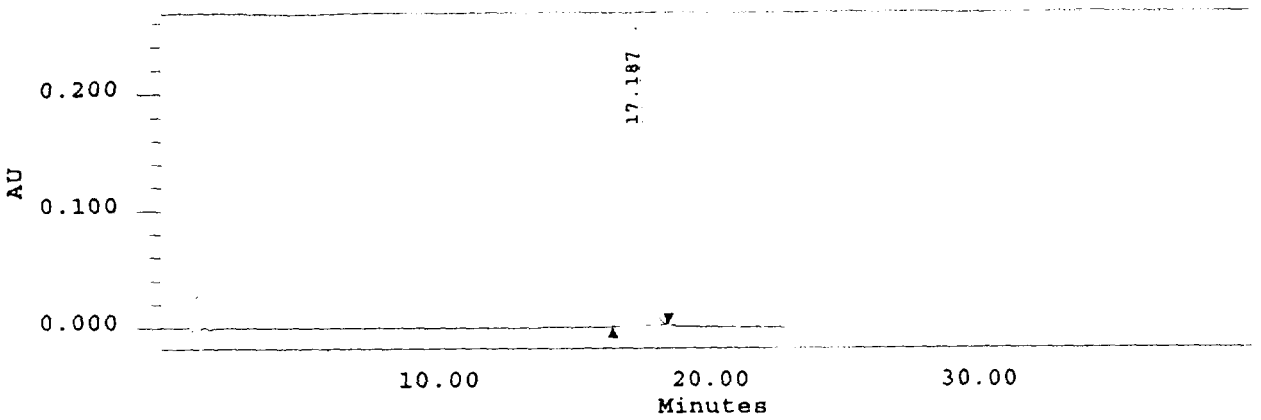
4. Plants:

NAME	GROWTH REGION	COLLECT TIME
C. chinensis	Anhui huoshan	1995.5
C. polycephalum	idem	1992.5
C. urticifolium	idem	1995.5
C. gracile	idem	1995.5
C. confine	idem	1995.7
C. omeiense	Er mei shan	1995.9
C. repens	li jiang	1996.7
C. megalanthum	idem	1996.7
var intermedium a	Yu long shan	1996.7
var intermedium b	idem	1996.7

All of above 9 samples were dried and the powdered.

5. Chromatographic conditions:

A Nova pak C-18 3.9× 150mm column (particle size 4 μm) was used. Peaks were monitored at 250nm(Clinopodiside A has a Max absorption at 247.8nm).The procedure was performed at room temperature. The flow rate was 0.8ml/min. The mobile phase was methanol-water(71:29). Following conditions Clinopodiside A was eluted within ca 20min at 3727 theoretical plates. Peak width at half-height is ca 0.7min and tailing factor is 1.045(fig 1) .



System MeOH:H2O=71:29

Start Time 16.270 min End Time 18.403 min Retention Time 17.187 min

Width @ 50% 0.6626 min Half Height 3727 Tailing 1.045

Fig 1 Chromatogram of Clinopodiside A

6.Preparation of plant samples

Weighted 2g plant samples into conical flask, added 40ml methanol, supersonicated half hour, laid aside overnight, then sonicated half hour again. Filtered, the filtrate was concentrated to suitable volume and added into a column of pretreated macroporous resin D-101,eluted successively with ca. 20-40ml of water to light yellow and then ca. 75-80ml of 95% ethanol. Ethanol eluate was collected and concentrated to dryness under reduced pressure. The residue was dissolved in 5ml methanol, which used as test solution.

The precision(RSD%) of this HPLC-method is 1.422.

The recovery of Clinopodiside A is 93.5%-105.2%.

7. Calibration curve

A stock standard solution of Clinopodiside A was prepared by dissolving 12.27mg of saponin in 5ml of methanol. The portions of 25, 50, 100, 150 and 200μl of the stock standard solution were measured accurately into each of five 2ml volumetric flask. Added methanol to volume and shake thoroughly. These solutions(20μl) were subjected to HPLC and the resulting chromatograms provided data for the calibration graphs(fig 2).

8. HPLC identification of Clinopodium Linn.

Volumes of 20μl of the plants' test solutions were injected for assay and typical chromatograms of various plants among Clinopodium Linn. were obtained(fig 3). Using standard plant as control, a HPLC identification method was established.

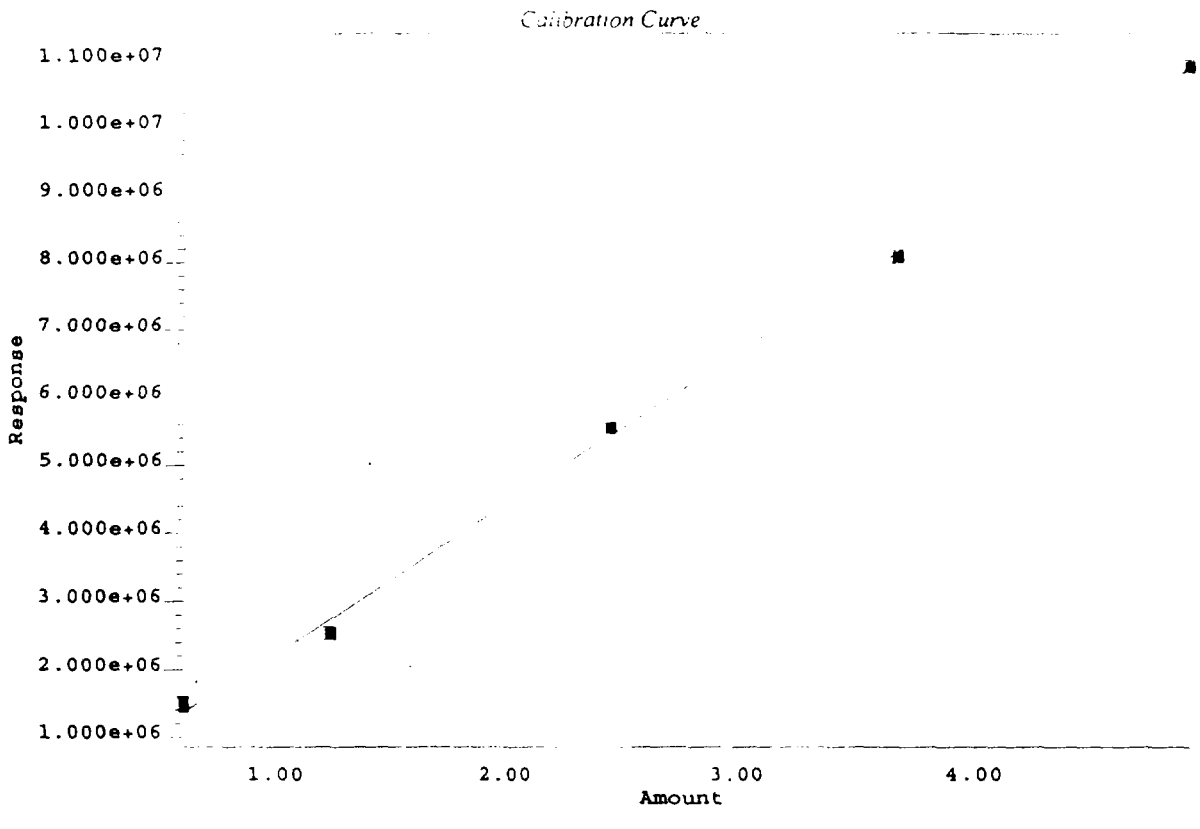
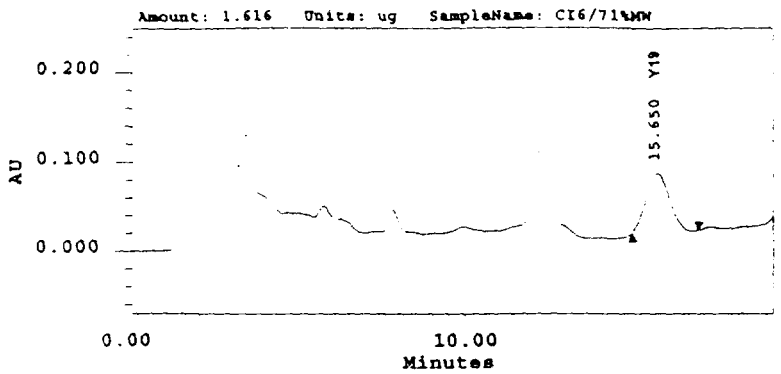
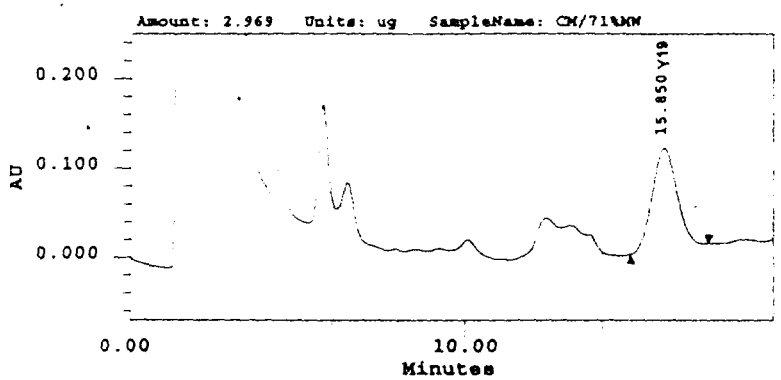


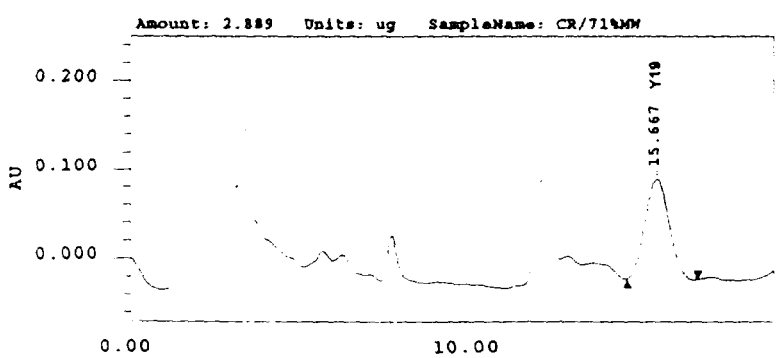
Fig 2 Calibration curve of Clinopodiside A



C. megalanthum var.intermedium



Clinopodium megalanthum



Clinopodium repens

Fig 3 Chromatogram of plants from Clinopodium Linn.

9. HPLC determination of Clinopodiside A on the plants from Clinopodium Linn.

The content of Clinopodiside A was determined in 10 samples from Clinopodium Linn.. The results are given in the result table. Analyzed the results, we suggested some other plants can also be considered as the sources of 'Duan Xieliu'.

Result Table

NAME	GROWTH REGION	COLLECT TIME	Clinopodiside A(10^{-2}%)
C. chinensis	Anhui huoshan	1995.5	1.331
C. polycephalum	idem	1992.5	1.79
C. urticifolium	idem	1995.5	2.78
C. gracile	idem	1995.5	1.03
C. confine	idem	1995.7	0.10
C. omeiense	Er mei shan	1995.9	
C. repens	li jiang	1996.7	3.67
C. megalanthum	idem	1996.7	1.80
var intermedium a	Yu long shan	1996.7	1.12
var intermedium b	idem	1996.7	1.060

Appendix I

Quality Control Requirement of New Preparation of Traditional Chinese Medicine (for clinical research)

1.Prescription and it's Basis

2.Literature and Research Data of Physico-Chemical Characteristic Concerned with Quality

3.Preparation Technology and its Research References

4.The Draft of the Quality Standard and Explanation of Medicinal Materials and Medicament

5.Literature and the Test Data of Initial Stability for Clinical Research

6.The Reports of Quality Detection and Hygienic Standard Detection of the Preparation for Clinical Research

7.Property and Specification of the Packing Material of the Medicament, Design Draft of the Label and Applied Instructions

Appendix II

General Requirement of Quality Control Standard of Medicament (Traditional Chinese Medicine) for Clinical Research

1.Quantitative Determination of the Effective Component or Indicative Component of 1-2 Species of Main Medicinal Materials in the Prescription

2.Qualitative Identification of Several to Half of the Medicinal Materials in the Prescription

3.Determination Content of Pb, Cd, Hg, As and Limit Test of Heavy Metal (expressed as Pb) in Medicine

4.Hygienic Standard

Bacterium	1g	not more than 1000
Mould	1g	not more than 100
Colibacillosis		not detect

5.Determination of Pesticide Residues (Organochlorine and Organophosphorus) in the Medicament

21858
(2 of 3)

88p.
diagrams

ICS—UNIDO Training Course on
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TECHNOLOGY MANAGEMENT MODULE

by

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Training Course on
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TOPIC 1

BASIC TECHNOLOGY MANAGEMENT CONCEPTS

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1. Introduction

Technology! The term has become a global buzzword. Some writers (Ayres, 1988) have even referred to technology as the "wealth of nations." In a manner of speaking, technology is like wealth. Those who already have it worry about protecting and accumulating it further. Those who do not have it feel deprived, and strive to get it. Technology is also a study in contradictions. It is universally accepted as central to economic growth and the creation of jobs; it is the foundation for improved health, standard of living and quality of life. However, viewed from another perspective, this wellspring of good has a dark side to it. It has been accused of wiping out jobs and careers, degrading the environment, reproducing and manipulating life forms in questionable ways, and even providing the means for destroying civilization.

Irrespective of the point of view, technology is clearly one of the dominant features of the modern world. Whether one supports or condemns, there is total consensus that managing technology effectively is critically important to the success and survival of individual companies and to national economic well-being and growth. As far back as 1967, Servan Schreiber (1968), in his acclaimed work "The American Challenge", pointed out that "technological advance depends on virtuosity in management." Yet, today, even as the "American Challenge" is being confronted by the "Japanese Challenge", which in turn is being defied by the "Newly Industrializing Country (NIC) Challenge", it is ironic that until recently the subject of technology management did not, general, receive the kind of popular attention that it should have in business and government, and management development programs.

The main objective of this session is to present some basic concepts related to technology management and elaborate its importance. For the sake of expository ease the rest of this session is presented in three parts. The first, presents a summary of how technology management is viewed in industrialized countries. This is followed by an elaboration of the thinking that is now developing in the NICs and developing countries of Asia.

2. Technology Management: Perspectives from Industrialized Countries

In 1986, at the First Conference on Engineering Management, one of the keynote speakers, Edward Roberts of the Massachusetts Institute of Technology, argued that the failure of the automotive, office equipment, and electronics industries in the United States of America were not the result of trade, economic, or political polices but from the inability of industry to implement programs in technology management (Gaynor, 1996). He emphasized the need for (Gaynor, 1996):

- Integrating technology into a firm's strategic objectives;
- Taking a proactive stance in introducing new technologies, new products, and new processes with a greater emphasis on cycle time;
- Increasing the productivity and performance of the firm's technical community;

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- Understanding the interdisciplinary needs in project management; and
- Analyzing the resources and infrastructure to effectively select the technical scope of the work effort.

Roberts lamented further that there is seldom any teaching of either engineering management or management of technology. He pointed out that there is a teaching of both engineering and management as separate disciplines, but no teaching of engineering and management combined (Gaynor, 1996).

This aspect is elaborated further by Collins et al. (1991) who argue that technology itself does not produce commercial results. It is its application that brings commercial benefits. Collins et al. (1991) point out that successful applications derive form the marriage of the technology with: human behavior; organizational and management issues; marketing, economic, and financial considerations; and legislation, regulations, and other government issues. This is shown schematically in Figure 1. This thinking has its origins at the National Research Council (1987) which defined management of technology as the, "Design and use of the means needed within organizations to achieve economic and social objectives through technological innovation. It is a human skill, combining elements of engineering, science, and management techniques, which is needed by organizations in order that they may fulfil their technological capabilities and thus maximize their strategic and competitive advantage in the market-place." More specifically, Collins et al. (1991) and McGaughey (1989), assert that acquiring technology management skills are seen as absolutely critical for:

- Responding to competitors who are using technology as a strategic weapon;
- Integrating technology strategy into the overall business strategy of the firm;
- Identifying and evaluating technological options and innovations and the factors relating to their success and failure;
- Directing research and development (R&D) itself, including aspects of commercialization and economic feasibility;
- Reducing product cycle time and simultaneously improving profits;
- Integrating technology into all aspects of the organization's management information system;
- Implementing new technologies in products and/or processes which will result in operators becoming multiskilled and managers becoming multifunctional;
- Monitoring and planning obsolescence and replacement when rates of change and complexity are increasing;

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- o Adapting processes for products in segmenting markets:
- o Identifying technologies that are available or are likely to become available;
- o Identifying and assessing mechanisms for accessing desired technologies; and
- o Learning to manage large, complex, and interdisciplinary or inter-organizational projects.

However, imparting these skills through formal technology management training faces many difficulties. The first difficulty that appears to have been faced by the industrialized country education systems is the identification of the target group. In general, target users could come from five institutional groups. These are:

- o Large national firms;
- o Small and medium enterprises;
- o Multinational enterprises;
- o Government policy formulation agencies; and
- o Public and private sector firms in the fields of banking, finance, consultancy, information, standards and testing etc.

Developing one course to cater to the needs of all these target groups would be very difficult. Thus, when we speak of technology management training, we have to take into consideration the needs of the target group for which it is being designed.

3. Technology Management: Perspectives from the NICs and Asian Developing Countries

In Asia, technology management has evolved quite differently from the way in which it has evolved in the industrialized countries. In today's liberalized world economy, it may be said that the main objective of developing technology management skills is to:

> Enable managers to manage technology strategically, based on an international perspective, in order to ensure organizational competitiveness and growth in a dynamic technological and business environment.

In this context, one of the key tasks of technology managers is to help upgrade organizational technological capability. Thus, one of the main aims of technology management training is to impart skills to managers to upgrade their organizational technological capability.

The term technological capability means different things to different people. Based on an exhaustive study of the work that has been carried out on technological capability development, Table 1 presents an eclectic classification of technological capability. A more

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detailed discussion on technological capability will be made by the author at a later session of this module. According to this eclectic classification, technological capability consists of three core capabilities namely:

- o operative capability;
- o transaction capability; and
- o innovative capability.

To nurture these three capabilities, the organization also needs, "supportive capability". The elements of these capability categories are shown in Table 1. Thus, a major area of interest, from a technology management perspective, in the NICs and developing countries of Asia is how to upgrade organizational technological capability.

4. Concluding Remarks

It is pointed out by many world leaders that we are witnessing the dawn of the "Asian Millennium." By the year 2000 it is expected that the Asian market will be as big as Europe's or North America (in GDP terms), and is likely to be four or five times that size by the year 2050. Such a projection has several implications from a technology management perspective.

- o Firstly, the Asia Pacific region will continue to witness considerable foreign direct investment in, and relocation of existing production to, the most cost-effective centers. The countries and firms that can benefit from such moves are those that have acquired relevant technological capabilities and technologically literate managers.

- o Secondly, in many instances, technologically advanced countries, and their firms, are becoming more and more prepared to transfer technology on more attractive terms. The days when companies kept technology to themselves for fear of helping the competition appear to be numbered. Now they realize that competitors are rising up anyway and it may be more prudent to "partner for profit." Unless developing Asian countries and firms upgrade their technological capabilities to take advantage of this trend, they will miss this great opportunity and become laggards in the race for prosperity.

- o Thirdly, there is a trend, especially in the Asia Pacific region, to follow the Japanese model of technological development where technology acquisition takes place from a strictly commercial standpoint and not from a military one. Thus, we need managers in the civilian sector who are well versed in technology management to derive benefit from this trend.

Thus, the introduction of good technology management training programs in the developing countries is timely. In this context, the introduction of a technology management module in the training program for experts in the "industrial exploitation of indigenous medicinal and aromatic plants' is most appropriate and laudable.

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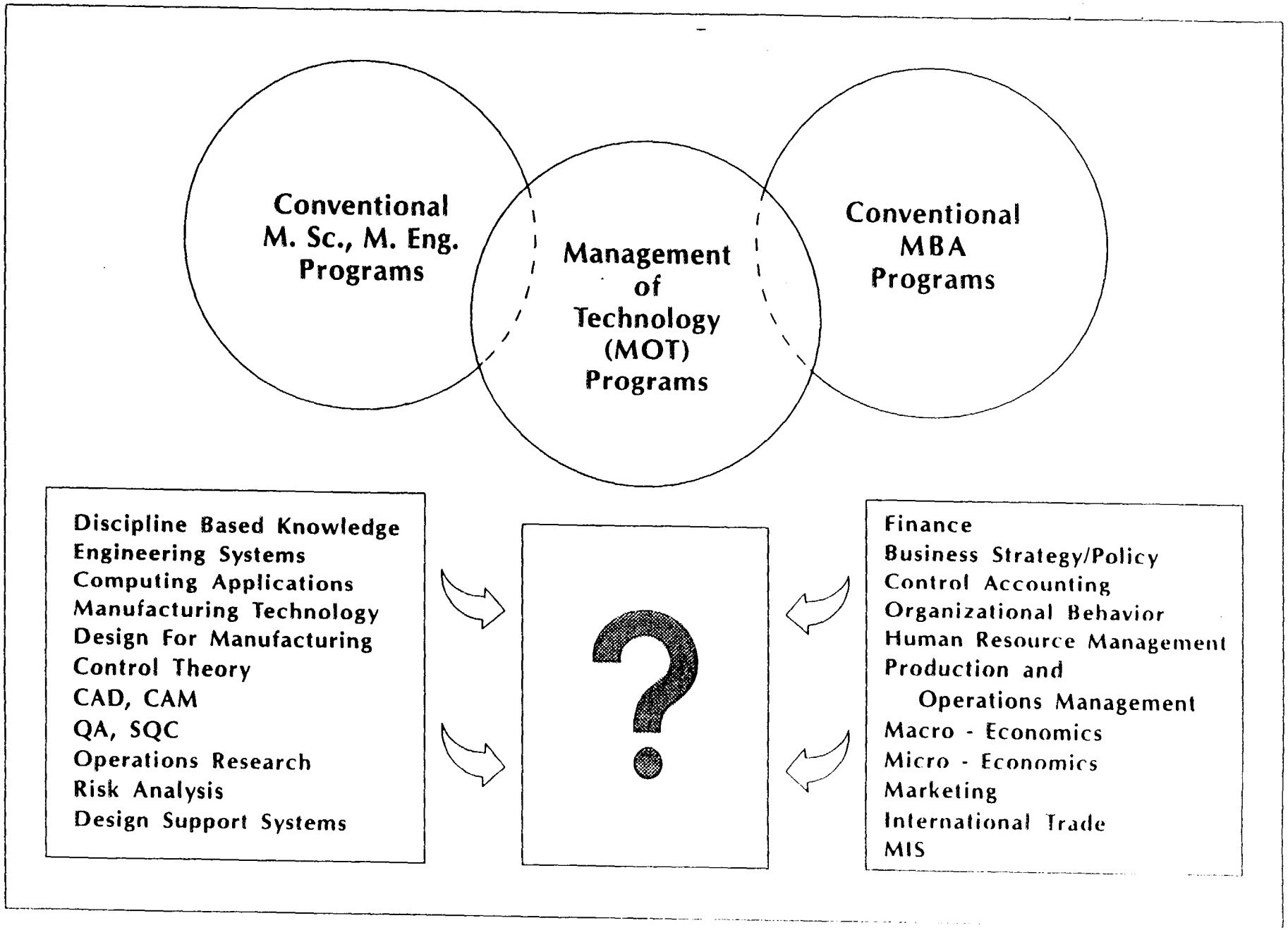

Figure 1 : Managment of Technology : Where it Lies

Source : Adapted from Natural Research Council (1987) and Collins et al (1991)

Table 1. An Eclectic Classification of Technological Capabilities

Description of the Major Technological Capabilities and Capability Elements

Operative Capability

Operative capability refers to the continuing ability of a firm to effectively transform inputs into outputs in accordance with the business strategy of the firm. More specifically it consists of the following capability elements.

O1. Capability to effectively utilize available plant and equipment.

O2. *Capability to plan and control production operations.*

O3. Capability to carry out troubleshooting and good predictive, preventive and emergency (breakdown) maintenance.

O4. Capability to quickly change over to new models.

O5. Capability to use computerized information and control systems to provide information support and networking for production operations.

Transaction Capability

Transaction capability refers to the ability of a firm to effectively plan and implement technology transactions. More specifically it consists of the following capability elements.

T1. Capability to justify and specify clearly the technologies to be bought/sold, based on detailed engineering studies and translation of basic process parameters into layout, plant and equipment.

T2. Capability to identify suitable sellers/buyers of technology and carry out sound technology, strategic and resource fit assessments.

T3. Capability to identify the most suitable mechanism(s) for buying/selling technology.

T4. Capability of a firm to negotiate effective terms for the transaction of the technology.

Innovative Capability

Innovative capability refers to the capability of a firm to come out with technological innovations and take them through to economic practice with a view towards strengthening current businesses, providing new business ventures, and exploring new technology bases.

I1. Capability of a firm to reverse engineer acquired technology.

I2. *Capability of a firm to carry out product innovations.*

I3. Capability of a firm to carry out process innovations.

I4. Capability of a firm to introduce application innovations.

I5. Capability of a firm to introduce system innovations.

I6. Capability of a firm to introduce core competence leveraging innovations.

Supportive Capability

Supportive capability refers to the capability of a firm to provide a foundation and impetus for the balanced development, integration and improvement of operative, transaction, and innovative capability. More specifically it consists of the following elements.

S1. Capability to formulate a technology-based development scenario in the light of a strategic vision.

S2. *Capability to identify funding sources and obtain funds at competitive rates for expansion and growth.*

S3. Capability to develop expeditionary and future-oriented market intelligence.

S4. Capability to effectively access necessary material inputs for production.

S5. *Capability for undertaking project planning and execution.*

S6. Capability for planning and implementing programs for sustained human resources development.

S7. Capability for knowledge creation and extracting latent skills.

TOPIC 2

CHALLENGES FOR MANAGERS OF TECHNOLOGY

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1. Introduction

It is no longer possible to devise effective corporate strategies without taking into account the underlying technological thrusts and their implications from the point of view of competitiveness, profitability, growth etc. A number of major technological forces now at work will have important impacts on the functioning of businesses and will require fundamental adjustments on the part of management with respect to the way business activities are conducted. The objective of this session is to examine the major challenges facing managers of technology.

2. The Major Technological Forces

The major technological forces that will impinge upon firm level activities are briefly outlined below

- First is the development of new manmade materials that will increasingly compete with and substitute for traditional materials generated from natural resources. Traditionally, technology has been used to process materials found in the ground or growing from it. However, recent advances in materials science and engineering are making it possible to start with a need and then develop a material to meet it. These "new materials" - super-polymers, composites, fiber optics, fine ceramics, and others now being developed in Japan, Western Europe, and the United States - will have a profound effect on the economic value of natural resources.

  The materials revolution could force a refocusing of public policy away from the prospects for traditional industries such as steel and copper and toward the emergence of entirely new industries and processes.

- Second, accelerating advances in the technology of computers, telecommunications, and information processing will provide enormous economies of scale in supplying services and transferring technology. The changes taking place in the area of information management are so far reaching that they have been characterized as the "information revolution."

  Advances in telecommunications represent only a part of the revolution taking place. Applied research is becoming faster as past knowledge becomes more readily available to researchers and experimentation is assisted by simulation and the bare beginnings of artificial intelligence. Product life cycles are shortening. Process and product technologies are becoming instantly transferrable through global computer-telecommunications links, widening dramatically the potential suppliers of goods and services in the world marketplace. Goods suppliers increasingly are able to provide accompanying engineering services, enabling much closer and more interactive producer-

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consumer relationships, thereby changing the nature of competition from selling previously designed machinery, equipment, and components to provision of design services, process technology, tailored equipment and components, redesign, and continuous engineering support. These developments sharply reduce the significance of geographic distance and dramatically shorten the response time needed to meet changing consumer demand.

- Third, industrial processes are being reoriented within the framework of computer-integrated manufacturing (CIM) and flexible manufacturing systems. This reorientation is based on multipurpose, reprogrammable equipment and systems, combined with entirely new materials processing techniques. The changing character of production processes will provide the opportunity for much greater flexibility, small lot production, minimal inventories, rapid market response, and product adaptation, while maintaining and even enhancing economies of scale in the use of plant and equipment. CIM will inevitably result in shorter product life cycles, and competitiveness will increasingly depend on the speed of response and the character of product-related services. There may be a substantial labor-displacing effect as a result of greater reliance on CIM, and this could have significant implications for enterprises in countries that rely on low labor costs for export competitiveness.

- Fourth, improvements in transportation, especially in the technology of aircraft, are bringing production centers and markets much closer in terms of time and relative cost. Lighter but stronger airframes and lighter, higher-performance aircraft engines will mean greater weight capacity, greater distance feasibility, and shorter landing and takeoff requirements, thereby intensifying the competitiveness of air transport relative to other modes of transportation and giving even greater emphasis to speed of response to consumer requirements.

- Fifth, rapid advances in the life sciences are likely to alter demographic profiles and enhance human capabilities across all age brackets. The share of services in total national employment is likely to continue to grow in virtually every nation, placing greater importance on the quality of the human resource base in maintaining and improving competitiveness and requiring greater emphasis on reforms of education and training at all levels and the quality and distribution of services.

- Sixth, biotechnology developments may open the way for major advances in the production (and location of production) of food, and for improvements in such diverse areas as industrial processes, management of wastes, memory technology, and even animal and human characteristics. Developments currently under way only reveal a

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glimmer of what these future thrusts might be. It can nonetheless already be said that developments in this field are likely to change greatly the nature of world food production and distribution, with major effects on agricultural and agribusiness technologies and competitiveness.

3. Implications for Managers of Technology

Throughout history, technological change has brought about changes in the pattern of world economic activity. What is new is the acceleration of the pace of change, combined with the emerging capability of changing the character of nature's building blocks to open entirely new avenues of production and even, potentially, new avenues of evolution.

Rapid economic change invariably means disruption. There are congenital tendencies in our economic institutions and political processes to shield disrupted enterprises or industrial sectors from global forces of change. Against these institutional tendencies, the emerging technology thrusts are accelerating the pace of change. One of the consequences of a shortened economic time span is faster product obsolescence in world competition. As the market life-cycle of many products shortens, there is a growing need for faster responses and faster adaptation of production systems, without time-consuming investment in new plant and equipment. In such a competitive environment. R&D cannot be attributed to particular products; it becomes an ongoing process necessary to remain a viable, competitive entity. Measurement of performance, accounting standards, tax treatment - all such traditional concepts become obsolete. This means treating the level of R&D spending as an underlying measure of the strength of corporation, much like capital asset value.

Some of the more important implications of these technological thrusts, at both firm level and national level are as follows:

- First, it is likely that there will be significant shifts in relative competitiveness among industrial sectors and shifts in relative economic power among nations. These shifts may not always move in a single direction. Building plants in other nations and securing components from foreign suppliers ("outsourcing") may prevail for some periods, while domestic consolidation and centralization may prevail in others. For example, the U.S. automotive industry may for a time move toward global sourcing, but there are strong economies to be gained from consolidation when new materials and CIM become more widely relevant to automotive production.

  In assessing the relative economic and political power of nations in coming years, it is apparent that countries that adapt quickly will tend to be stronger, and those that have difficulty adapting will tend to fall behind. In this regard, relatively rigid, centrally managed economies will have difficulty keeping pace, and the United States, Japan, Canada, Western Europe, and the NICs will probably stretch their technological lead over the centrally planned economies.

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- Second, growing world competition from new entrants at home and abroad can be expected to be generated by the accelerated international diffusion of technology. Countries that try to develop indigenous technologies through protectionist measures and exclusion of foreign technologies and communication will eventually find its firms falling back, "plugged out" form world competition.

- Third, private enterprise will have to become far more knowledgeable about worldwide developments among both present and potential competitors. To limit risks from competitive surprises and enhance the ability to synthesize a variety of technologies, companies may increasingly seek to devise cooperative arrangements among two or more industrial partners in various parts of the world. Engineers operating at different geographic points will increasingly work interactively through global telecommunications networks to develop new technologies cooperatively. These tendencies will increasingly obscure the national origins of particular technologies. It is also likely that there will be a growing emphasis on global provision of services (R&D, design, engineering, procurement, trading, finance, customer support, and the like).

- Fourth, the competitiveness of private enterprises will tend to depend upon the basic strategies of those enterprises. Planning for change and adapting quickly to it may become the most vital element in maintaining and enhancing competitiveness. This will often require increased emphasis on diversification and risk management, through diversification of markets, products, production location, production methods, financial arrangements, and R&D.

4. Concluding Remarks

The pace of technological change is posing a tremendous challenge to both firms and governments. In fact some analysts are of the view that governments may find that attempts to manage technology, in conventional ways, may be made increasingly irrelevant by the accelerating pace of change. It may be more useful for government to play the following important roles:

- First, governments could try to improve their macroeconomic policies to encourage faster innovation, investment, and growth. They could try to improve the tax treatment and other incentives for innovation, with particular attention to stepping up the speed of innovation and the pace of competitive responses to foreign challenges. Governments could create an environment that favors creation of new businesses and institutional change.

- Second, governments could educate their publics, including their business enterprises, about the nature of the forces now at work and the fundamental structural changes that will be necessary to meet them.

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TOPIC 3

UNDERSTANDING TECHNOLOGY

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1. Introduction

Acknowledging the need to acquire technology and use it as a competitive weapon is one thing but effectively introducing it into the organization and reaping the benefits is more complex. Recent literature contains many examples of such failures faced by many firms including technologically advanced multinationals. The forty billion dollar robotic leap of General Motors, flooding plant floors with advanced instrumentation technologies, and the disappointment at its inability to match up to shopfloor realities is a popular example that is often quoted.

A fundamental problem that leads to such mistakes is that it is not clear to many managers what technology really is. Technology continues to be treated as a "black box" by many managers and writers. It would be futile asking managers to manage technology effectively when it is not clear what technology really is. Thus, before business leaders and management "gurus" exhort managers to acquire the skills to manage technology effectively it is imperative that this issue be first addressed. This session is an attempt to meet this need in a limited way. The ideas presented in this sessions are based on two papers (Ramanathan, 1994 and Ramanathan, 1997). This session will therefore aim at trying to create an understanding of what technology really is. The focus will be on manufacturing technology.

2. The Elements of Process and Product Technology

In any manufacturing operation, it would be necessary to understand what product and process technology is involved. Product technology consists of two major categories: technology associated with the design of a product, and technology associated with the usage and maintenance of the product. Process technology refers to the technology needed to make the designed product. Both these will be explained below.

Process Technology

Manufacturing process technology may be defined as the manifestation of four elementary and interacting components namely: an object-embodied form called technoware; a human-embodied form called humanware; an information-embodied form called inforware; and an institution-embodied form called orgaware (Ramanathan, 1994). These components are elaborated below.

- Technoware comprises a material transformation subsystem, and an information processing subsystem. The material transformation subsystem performs desired mechanical operations that the technoware has been designed to perform. The information-processing subsystem carries out a three stage control sequence,

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namely. sensing-analysis-actuation. The information processing subsystem may be completely or partially built into the technoware. In some cases it may be totally absent in the technoware.

- Humanware consists of the skills needed to realize the potential of technoware and consists of "contact humanware" and "support humanware". Contact humanware refers to the operators of the technoware, while support humanware refers to the maintenance crew and indirect technoware use facilitators such as software specialists (for CNC machines) and production management personnel.

- Orgaware refers to the support net of principles, practices and arrangements that govern the effective use of technoware by the humanware. It may be viewed in terms of what may be called work conventions, work organization, work facilitation, work evaluation and work modification. Tables 1, 2, and 3 elaborate orgaware through illustrative examples.

- Inforware represents the accumulated knowledge needed to realize the full potential of the technoware, humanware and orgaware. Inforware, could be considered in terms of three categories: technoware-specific inforware (TSI); humanware-specific inforware (HSI); and orgaware-specific inforware (OSI). TSI refers to inforware needed to operate, maintain and improve the technoware. HSI is the inforware needed to obtain a good understanding and appreciation of the manufacturing process and the technoware being used. OSI is the inforware needed to ensure effective usage of, and timely interactions between, the available technoware and humanware. A more comprehensive breakdown in terms of the elements of TSI, HSI, and OSI are shown below.

  1. Technoware-Specific Inforware (TSI)

  Technoware attribute technoware (tai): Information pertaining to the technical specifications of the technoware.

  Technoware operating inforware (toi): Information pertaining to standard operating procedures and software needed to activate the technoware.

  Technoware maintenance inforware (tmi): Information needed to maintain technoware and the software needed to operate the technoware.

  Technoware performance-enhancing inforware (tpi): Technoware performance-enhancing heuristic knowledge developed in-house by the firm's humanware.

  Technoware design inforware (tdi): Engineering drawings, design specifications, and design calculations needed for manufacturing the technoware.

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2. Humanware-Specific Inforware (HSI)

Humanware foundation inforware (hfi): Information that provides insights into the functional requirements of a manufacturing system; the knowledge of the possibilities, limitations and manipulability of various natural processes and structures which might be used in technical practice; and a range of design concepts through which such processes and structures are harnessed to the performance of various functions.

Humanware back-up inforware (hbi): Information such as tables of engineering data and functions; documentary standards; state-of-the-art measurements; standardized measurement and calibration methods; and national and international standards of physical, chemical and engineering measurements.

3. Orgaware-Specific Inforware (OSI)

Orgaware back-up inforware (obi): Information such as: demand forecasts and customer specifications needed to determine the master production schedule (mps); bills of materials, on-hand inventories, order status of production items, replenishment rules and lead times needed for materials requirement planning (mrp); technoware and labor contact humanware capacity information for order scheduling, for planning overtime and/or subcontracting, if necessary, and for revising mps and mrp if needed; and supplementary details on costs, technoware downtime, yields, rejects etc.

Orgaware enhancing inforware (oei): Information needed for enhancing the planning and control of technoware and humanware. This includes algorithms, heuristics and rules such as those provided by operations research and statistical techniques, and also computer software that facilitate the scope of application of these.

The four components of process technology are complementary to one another and are interrelated. They are required simultaneously in a manufacturing operation and no transformation can take place in the complete absence of any of the four components.

It is important to note that there exist dependent relationships between the four components. For instance, technoware with no information-processing subsystem built into it would require well trained contact humanware to operate it. On the contrary, advanced technoware with a sophisticated built-in information processing subsystem may not need highly skilled contact humanware to operate it but would certainly require high calibre support humanware to provide the necessary programming and maintenance support. The mix of technoware and humanware to be used would also determine the nature of the orgaware to be used. For instance, the unique characteristics of the orgaware used with commendable success by the Japanese in an FMS environment have been well elaborated in the literature. On the contrary, the orgaware to be used in an engineering parts manufacturing unit using conventional

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machine tools would be quite different. However, it may be useful to point out that the introduction of advanced technoware in an organization often necessitates the hiring of highly qualified support humanware and the changing of the orgaware to suit the new environment.

Product technology

In the case of product technology, there are two major categories of inforware (Ramanathan, 1997). These may be referred to as product design inforware (PDI) and product usage inforware (PUI). The various elements that make up these two categories of product related inforware are elaborated below.

1. Product Design Inforware (PDI)

- *Design foundation inforware (dfi)*: Information that provides insights into: the functional requirements of the product design; design concepts; simulation techniques and analytical procedures needed for understanding and predicting product performance; computer-aided design tools; and customer needs.

- *Design back-up inforware (dbi)*: Information such as organized technical data needed for designing a product. This includes information such as tables of engineering data and functions; documentary standards; state-of-the-art measurements; and national and international performance standards.

- *Design specifications inforware (dsi)*: Information such as engineering drawings of the product; design specifications; and design calculations used.

2. Product Usage Inforware (PUI)

- *Product operating inforware (poi)*: Information such as standard operating procedures and software needed to use the product. This could include information for installing the product. Sometimes, it could also include information for computer-based training (CBT). CBT tools can often be customized to suit the client's needs.

- *Product maintenance inforware (pmi)*: Information needed to maintain, repair, and service the product and related software. This could include maintenance manuals (for both hardware and software), trouble-shooting checklists, and parts listings.

- *Product performance-enhancing inforware (ppi)*: Knowledge, usually of a heuristic nature, that involves information needed for operation optimization, and upgrading product performance.

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Table 1. Comparison of the Orgaware in Lean and Buffered Production Systems

Determinants of Orgaware	Description of Orgaware	
	Lean Production Systems	Buffered Production Systems
Work conventions	o Seek perfection the first time	o Learning through trial and error
	o High-risk but high-return approaches	o Low short-term risk approaches with low potential for long-term performance gain
	o Role of senior management is "visioning" - establishment and communication of common goals	o Role of senior management is "bossing" - top-down control to ensure attainment of organizational goals
Work organization	o Production of a large variety of products	o High-volume production of few standardized products
	o Team approach to work organization with emphasis on autonomy and networking of groups and individuals	o Central administrative coordination and control
	o Small number of white-collar staff for monitoring performance and suggesting improvement measures	o Heavy reliance on white-collar workers for performance monitoring and suggesting improvement measures
	o Conserve resources (especially inventory, and repair areas and facilities) and time through approaches based on a "just-in-time" philosophy	o Cushion the system from any and all unforeseen events by stocking up resources (especially inventory, and repair areas and facilities) based on a "just-in-case" philosophy
	o Suppliers and subcontractors must be regarded as part of the production team	o Through competitive sourcing compel suppliers to accept minimal profit margins

Table 1 (continued). Comparison of the Orgaware in Lean and Buffered Production Systems

Determinants of Orgaware	Description of Orgaware	
	Lean Production Systems	Buffered Production Systems
Work facilitation	o Multiskilled and highly trained employees with ability to handle a variety of tasks	o Extreme forms of functional specialization, narrow job descriptions and low emphasis on continuous training
	o Extensive sharing of information	o Low emphasis on information sharing
Work evaluation	o Employees are encouraged to measure their own performance. Emphasis is on "grass-roots" involvement with all aspects of operation at the work-force level	o Employee performance is monitored independently by white-collar supervisory and industrial engineering staff. Little or no emphasis on inducing "grass-roots" involvement.
	o Evaluation criteria are based on flexibility, quality and delivery	o Evaluation criteria stress cost reduction
Work modification	o Encouragement for continual and incremental improvement of products and processes through worker empowerment and workforce involvement. Breakthroughs are not abjured but placed in a different perspective	o Innovations are generated by research and development staff working independently in industrial research laboratories. The focus is on breakthroughs. Incremental and continuous improvements are not adequately emphasised
	o Innovative activities focus on improving quality, reliability and features.	o Focus of innvoative activities is on cost reduction.

Source: Ramanathan (1994)

Table 2. Description of Orgaware in Japanese Firms Using FMS

Determinants of Orgaware	Characteristics of the Orgaware of Japanese Firms Using FMS (Flexible Manufacturing Systems)
Work conventions	o Faith in the technological literacy of the company's workers. o Emphasis on the management of intellectual capital and not only of equipment. o Treating manufacturing as a service to special market segments
Work organization	o Reliance on small, cohesive teams of highly skilled generalists. o Emphasis on teamwork for advance problem solving and process improvement. o Meshing of FMS installation project team with the operating team to ensure smooth transition and enhancement of learning to enable process mastery and productivity enhancement. o Division of teamwork with a view towards creating time to undertake process improving activities such as test cutting of new parts, observing machine behavior, and examining performance statistics. o Worker empowerment to plan production, and manage quality and delivery performance. o Management focus not on routine day-to-day problems but on strategies for meeting competitive pressures on product performance.
Work facilitation	o Extensive use of college-educated engineers and highly competent engineering oriented people. o Extensive training to upgrade skills (three times longer than in the United States). o Extensive information exchange through group activities.
Work evaluation	o Evaluation based mainly on ability to attain: flexibility in operations; quality; reliability; increased uptime; and untended operations.
Work modification	o Emphasis on purposeful incremental improvements on a sustained basis (no "if it ain't broke, don't fix it" attitude). o Continuous creation of new physical assets in the form of better programmed and better managed equipment. o Emphasis on the need for managing process improvement,not just output, on a sustained basis.

Source: Ramanathan (1994)

Table 3. Reengineering Interpreted as a Means of Changing Orgaware

Determinants of Orgaware	Reengineering Approaches for Changing Orgaware
Work conventions	o Persuading all employees to embrace - or at least not to fight - the prospect of major change o Inducing changes in company culture and values - from protective to productive o Changing attitudes of managers - from supervisors to coaches o Changing attitudes of senior management - from scorekeepers to leaders
Work organization	o Changing work units - from functional departments to process teams o Changing jobs - from simple tasks to multidimensional work o Changing organizational structures - from hierarchical to flat
Work facilitation	o Changing roles of employees - from controlled to empowered o Changing job preparation - from training to education
Work evaluation	o Changing the process of setting evaluation criteria - from top down mode to consensus mode o Changing focus of performance measures and compensation - from activity to results o Changing advancement criteria - from performance to ability
Work modification	o Innovating through "benchmarking" o Enhancing things that bring value to the customer and changing or eliminating things that don't o Changing from an "if it ain't broke, don't fix it" approach to "if it ain't broke, keep looking" approach

Source: Ramanathan (1994)

The above approach of looking at technology is very useful when transfer of technology is being planned. In a manufacturing technology transfer situation, if process technology transfer is considered, it may be said that technology transfer is successful only if it leads to the eventual acquisition and balanced development of all four components of process technology. If product technology transfer is considered, comprehensive transfer may be said to have taken place only if both PDI and PUI have been transferred. Unfortunately, in selecting technology transfer mechanisms and negotiating the package, most transferees of technology do not explicitly consider the process and product technology in terms of the various elements of technology. Thus, understanding what technology really is from a business perspective is important from both technology transfer planning and negotiating perspectives.

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TOPIC 4

CREATING TECHNOLOGICAL COMPETENCIES

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1. Introduction

In today's context, we see that location specific factor based cost advantage cannot be retained for long. To survive and grow, firms must learn to compete on the basis of technology. This session will try to create an understanding of how technology can confer competitive advantage on a firm. The concept of core competence in this context will also be introduced.

2. The Influence of Technology on Competitiveness

Though a firm may have many strengths and weaknesses vis-a-vis its competitors, it attains competitive advantage either due to:

- Cost advantage; or
- Differentiation

In a cost advantage strategy a firm tries to become the low-cost producer in the industry. However, its product must be seen as comparable to the products of the other competitors in terms of quality and other expectations of the buyers. In a differentiation strategy a firm tries to produce something that is unique with respect to certain dimensions that are widely valued by buyers. The firm may position itself to cater to some or all of those dimensions. For providing these valued attributes the firm will charge a premium. Firms may also adopt these strategies in specific segments of the industry and specialize in niches.

In implementing these strategies a firm should look at the influence of technology on the following:

- its value chain (Figure 1); and
- its industry structure (Figure 2).

The influence of technology on industry structure should be seen from the perspective of firms already existing in the industry and also from the perspective of potential entrants, suppliers, and buyers. When firms go in for new technology they should assess it from these perspectives as well and not only on conventional aspects such as how much it costs to buy or how modern/old it is.

A clever firm tries to use technology to configure its value chain in such a way that it can help it to reduce cost or improve uniqueness. In this context it should examine its technological core competencies. Technological core competencies may be defined as the collective knowledge in an organization about how to coordinate the multiple technologies required for product design and production. This collective knowledge will depend on how well developed the technological capabilities of a firm are.

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3. Technological Capabilities as the Foundation of Core Competencies

Often owning technology is confused with having technological capability. Actually, to compete, a firm must have the ability to:

- o Use the technology it has very effectively so that it can recover the investment made in it and generate surpluses for further growth;
- o Buy or sell useful technology at good prices so that it can either continuously improve the sophistication of its technology or make money from what it owns;
- o Adapt, improve and eventually develop its own technology: and
- o Provide the necessary support to develop and improve the above three abilities

Thus, having the technology components is only one side of the "technological competency coin." Having the abilities mentioned above - which we may call "technological capabilities" is the other side.

Technological capability gives power to a firm. While a Firm A may sell technology to another Firm B, it will not upgrade the technological capabilities of B because no entity likes to distribute power to others. Technological capability must be accumulated by firms on their own. Since the mid-1980s many classifications of technological capability have been used. A recent (Ramanathan, 1997) classification will be presented in this session.

In accordance with the abilities discussed above we can view technological capabilities as consisting of four categories. These are:

- Operative capabilities;
- Transaction capabilities;
- Innovative capabilities; and
- Supportive capabilities.

Operative capability refers to the continuing ability of a firm to effectively transform inputs into outputs in accordance with the business strategy of the firm. More specifically it consists of the following capability elements. It consists of the:

- o Capability to effectively utilize available plant and equipment;
- o Capability to plan and control production operations;

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- Capability to carry out troubleshooting and good predictive, preventive and emergency (breakdown) maintenance;
- Capability to quickly change over to new models;
- Capability to use computerized information and control systems to provide information support and networking for production operations.

Transaction capability refers to the ability of a firm to effectively plan and implement technology transactions. It consists of the:

- Capability to justify and specify clearly the technologies to be bought/sold, based on detailed engineering studies and translation of basic process parameters into layout, plant and equipment;
- Capability to identify suitable sellers/buyers of technology and carry out sound technology, strategic and resource fit assessments;
- Capability to identify the most suitable mechanism(s) for buying/selling technology; and
- Capability of a firm to negotiate effective terms for the transaction of the technology.

Innovative capability refers to the capability of a firm to come out with technological innovations and take them through to economic practice with a view towards strengthening current businesses, providing new business ventures, and exploring new technology bases. It consists of the:

- Capability of a firm to reverse engineer acquired technology;
- Capability of a firm to carry out product innovations;
- Capability of a firm to carry out process innovations;
- Capability of a firm to introduce application innovations;
- Capability of a firm to introduce system innovations; and
- Capability of a firm to introduce core competence leveraging innovations.

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Supportive capability refers to the capability of a firm to develop, integrate and improve operative, transaction, and innovative capability. This includes:

- o Capability to formulate a technology-based development scenario in the light of a strategic vision.
- o Capability to identify funding sources and obtain funds at competitive rates for expansion and growth.
- o Capability to develop expeditionary and future-oriented market intelligence.
- o Capability to effectively access necessary material inputs for production.
- o Capability for undertaking project planning and execution.
- o Capability for planning and implementing programs for sustained human resources development.

A firm may not need all the technological capabilities from the beginning. Depending on its vision and competitive environment a firm may gradually accumulate the desired technological capabilities. However, for a particular transformation operation a firm must have the necessary four components of technology to compete. The following observations may be made with respect to technological capabilities.

- o With the gradual development of an enterprise the sophistication of both the components and capabilities must increase.
- o For different types of capabilities, a firm requires the right kind of technology components. Depending upon the type of capability, the relative importance of the four components may change.

  Example: For innovative capabilities H and I will, in general, be more important than T and O.

4. Improving Technological Capabilities and Creating Competencies

The accumulation of technological capabilities is a process of institutional learning. It must reside in an enterprise and must not be diminished if an individual leaves the firm. Thus, putting in place the necessary mechanisms for fostering collective learning is very critical for technological capability development. Basically, learning takes place "by doing" and "by

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changing." There are many ways to "do" and "change." In fact today we talk of "learning organizations."

Before trying to improve technological capability, it is important for a firm to first measure its existing technological capability through the use of qualitative and quantitative indicators. Methods are available to do this. The firm should then "benchmark" its existing capabilities with a "target leader" in order to decide where and by how much it should improve.

Technological capability development is a dynamic process. In today's competitive environment there can be no stopping of the "component enhancement" and "capability development" processes. If these two are done the creation of technological competencies for competitive advantage will be greatly strengthened. Two examples are given in the text to illustrate technological core competence build up.

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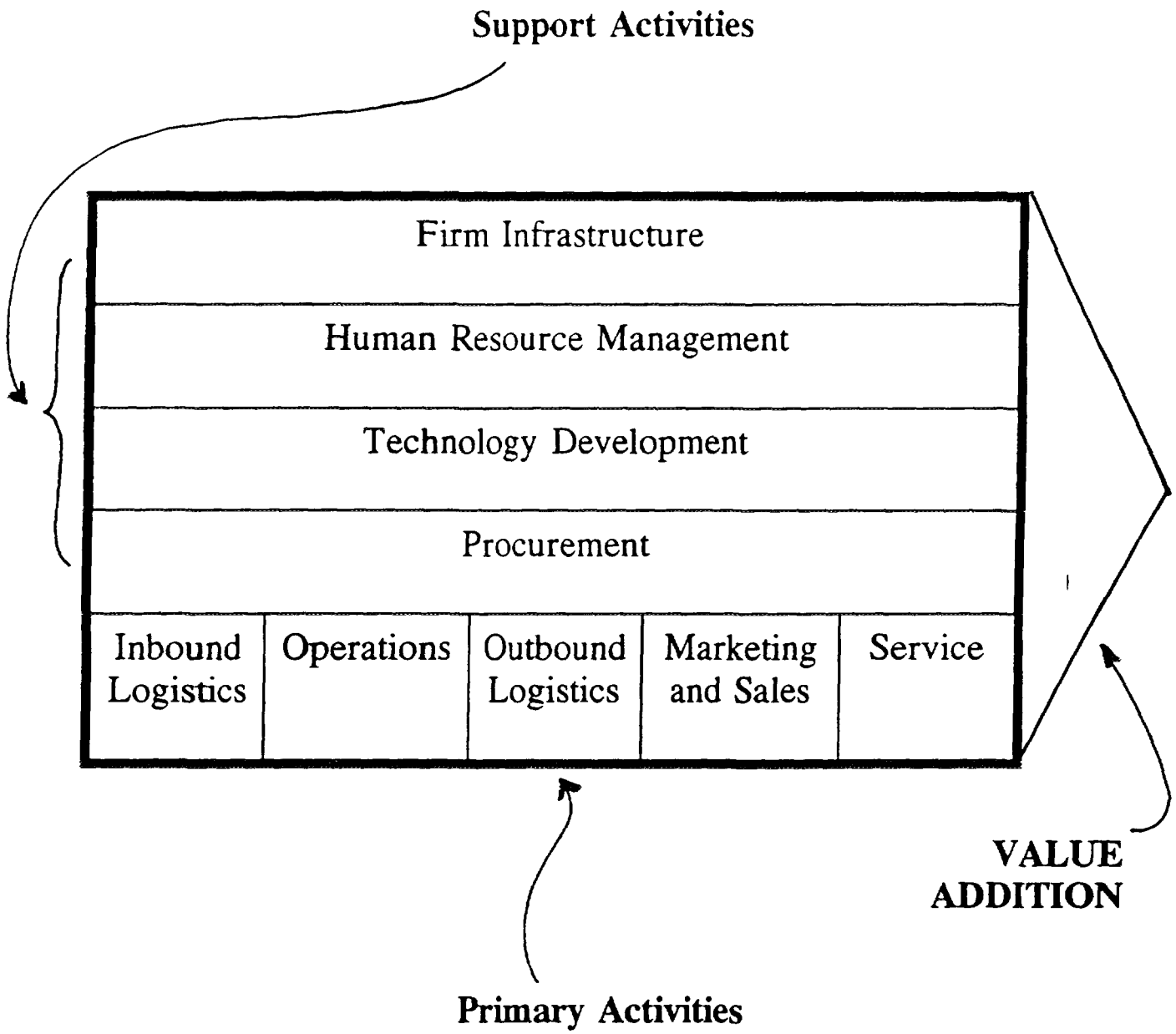
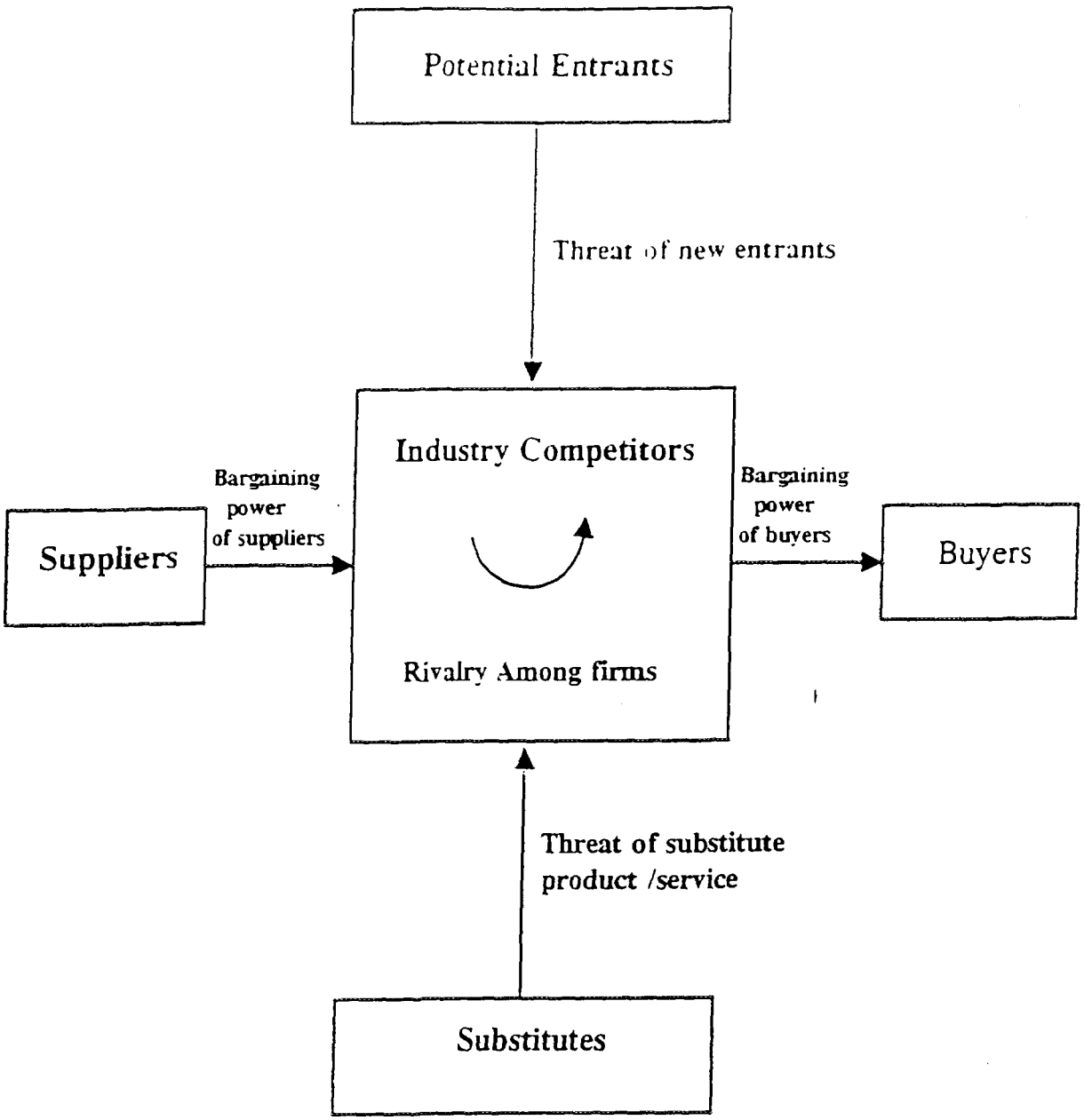


Source: Porter, M.E. (1985), Competitive Advantage, Free Press, New York

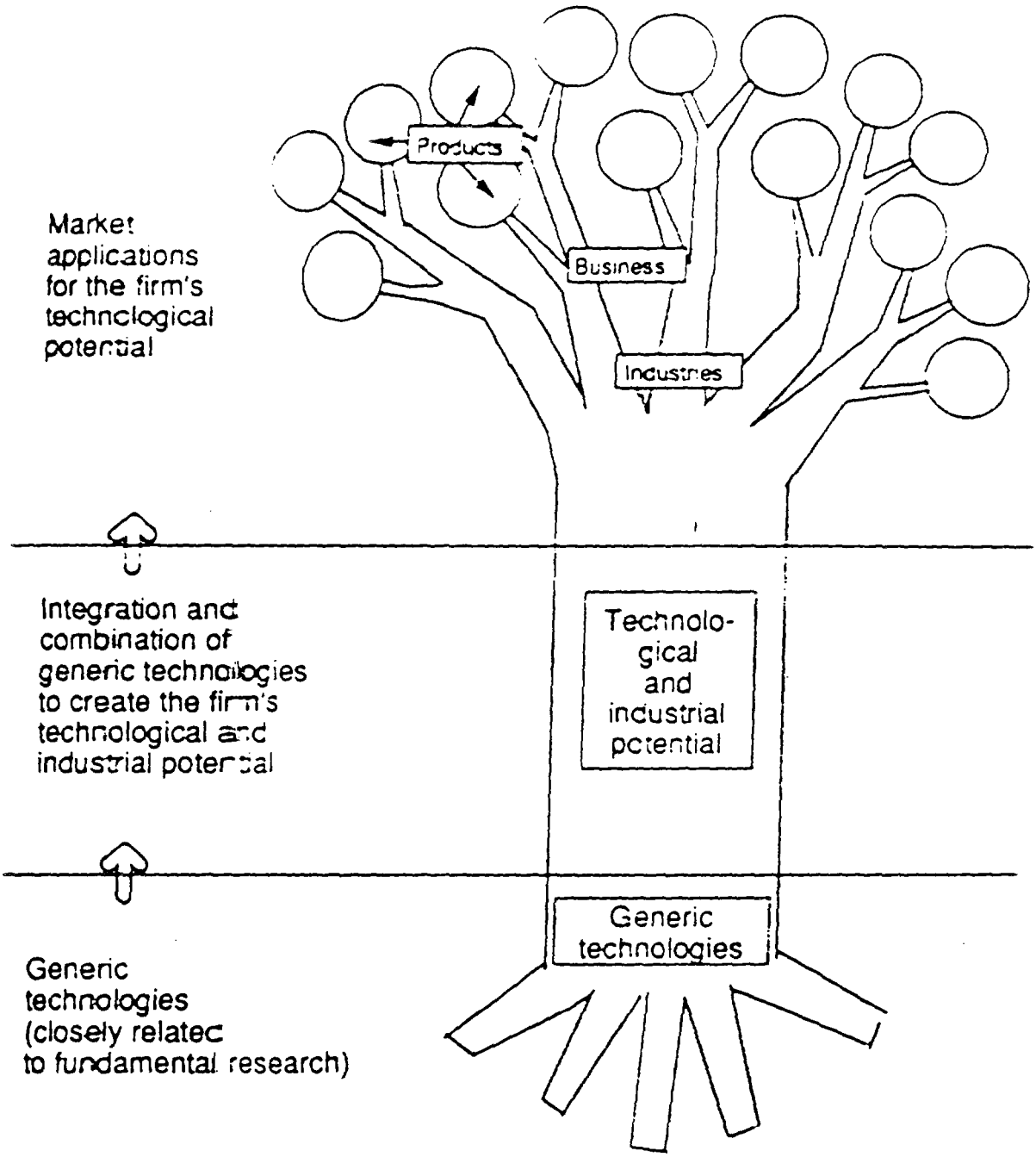
Figure 1: Porter's Value Chain



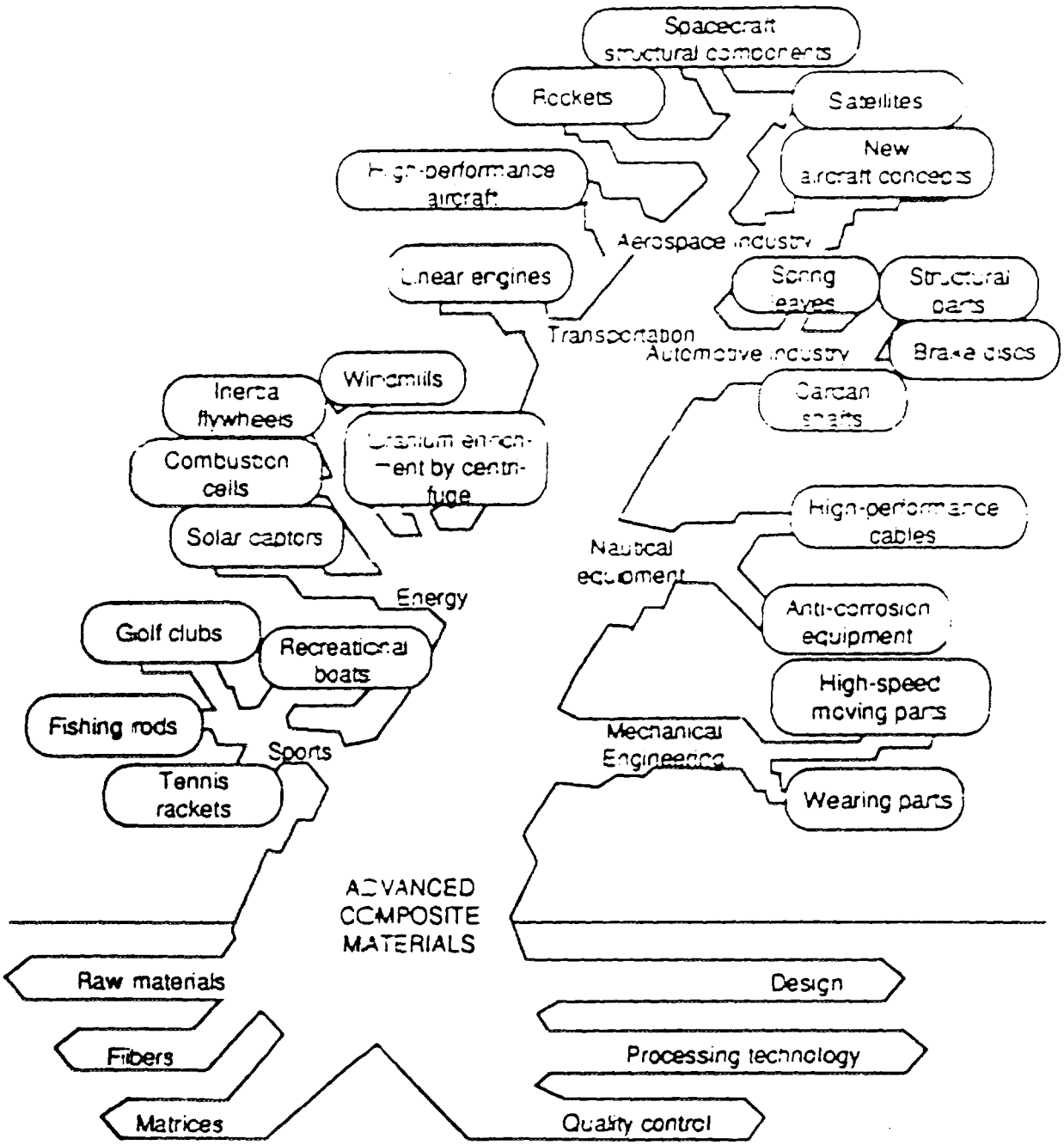
Source: Porter, M.E. (1985), Competitive Advantage, Free Press, New York

Figure 2. Porter's Industry Structure Representation

Technological core competencies may be defined as the collective knowledge in an organization about how to coordinate the multiple technologies required for product design and production.



The Technological "Bonsai"



An Example of Toray's Technological Core Competence

TOPIC 5

STRATEGIC INNOVATION FOR NEW BUSINESS

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Technology Management Module
Training Course on
"Industrial Exploitation of Indigenous and Aromatic Plants"
Organized by UNIDO, ITPD/TS and ICS
Beijing, China
June 10-25, 1997

1. Introduction

Research and development (R&D) management has, over the years, come to mean the effective management of R&D activities the results of which are technological innovations. Technological innovations enhance a firm's competitiveness and hence the efficient management of R&D activities are critical from a strategic perspective. The sustained financial well-being of firms and nations thus depends to a large extent on their ability to continuously innovate and to maintain steady progress in technological advance. Until very recently it was thought that R&D was relevant only to firms in the industrialized developed countries which are generally in the forefront of developing new technologies. However, recent experience in the Newly Industrializing Countries (NICs) such as Korea, Singapore, and Taiwan, and technologically advanced developing countries such as China. India and Brazil has shown that R&D efforts can indeed contribute towards economic development and self-reliance of the less affluent countries. This realization has led to an intensification of interest in developing countries in studying the strategic management of innovation.

However, initiating and sustaining efforts for strategic innovation in a developing country setting can be quite difficult due to several reasons. The more important include the following (Choi: 1989, 1986):

- Low public interest in science and technology, and lack of popular esteem for scientific and technological accomplishments;
- Inability of government R&D institutes to create a "critical mass" in terms of people, facilities, information, and funding;
- Non-availability of necessary scientific and technological manpower at the national level;
- Heavy reliance on imported technology and lack of initiatives to modify and improve it for domestic application;
- Poor commercialization capabilities of government R&D institutes which leads to wastage of resources, and strained relationships with industry;
- Poor capability at all levels for assessing the economic implications of R&D efforts; and
- Sub-critical involvement of industry in fostering national R&D initiatives.

It is against this background that the management of innovation at the firm level has to be viewed. In addition, innovation strategy is an integral part of a firm's overall technology strategy. Thus, any examination of a firm's innovation strategy must be seen in this context. For the sake of convenience the terms "innovation management" and "R&D management" are used interchangeably in this topic.

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In this session we shall attempt to elaborate the strategic management of innovation at the firm level, in a developing country setting, in relation to the firm's overall technology strategy. In order to accomplish this objective, the rest of this topic is presented in four parts. The second part, which is the next, elaborates a generic classification of technology strategies. This is followed by an explanation as to how one can develop a typology of R&D initiatives in terms of increasing degrees of sophistication and complexity. The fourth section then suggests the nature of R&D activities that firms following different technology strategies can undertake. Lastly, recommendations are made with respect to supportive interventions that are needed to successfully embark upon and sustain a steady growth of R&D activities.

2. A Generic Classification of Technology Strategies

Basically there are two ways by which a firm can gain access to a technological innovation. The first is to generate the innovation through in-house R&D. The second is to purchase the technology from another firm which has developed it. The latter is commonly referred to as technology transfer. Very often the question is raised whether R&D is really necessary for all types of firms. Some managers argue that it may be cheaper to buy the technology than generate it in-house through R&D. This kind of argument is especially common in developing country firms which are acutely aware of the fact that technologically they are far behind the firms in the technologically advanced countries. An answer to this question is best sought by looking at the generic technology strategies adopted by firms. Experience shows that firms generally tend to follow four generic technology strategies (Sharif and Ramanathan, 1995; Zahra, Sisodia, and Das, 1994). These are:

- the technology leader (or first-to-the market) strategy;
- the technology follower (or fast follower) strategy;
- the technology exploiter (or imitator) strategy; and
- the technology extender (late entrant) strategy.

Each of these strategies are elaborated below.

Firms that follow the technology leader strategy are usually the industry leaders. These firms, in general, reach such a status by continuously upgrading their technologies and by becoming producers of state-of-the-art technologies. They also cater to a very high value market. For instance, Cray and Fujitsu may be considered to be technology leaders in the production of supercomputers. Such firms are very innovative and invest heavily in R&D. They also determine to a great extent the technological trajectory that the industry will follow in the future.

There are also very large and successful firms which are very cautious and do not attempt to become technology leaders. They permit other firms - the technology leaders - to do the pioneering work and quickly move in as "followers" if they feel that the pioneering efforts are likely to lead to success. The technology followers also have high technological capabilities and

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invest heavily in R&D. However, their greatest skill is in quickly adapting and modifying the advanced technologies developed by the leaders and catering to similar markets. In some instances the products of the followers may be superior to that of the leaders although they will not have the advantages of being the "first-to-the market."

A third category of firms follow what may be called the technology exploiter strategy. Such firms have the ability to acquire standardized technologies from around the world, adapt it to suit their conditions if necessary and use it effectively to cater to medium value markets. Firms in countries such as Korea and Taiwan have earned a reputation for being excellent technology exploiters. There are many instances where firms in these countries have successfully exploited standardized technologies and built up huge export markets. These firms also carry out R&D to assimilate and improve imported technologies.

The last generic technology strategy followed by some firms, especially in many developing countries, is what may be called the technology extender strategy. These firms usually pick up mature and obsolete technologies which are freely available in the international markets and use them to produce output to cater to low value markets. Such firms hardly carry out any R&D.

If the technology transfer (TT) and in-house technology development (R&D) mix of the firms adopting the different technology strategies are examined, it can be seen that while technology extenders would almost certainly depend entirely on TT, the technology leaders would have to depend almost entirely on in-house R&D. This is shown schematically in Figure 1. The figure shows that the technology followers also have to depend heavily on R&D to quickly adapt and modify the advanced technologies generated by the leaders. The technology exploiters also need R&D to adapt the standardized technologies that they purchase in the international markets. Thus it may be said that as a firm makes the transition from a technology extender to a technology leader its dependence on in-house R&D would go on increasing. It may even be said that without R&D a firm cannot go beyond the technology extender stage.

The example of Japan provides a good example of the need for the firms in any country to develop R&D capabilities. Immediately after the Second World War, Japan was said to be thirty years behind the industrialized western nations in science and technology. It was even said that speedy economic recovery was impossible. However, now it is well known that Japan is considered an economic threat by the western industrialized nations. Japan was able to achieve such phenomenal growth mainly due to the large capital investments it made in plant and equipment. These investments were in the form of imported foreign technologies. Before the War, Japan had imported only 231 items of technologies. Twenty years later after the War, the total number of technologies that had been imported had risen to about 7,500. Statistics show that between 1950 and 1960, the output of production utilizing these imported technologies occupied about 25.5% of total business output in Japan. It may thus be said that after the War, Japanese firms relied heavily on technology transfer from abroad.

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However, it was always recognized by the Japanese Government and the firms that little can be achieved through the importation of imported technology unless capabilities are developed to modify and improve these technologies for lateral domestic applications. Thus, great emphasis was placed on R&D for assimilating and improving these imported technologies. Statistics from the Ministry of International Trade and Industry (MITI) shows that in 1963, Japanese private industries spent, on an average, 42 million yen as royalty payments per imported technology and 58 million yen on R&D for assimilating each of these. The Japanese experience suggests that even at a stage when firms are heavily dependent on technology importations, they need to spend money on R&D for assimilating and improving these. Without R&D efforts it will be impossible for firms to move from the stage of technology extenders to technology exploiters and further upwards to technology leaders. The next section elaborates upon the nature of R&D efforts that firms tend to undertake at different stages of technological development.

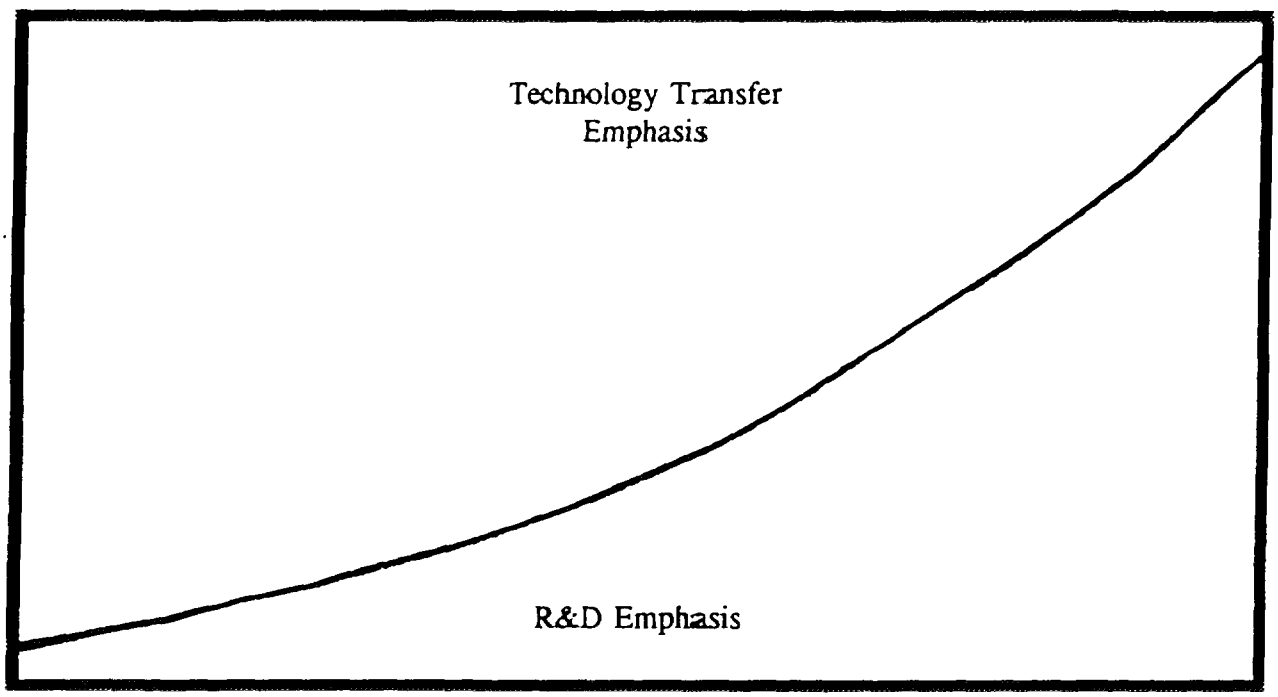

Figure 1: A Schematic Representation of the Technology Transfer R&D Mix for Different Technology Strategies

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3. A Typology of Innovation (R&D) Efforts

A basic and very important activity that firms often undertake at the initial stages of their formal R&D efforts is what may be called "reverse engineering". Dobbs-Higginson (1993) in his discussion of Taiwan states that, "Like the Formosan pirates of old, many of the new Taiwanese turned to commercial piracy, ignoring patents and copyrights enforced everywhere else in the West. To be fair, the same could be said of most Asian economies in their initial emerging years, and of China today. This helped to fuel an economic miracle as impressive as, if not more so than, any other in Asia". Friedland (1994) gives a classic example of how, Tokuji Hayakawa, the founder of Osaka-based Sharp Corp., imported a crystal radio set from the United States in 1925, efficiently reverse engineered it, and made Japan's first vacuum-tube radio, the Sharp Dyne.

Bae and Lee (1986) outline the merits of reverse engineering as follows: low cost; new product development without technological dependency; indigenously accumulated technological capability; and the possibility of developing locally appropriate technology. They also add that its demerits are (Bae and Lee, 1986): likely failure if the technological gap is substantial; longer time duration needed than in formal technology transfer; not useful for high technology acquisition; and the need to have some technological capability for carrying out imitation. Cooper (1991) states that, "It is, however, a rather limited view of innovation theories that they are, or should only be concerned with the initial introduction of new products and processes. Clearly, the imitative phase is important too - and in a sense, needs to be looked upon as integral to any explanation of innovative behavior". Cooper (1991) also suggests that the skills initially applied to reverse engineering activities may eventually become the basis for more sophisticated innovative activities. However, with the increased emphasis, today, on intellectual property protection, especially after the 1993 Uruguay Round, blatant imitation as in the past may be difficult. However, it is unlikely that imitative activities will cease altogether.

Abernathy and Utterback (1978) have shown that when a firms starts formal R&D, it initially focuses on product change and then later shifts predominantly to process change. R&D for product innovation can itself be of several types. Henderson and Clark (1990) propose different types of product innovation as follows:

- **Incremental innovations** where core sub-technologies are *reinforced* but linkages among sub-technologies remain *unchanged*. Examples include, software, such as successive generations of Microsoft Word or Wordperfect, where only established designs and sub-technologies were used.

- **Architectural innovations** where core sub-technologies are *reinforced* and linkages among sub-technologies are *changed*. Examples include, products such as personal computers where existing sub-technologies were linked in a new way.

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- **Modular innovations** where core sub-technologies are *overturned* but linkages among sub-technologies remain *unchanged.* Examples include products such as digital telephones where there were changes in the core sub-technologies but no changes in the product's overall architecture.

- **Radical innovations** where core sub-technologies are *overturned* and linkages among sub-technologies are also *changed.* Examples include products such as transistors, new materials and processes such as instant photography which established not only new sub-technologies but also new system designs.

R&D for process innovations mainly focus on improvements of a process for making a product may efficiently. It may involve R&D for bringing about: improvements in the manufacturing process; integration of manufacturing process steps leading to reductions in cycle time; reductions in the number of process types; and improvement of manufacturing process yields. Often process innovation lags behind product innovation.

The Asian and Pacific Centre for Transfer of Technology (1989) has shown how Japan was able to develop its competitiveness further in the steel and electronics industries by proceeding beyond product and process innovations and going in for application innovations. R&D for application innovations aims at the utilization of an existing idea, design method, or testing concept to improve, sometimes dramatically, existing products and processes. An example is the application of fuzzy logic to improve products and processes. R&D to generate application innovations cannot, in general, be carried out without adequate experience in R&D for product and process innovations.

Bowonder and Miyake (1994), also refer to two types of R&D activities that are more sophisticated and complex than R&D for coming out with product, process, and application innovations. The first of these two may be called R&D for system innovations. This involves the introduction of new systems through linking or integration of a variety of subsystems, and involve product, process and application innovations. An example could be an improved fuzzy logic based improved continuous tandem cold rolling mill for producing special steels.

The second is what Bowonder and Miyake (1994) refer to as R&D that leverages existing core competence to come out with breakthroughs in product, process, application, or system innovations. An example would be the case of Hitachi Ltd. developing the world's largest Gallium-Arsenide (Ga-As) single crystal and then using Ga-As technology in its satellite broadcasting technology. When a firm has core competence in several areas it can embark on "fusion R&D" to come out with radically new product, process, application, or system innovations. An example would be the fusion of core competencies in information technology, building automation technologies, building equipment system technology and integrated administration services to develop "intelligent buildings".

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R&D activities may thus be ranked in increasing order of sophistication/complexity as follows:

- o R&D for reverse engineering
- o R&D for product and process innovation
- o R&D for application innovation
- o R&D for system innovation
- o R&D for core competence leveraging innovations

The above typology is useful because it shows that when talking about R&D activities one needs to be take into consideration, the attributes of the firm and its strategic posture.

4. The Dynamics of R&D at the Firm Level

The typology of R&D activities and the classification of technology strategies suggest that, at the very outset, one must dispel the popular view that R&D is associated with basic research and momentous discoveries. In fact what is clear is that building up R&D capabilities is a time consuming process and has to be started gradually and nurtured with "patient capital." The best way to initiate R&D would be start off by focusing on efforts that answer market needs.

This means that a developing country firm, that is following a technology extender strategy, could start off by carrying out R&D for reverse engineering. This could help assimilate imported technology and create the knowledge base needed to make modest improvements in products and processes. For instance, through reverse engineering, products such as "coir spinning machines", "fruit cutting machines", "rice milling machines" etc., can easily be made and even improved with some ingenuity. Very often such machines, which are in great demand in many agriculture-based developing countries, are easily available in the international market place, and are in general not protected by patents.

The confidence gained through such R&D, and its successful commercialization, can spur the firm on to the beginnings of the technology exploiter stage where the firm may wish to license out technology from outside and combine this with its in-house R&D to come out with product, process, and application innovations. Anam of Korea, Acer of Taiwan, and Creative Technologies of Singapore, are all examples of companies that started small and through a deft combination of licensing and their own R&D for product, process and application innovations managed to move from a technology exploiter stage to a technology follower stage.

By the time a firm becomes a technology follower, R&D efforts with respect to product, process, and application innovations could become strengthened further. Even within these types of R&D the firm could move to higher levels. For instance, Anam of Korea today undertakes the design and development of special chip packages for Motorola and IBM. It also makes semiconductors for a variety of applications that includes computer memory cards and cellular

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phones. R&D activities of Acer has also progressed from making better PCs - such as its Aspire line, to different types of electronic items that can cater to the "digital living room". In this case it is competing with technology leaders such as IBM, NEC, and Fujitsu. Some firms such as Ricoh are coming out with sophisticated products based on a principle called, "creative office automation" where they are combining items such as a laser jet printer, fax, and scanner into one machine for greater operational flexibility in the office.

The considerable R&D capability that a firm builds up, during its gradual progression up the R&D typology, eventually brings it to the technology leader stage where its R&D activities cover the full spectrum of the typology. System innovations and core competence leveraging innovations provide the competitive edge. For instance, the cumulative R&D expenditure of NEC, Fujitsu, and Sony, till the year 2000, to develop plasma displays for flat screen, high resolution TVs is likely to exceed US$ 1 billion. Their activities involve R&D for system innovation, and R&D for core competence leveraging innovations.

The brief discussion on the progression of R&D in relation to the technology strategy of a firm highlights the following:

- It is not sensible to talk of "technology transfer or R&D." It will be far more useful talk of "integrating technology transfer with R&D." R&D can be a potent means of helping a firm to move forward without forever having to play second fiddle.

- R&D is not always hi-tech. The legendary Sony Walkman was not the result of painstaking basic research. It was developed by cleverly adapting Sony's existing audio technology.

- R&D must be initially "market driven" to gain credibility and generate surpluses, part of which can be used as "patient money" for funding long-term research, as competition forces a firm to move up the technology strategy ladder.

However, carrying out effective R&D and progressing up the R&D activity spectrum requires certain supportive interventions both at the firm and national level. Some of the more critical interventions needed are described in the next section.

5. Interventions for Supporting R&D Progression

Experience suggests that in order to foster an R&D culture and steer R&D activities towards greater sophistication several supportive interventions are needed. These are described briefly below.

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1. Vision and pride

In today's context, it would be very difficult for a firm to fund R&D effectively unless there is total commitment from top management. Top management must have the urge to be technologically strong. It must hurt their pride to be always dependent on others for technology. If this vision and pride is not there R&D can never take off. There are examples of firms in developing countries that are very profitable without doing any R&D. How long they can sustain this another issue altogether.

2. Funding

While there are examples of small and medium companies in Asia (Porro Technologies of Hong Kong, and Microtek of Taiwan) which plough back almost 10% of their annual turnover into R&D, not all firms can pump in money steadily to support R&D. Two possible ways of lowering the R&D cost burden of firms could be:

- o Providing government support in the form of low-cost capital, matching grants, tax holidays, and accommodation in science and technology parks; and
- o Facilitating cooperation between industry, universities, and government R&D institutes by providing incentives for contract research.

3. Linking R&D to the Market

There could be situations where R&D efforts can produce a technological masterpiece that no one wants. The Taiwanese "Teammate Consortium", under the aegis of Industrial Technology research Institute (ITRI) in 1991, for producing a notebook computer led to a situation where 125,000 notebooks remained unsold! To avoid such problems, it is important for:

- o R&D efforts to be well supported by: a good marketing - production - R&D interface so that product development time is reduced; and
- o The firm to have good "antenna shops" or "advanced listening posts" so that user feedback is quickly obtained.

In addition, many other interventions at the national level are needed to foster an R&D culture in a country. These aspects are beyond the scope of this topic and will be covered later in this module. It may even be discussed by other speakers in the training program. This topic is a preliminary attempt to develop a strategic perspective for innovation management at the firm level in a developing country setting. It is hoped that the ideas presented can provide a stimulus for further elaboration and refinement of the proposed framework.

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TOPIC 6

R&D LINKAGES BETWEEN UNIVERSITIES, INDUSTRIES, AND R&D CENTERS

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Technology Management Module
Training Course on
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Organized by UNIDO, ITPD/TS and ICS
Beijing, China
June 10-25, 1997

1. Introduction

Firm level value addition, technology transfer, R&D, and expression of technological capability all take place within a country's technology infrastructure which, if supportive, will be conducive to the success of firm level activities. The technology infrastructure consists of three major components: the technology mentors; the technology guiders; and the innovation triangle (Sharif and Ramanathan, 1995). This is shown schematically in Figure 1.

The technology mentors are national/sectoral institutions which play a catalytic role in enhancing technology-based economic activities. They include: investment promotion boards and venture capital institutions which provide funding; and testing, quality assurance, standardization and intellectual property protection institutions which can protect and promote technology.

The technology guiders are institutions which can provide guidance and identify opportunities for technology-based development. These include technology transfer and consultancy services, and science and technology information services.

The innovation triangle comprises the linkages between three categories of institutions - the universities which are engaged in science and technology education and research; R&D institutions; and industry. Good linkages between these three types of institutions can accelerate technology-based development. Figure 1 also shows that the three components in the national technology infrastructure carry out a chain of activities that are important for technology-based development. These are:

- o knowledge - skill development;
- o product - process development; and
- o organizational system - package development.

If the three components work effectively, then these chain of activities are strengthened.

In this session the focus of our attention will be on the innovation triangle. We will pay special attention to the role between university - industry linkage and R&D institute - industry linkages from the technology development perspective. We shall,examine the university - industry linkage first and follow it up with R&D institute - industry linkage.

2. University - Industry Linkages

Establishing good links between universities and industry is quite difficult. The main reason for this is the difference in orientations. Some major differences in orientations are summarized below.

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Item	Industry	Universities
Attitudes and values	Business attitude Profit oriented Customer satisfaction	Scientific attitude Knowledge oriented Knowledge enhancement
Objectives	Profit and growth	Professional excellence
Rules	Organizational rules Organizational rationality	Scientific norms Professional ethics
Recognition	Contribution to firm's goals	Contribution to state-of-the-art
Knowledge use	Know-how emphasized Learning when required	Know-why emphasized Continuous learning

Source: Adapted from Shenhar (1993)

While differences in orientation can be a problem, there are good reasons for universities and industry to establish linkages. The main motivations for universities are as follows (Shenhar, 1993; Souder, 1993):

- secure financial resources to sustain research efforts;
- motivate and retain their faculty;
- ensure that teaching and research are of relevance to industry;
- provide avenues for faculty consulting;
- provide openings for student employment; and
- establish credibility in an era where government support is being reduced.

The main motivations for industry are as follows (Shenhar, 1993; Souder, 1993):

- gaining access to specialized skills;
- gaining access to specialized equipment, instrumentation etc.;
- cost reduction of R&D;
- cost reduction of consultancy;
- tap the creative potential of high calibre individuals;
- maintain a window to new technologies;
- recruitment of skilled S&T humanpower.

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Basically there appear to be three approaches to foster university - industry linkages. These three approaches may be called: the Agency Model; the Membership Model; and the Science and Technology Park Model. Each of these will be described below briefly.

Agency Model

Since universities do not have well established links with industry, an active intermediary is needed to facilitate interaction. The establishment of an institution which can play the role of the active intermediary is an essential prerequisite.

In the case of Korea, the Korea Institute for Science and Technology (KIST) played and continues to play this role. Today, under the support of the Korea Science and Engineering Foundation (KOSEF), the Science Research Center (SRC) and the Engineering Research Center (ERC) play this role.

Membership Model

The membership model is popular in the United States of America and is essentially an arrangement where firms must become members to be affiliated with a university. A membership fee must be paid to retain and renew membership. Members may then take advantage of a wide variety of services offered by the university.

To introduce this arrangement, the university must have high credibility in terms of image, quality of industrial research, calibre of faculty and students, and reputation for S&T achievements.

Science and Technology Park Model

This model has become very popular today. In this model, property, close to a well known university, is developed to enable firms to set up operations. Such parks have been known to grow spontaneously (such as the Boston Park and Route 128 close to MIT). Others, however, are established as a result of clear policy initiatives. The Stanford Park in Silicon Valley was initiated by Prof. F. Terman of Stanford University. Similar initiatives are seen today in Singapore, Korea, Malaysia, and Thailand.

The establishment of approaches to facilitate university - industry interaction alone will not automatically lead to good linkages. Some types of industries may not be keen to establish linkages (eg. automotive industry). In this context, the following observations (Rosenberg and Nelson, 1996) regarding university - industry cooperation are of interest:

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- o Firms which are strong in R&D with respect to quickly bringing out new products and processes are unlikely to seek joint research with universities;

- o R&D which involves detailed familiarity with existing technology and user needs is likely to be done by industry on its own;

- o Industries related to forestry, agriculture, chemistry, and pharmaceuticals are likely to work closely with universities; and

- o Electronics and instrumentation related industries are likely to seek new ideas from universities. However, the bulk of the design and development will be done by industry themselves.

Thus, it is important to remember that university - industry linkages is likely to vary form industry to industry. Furthermore, all university - industry linkages may not be related to R&D contracts. The following are areas where the scope for cooperation is very high (Liyanage and Minchell, 1994):

- Pre-competitive research
- Trouble shooting and problem solving
- Breakthrough innovation
- Pilot plant testing
- Information gathering
- Training

The possibilities and limitations must be remembered when relationships are planned.

3. R&D Institute - Industry Linkages

Whether a country is developed or not, if it wishes to be self-reliant (not self-sufficent) in the long-run, it needs good, specialized R&D institutes. Some of the more important roles of national R&D institutes include the following:

- o Help small and medium industry to solve their technological problems with respect to production, new designs, quality improvement, material substitution etc.;

- o Facilitate the assimilation of technology imported into the country;

- o Function as a channel for introducing new technology by keeping abreast of international developments and "benchmarking: studies;

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- Solve specialized problems for large firms which may not want to hire a specialist only to solve a specific problem; and

- Upgrade the skills of engineers and scientists working for it by exposing them to real-life problems and strengthening their creativity.

Unfortunately, in many developing countries the R&D institutes have become ineffective due to the following reasons:

- Lack of funding:
- Tendency to pursue "supply push" research due to poor links to industry;
- Poor remuneration leading to "brain-drain";
- Lack of skilled personnel;
- Lack of equipment and instruments;
- Low motivation; and
- Poor leadership:

All these collectively have contributed to low credibility of national R&D institutes in many developing countries.

In this context, the example of Singapore is worthwhile noting. To support its strategic areas of thrust, Singapore has established research institutes in four key areas - manufacturing, information technology, electronics, and molecular and cell biology. The following are the government sponsored key R&D institutes in Singapore.

- The Institute of Molecular and Cell Biology (IMCB)
- The Institute of Systems Science (ISS)
- The institute of Microelectronics (IME)
- The GINTIC Institute of Manufacturing Technology (GIMT)
- The Information Technology Institute (ITI)
- The Center for Wireless Communications (CWC)
- The Magnetics Technology Center (MTC)
- The National Superconducting Research Center (NSRC)

These institutes are expected to work closely with industry in offering industry oriented design, development, solutions and guidance. Some examples of the work they have undertaken are outlined below.

> The IMCB is collaborating with British pharmaceutical giant Glaxo Inc. to study how information is transmitted from one human cell to another. It is expected that this research will lead to the development of drugs to attack cancer and brain diseases associated with aging such as Alzheimer's Disease. The team is headed

by a world renowned Singaporean - Dr. Y.H. Tan. On its own,IMCB has developed orchids infused with firefly genes that glow in the dark, proving that molecular transfer methods work. It has also developed breeds of rats implanted with human DNA so that specific genes can be tested for links with diabetes.

Another showcase example is the Apple ISS Research Center that has been started in 1992 as a joint partnership between Apple Computer Corp. and ISS. Over the next five years the center is expected to spend more than US$ 10 million to develop voice- and handwriting- recognition software for computer and multimedia products in Asian languages. ISS is also working on neural networks, fuzzy logic and broadband networks. It has developed among others, computer-aided translation systems for translating manuals from English to Chinese, and a container identification verification system for the Ports of Singapore Authority (PSA).

The IME collaborates with major disk drive and microelectronic companies in material, process and failure analysis; reliability enhancement; design repair; and package/assembly process optimization. It also works with integrated circuit fabricators utilizing crystal technology and electron microscopy. Companies currently working with IME include Heinmann Optoelectronics, Tech Semiconductor, Texas Instruments and Hewlett Packard.

The GIMT aims at promoting the use of innovative manufacturing technologies for productivity enhancement. Since 1987 it has been involved in over 180 projects with over 70 firms like Singapore Aerospace, Singapore Press Holdings, Singapore Computer Systems, IBM, Matsushita Refrigeration, Siemens Nixdorf, and Philips. GIMT and Philips have developed a Knowledge Based Daily Production Scheduling System to automate the process of manual scheduling of the production of PCBs.

The ITI specializes in software engineering, knowledge systems, office communications, image processing, and data visualization. It has developed along with the Singapore Press Holdings a software package called ALEXIS that automates the layout of advertising sections in the Straits Times. It has also developed a Ship Planning System for the PSA which has enabled shippers to reduce container turnaround time by 50%.

The CWC focuses on research into modulation and transmission, wireless

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networking and cellular technology. It is developing with Singapore Telecom, performance measurement of digital cellular mobile radio systems.

The MTC focuses on technologies related to the disk drive industry and offers support on data storage systems, consumer electronics, and miniature power supplies. Industry leaders working with MTC include, Wearnes, Micropolis, Hewlett Packard, and Seagate.

The NSRC collaborates with industry on projects involving high performance computing and aims at helping companies to overcome barriers in integrating high performance computing into their operations. At present the NSRC is working with NEC to enhance the competitive advantage of Singapore's financial sector through the development of financial neural network models on NEC supercomputers. Prototypes for stock price prediction, stock selection, portfolio management and exchange rate analysis are under development.

These examples suggest that if the problems outlined above are removed, national R&D institutes can indeed establish effective linkages with industry.

4. Concluding Remarks

This session has dealt with the important issue of establishing good linkages within the innovation triangle. It is hoped that the discussion would have highlighted the fact that fostering the linkages require a careful understanding of the problems and prospects involved in such an exercise.

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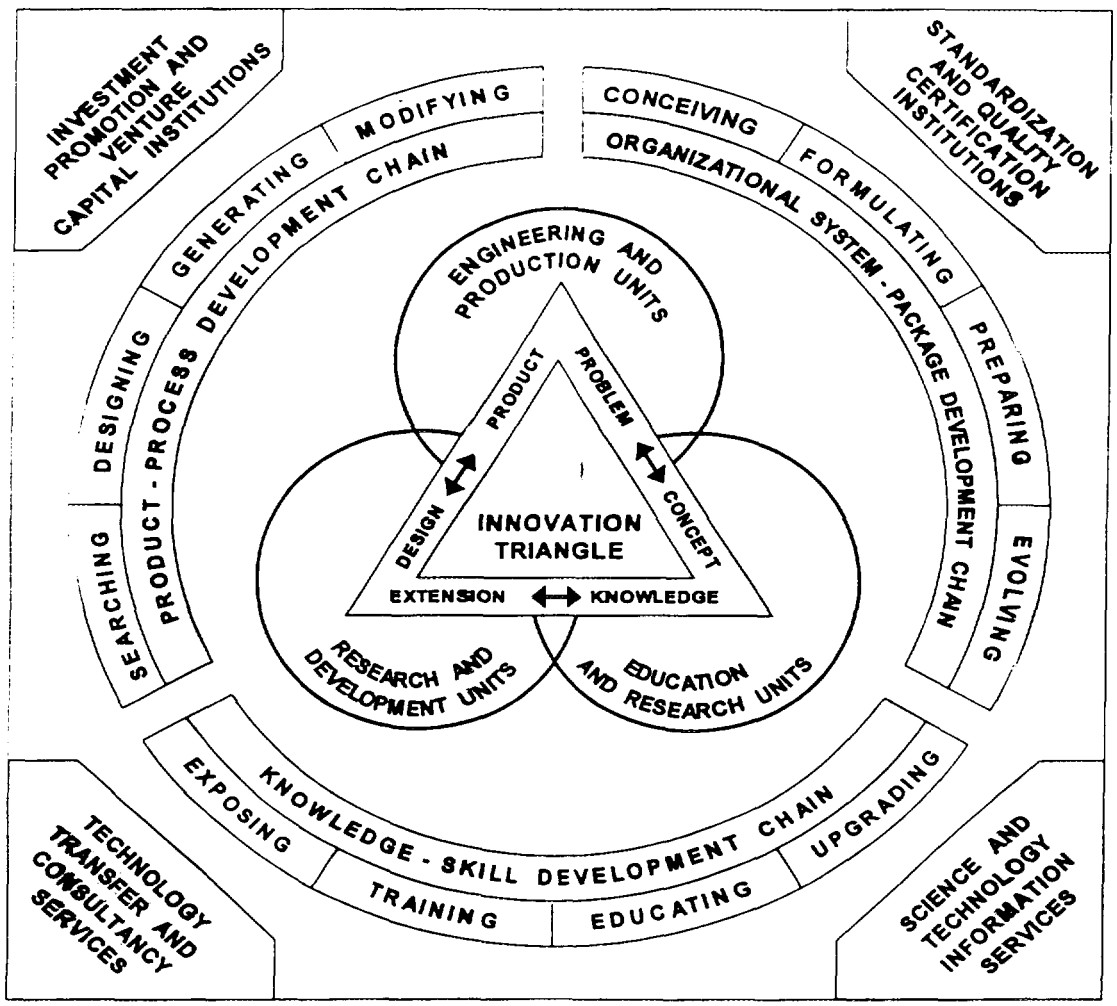

Figure 1: The National Technology Infrastructure

TOPIC 7

IDENTIFYING SOURCES OF TECHNOLOGY

by

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Technology Management Module
Training Course on
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Organized by UNIDO, ITPD/TS and ICS
Beijing, China
June 10-25, 1997

1. Introduction

There is a basic difference between technological and scientific information. Scientific knowledge deals with "know-why" and, in general, is available in the public domain. Technological knowledge, on the other hand, deals with "know-how" and is of a proprietary nature. This proprietary knowledge is often used for 'value addition" with a view towards making profits. Thus, while scientific knowledge is easily accessed, usually through formal training in schools and universities, at a known cost, technological information has a price tag on it. The price one pays for technology depends on the bargaining power of the buyer of such information.

This session is intended to provide a brief introduction to the possible sources of technological information. The presentation will be made in two main. First, there will be a brief discussion on the weaknesses of developing countries with respect to information collection. This will then be followed by outlining the important sources of technological information. A few important sources will be elaborated.

2. Problems Faced by Developing Countries in Collecting Business Information

In many developing countries the state-of-the-art with respect to business information collection and analysis is very low. While some of the larger firms in these countries may be able to afford to hire consultants to generate the information they need, the small and medium enterprises in these countries face great difficulties with respect to access and use of business information. Some of the more important reasons are as follows:

- o Thinly spread (over geographic space) industrial enterprises;
- o Poor physical infrastructure in terms of telecommunications, transportation etc.;
- o Language barriers and lack of good translators;
- o Lack of appreciation of the value of information;
- o Lack of a culture and skills in using information for decision-making;
- o Lack of skills in identifying information needed for a project;
- o Tendency to mix up libraries with commercial information sources;
- o Non-availability of financial resources, or unwillingness to spend money, to get useful information;

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- o Foreign exchange restrictions that make it difficult to pay overseas suppliers of information; and

- o Lack of potent government support for establishing a good information infrastructure on a sector-wise/industry-wise/national basis.

3. Sources on Potential Suppliers of Technology

In this session we will focus only the sources of information that can identify potential suppliers of technology. We will not consider sources of information that will be needed for project preparation and appraisal. Some of the main sources for identifying potential suppliers, not in order of importance, are:

Profit Oriented Sources

- o Engineering and consulting companies;

- o Commercial, technical databases;

- o Private consultants and technology brokers;

- o Engineers and researchers who work as part-time consultants;

Non-Profit Oriented Sources

- o UN agencies such as UNIDO, APCTT of ESCAP;

- o Trade and professional associations;

- o Universities;

- o Government research institutes;

- o Commercial sections of embassies;

- o Licensing news services;

Media Sources

- o Patent literature;

- o Scientific reviews;

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- o Technical journals;
- o Conference proceedings;
- o Professional referral periodicals (Chemical Abstracts for instance);
- o Brochures and publications of industry promotion agencies (EC-ASEAN Cogen for instance);

Personal Sources

- o Personal contacts (suppliers, friends, colleagues etc.); and
- o Contacts with manufacturing firms.

Profit-oriented sources are in the business of supplying information and often tend to charge substantial amounts. Non-profit oriented sources are those that may either provide the information free, at a subsidized rate, or at cost. Media sources are those that have the information in a published format. Personal sources as pointed out refers to information one obtains through personal networks. Some brief comments on some of the more important sources will now be made.

Industrial and Trade Fairs

This source is valuable because it could:

- provide an opportunity to establish contacts;
- help to get information on alternative suppliers;
- help to get preliminary information on the expectations of suppliers; and
- be a meeting point for industry associations.

Engineering and Consulting Firms

This source is valuable because it could:

- help not only in identifying sources but also advise on the relative merits and demerits of different sources based on the needs of the buyer;
- advise on adaptation of the technology being sought and identify the sources that could carry out the adaptations;
- later help in developing the project proposal.

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UN Agencies

UN agencies such as UNIDO, WIPO, and ESCAP-APCTT have, over the years built up a vast network of focal points, publications, and computerized databases on a variety of industries and technologies. Since their focus is on service and fostering economic development, their services can usually be obtained at attractive rates or even free of charge in certain situations.

Patent Literature

Patent literature consists of published patents and patent applications, as well as referral publications that give information on patents released by various national and international agencies. Patent literature is useful because:

- they tend to give the most recent developments;
- they disclose the problem and solution in technical terms;
- patents have prescribed formats which makes it easier to compare the technology with existing ones; and
- owners of the patent are clearly identified.

However, sometimes, firms do not disclose their inventions and may hold it as a trade secret. WIPO has a database that can provide patent information. Some national governments have also computerized their patent databases thereby making access easier.

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TOPIC 8

ASSESSMENT AND SELECTION OF TECHNOLOGY

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1. Introduction

From a business perspective, the term "choice" refers to a very strategic action that can significantly influence the long-term sustainable development of a firm. From a management of technology perspective, firms are usually confronted with many problems related to choice such as choice of technology, choice of technique, choice of mode of technology acquisition, choice of R&D projects, choice of product and/or service mix, and choice of markets and market segments. In general, it may be said that management of business activities almost always involves the handling of choice related issues and problems.

Out of all the technology related choice problems, the issue of choice of technology began to assume considerable importance in the late seventies in both the developed and developing countries. In the industrialized developed countries the issue gained importance due to a convergence of a wide variety of concerns. These included the need to:

- o find a more harmonious and sustainable relationship with the environment;
- o identify a way out of the accelerating energy and resource crises;
- o reduce alienating work;
- o develop more socially conducive work places; and
- o revitalize local culture to counter the increasingly homogenous and sterile mass culture propagated through the electronic media.

On the other hand, the issue of technology choice gained importance in developing countries due to a different set of concerns. The most prominent was the recognition that imitating industrialization strategies adopted by developed countries had not been successful in solving the problems of poverty and inequality. There are many reasons for this. The world's technological resources, which are the necessary base for industrialization, are essentially controlled by the most advanced nations, and have been primarily developed to serve their economies, factor costs and consumer life-styles. Commercial interests from these nations have had a very dominant effect on the industrialization process in developing countries. Technology transfer mainly served business interests in utilizing: natural resources without any concern for environmental issues; cheap labor; and elite consumer markets. The result, for hundreds of millions of people, had been the modernization of poverty and, in many cases, introduction of imported technologies had resulted in a fundamental and a massive assault on local culture. Therefore, the issue of technological choice arose essentially as an effort to import, adapt if necessary the imported technology, and develop technologies appropriate for their surroundings and compatible with their resource endowments.

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These efforts also led to the coining of many terms such as "intermediate technology", "appropriate technology", "progressive technology", "third world technology", "alternative technology", among others such as "grass roots technology", "kind technology", "barefoot technology", "evolutionary technology", "non-violent technology", "non-polluting technology", "soft technology", "indigenous technology", "self-help technology" and "green technology". The proliferation of such terms each coined to deal with very specific orientations of the analysts appears to have led to considerable confusion. This has led to inappropriate technology choices in many cases because the specific orientations introduced by these analysts to examine special issues tend to be rather loosely applied without examining their relevance in the situation under consideration. The major reasons given by several analysts identifying the constraints that adversely affect the choice of appropriate technologies may be elaborated as follows:

- The absence of clearly stated criteria which lead to biases in assessing and selecting technologies.

- The predominance of exogenous planners in technology assessment and selection and, in general, their inability to appreciate the context and setting in which the technology is to be used.

- Lack of coordination by different planning entities, and their inability to reach a consensus on the criteria to be used, and their prioritization, in the assessment and choice of technologies.

- The inability of many developing country firms to comprehend future complexities, and their restricted field of perception that makes it difficult for them to project their aspirations into the future.

- The influence of misconstrued sociopolitical paradigms in establishing technology choice criteria -the misinterpretation of "self sufficiency" for " self-reliance", for instance.

- The non-availability of "clean information" to many developing country firms for taking technology choice decisions. Due to their inability and lack of skills to collect relevant data and analyze it independently many firms base their decisions on "edited" information from potential technology suppliers that often tend to stress only the main message that the provider of such information seeks to convey.

All these limitations tend to work in a synergistic manner in weakening the technology choice process as a result of which technology that is not appropriate is often selected. In making technology choice decisions, developing country decision-makers therefore need to develop assessment criteria that will incorporate not only pure technoeconomic aspects but also other, perhaps even more critical, dimensions relevant to a particular setting.

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This session will attempt to provide such an integrated approach for assessing technology. The approach will be also illustrated using an example of a biomass energy technology. Concluding remarks on the application and possible extensions of the proposed approach are then made.

2. Developing Criteria for Assessing a Technology

Making decisions regarding the choice of technology has basically taken two approaches which for expository purposes may be called the "pure technoeconomic approach" and the "contingency approach". The pure technoeconomic approach advocates the assessment of technology based on technical criteria and well established economic analytical procedures such as cost benefit analysis. This approach usually leads to the selection of a technology which satisfies all the stipulated technical criteria and promises the highest economic efficiency or highest net benefit. This approach is useful when the chosen technology is to be utilized in surroundings similar to the one in which it was developed and successfully commercialized, and for similar purposes. However when the surroundings of the potential adopter of the technology and the objective functions differ the pure technoeconomic approach needs to be modified.

Analysts such as Dahlman and Westphal (1981), Fransman (1985), and Sharif (1983) have thus advocated the incorporation of other factors such as the technological capability of the potential user, nature of the supportive infrastructure and raw material availability. This contingency approach, they argue, is more suitable for firms in many developing countries.

However the use of either of these two approaches requires the evaluation of the candidate technologies in relation to some predetermined criteria. Analysts have sometimes been accused of using criteria that favor the selection of technologies that they prefer. Others argue that criteria used do not adequately reflect the concerns highlighted by the technoeconomic and contingency approaches. Thus, one of the critical steps in the choice of a technology is to establish a set of acceptable and usable predetermined criteria which can be used to evaluate candidate technologies. The literature on "appropriate technology" and "diffusion of innovations" are rich in terms of such criteria. Some of the important choice criteria suggested by these two important areas in management of technology will be outlined below.

Technology Assessment Criteria From Appropriate Technology Literature

Technology is a result of R&D efforts. However, different R&D efforts at different places produce different technologies for achieving the same or similar goals. This is because the operating domain, (determined by parameters such as population, resources, economic, technological, environmental, socio-cultural, and politico-legal systems) which acts as a guiding force for the production of technology, is different even though the driving force, exerted by various needs, may be the same. Moreover, the objective function used in the development of technology at different places could also be different. Two basic components of the objective

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function are - maximization of opportunities (positive effects) and minimization of losses (negative effects).

Therefore, any technology is "appropriate", at the time of development, with respect to the operating domain for which it has been developed, and in accordance with the objective function used for development. It may or may not be appropriate at the same place at a different time, because the operating domain and/or the objective function may have changed. Similarly, it may or may not be appropriate at a different place at the same time or at different times, because the operating domain and objective functions may be similar or different. Thus, technological appropriateness is not an intrinsic quality of any technology, but is derived from the operating domain in which it is to be utilized and also from the objective function used for evaluation. It is, in addition, a value judgement of those involved.

According to this simple conceptual framework, any technology is appropriate at the time and place of original application. It is still appropriate at a later time and/or at a different place - if the operating domain as well as the objectives are similar to the origin. And, it is not appropriate at a later time and/or at a different place due to three reasons:

- o different or changed operating domain;
- o different or changed objectives; and
- o different or changed operating domain and objectives.

The simple examples of the chemical pesticide DDT, and coal-based technology for power generation provided by Sharif (1983) illustrate this thinking. DDT which was once appropriate is now banned by many industrialized, developed countries due to its negative impact on the environment. On the contrary coal-based power generation technology which was once given up due to more attractive oil-based technologies, and its "dirtiness", has now become appropriate due to the fear of oil shortages.

These examples serve to stress the fact that technological appropriateness needs to be explained not only with reference to the intrinsic properties of the technology but also with respect to the operating domain, as viewed by those involved. Based on these considerations, Bowonder (1979) and UNIDO (1981) have proposed a set of choice criteria that may be used to decide the suitability of a technology. These criteria are summarized, in an adapted form, in Table 1.

Technology Choice Criteria From Diffusion of Innovations Literature

Considerable work from multidimensional viewpoints has been carried out in the area of diffusion of innovations over the last few decades. A comprehensive review of such work has been outlined in Ramanathan (1982). Summaries are also available in Sharif and Ramanathan (1981, 1982, 1984). This extensive literature on the diffusion of innovations shows that adoption

decisions are taken by potential users, especially at the firm level, based on some or all of the following demand and supply side criteria:

Criteria Based on Demand Side Factors

- Profitability of the investment in an innovation;
- Size of the investment required to adopt the innovation;
- Technological complexity of the innovation;
- Age, condition, and rate of obsolescence of the existing capital equipment that an innovation seeks to displace;
- Quality characteristics of the innovation;
- Interaction of the innovation with other concurrent innovations (i.e., type of interaction - independent, complementary, contingent, or substitute);
- The number who have already adopted the innovation and the number who have not yet adopted it;
- The social, psychological, economic and locational characteristics of those potential adopters;

Criteria Based on Supply Side Factors

- Supplier actions pertaining to market selection, market segmentation, promotional communications, pricing and infrastructure development (after sales service, spare parts supply, trouble shooting etc.); and
- Actions of related private and public organizations such as infrastructure development, promotional communication and regulation/promotion of the innovation.

Thus it appears that when developing criteria for the choice of a technology, it may be useful to incorporate the criteria suggested by both "diffusion of innovation" and "appropriate technology" literature in an integrated manner. The next section presents an integrated approach for technology choice.

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The proposed integrated approach could thus provide a useful analytical framework for handling the problem of technological choice. The next section illustrates the salient features of this approach, albeit in a restricted manner, using an example from biomass technology.

4. Application of the Integrated Approach for Assessing the Suitability of a Biomass-Based Power Plant

As an illustrative example, the appropriateness of a 2.5 MW wood wastes power plant will be analyzed using the integrated approach. The example is based on the information found in reports published by the ASEAN-EC Cogen Programme (1991). The analysis is presented in five parts. The first part presents background information related to the relevance of the wood wastes power plant technology (WWPPT). The remaining three parts deal with the application of the three categories of criteria - TECC, OCCC and ODCC to the technology. The last part presents some observations regarding this technology. All economic and technical information quoted in the analysis are taken from the ASEAN-EC Cogen Programme reports mentioned above.

Wood Wastes Power Plant Technology : An Overview

The Association of South East Asian Nations (ASEAN) comprising the Sultanate of Brunei Darussalam, the Republic of Indonesia, Malaysia, Republic of the Philippines, Republic of Singapore, and Thailand are currently enjoying the largest economic growth rates in the world, resulting in an ever increasing demand for energy and infrastructure. With the exception of Brunei and Singapore, in all the other four countries the demand for energy is expected to surpass the supply. Thus, the governments of these nations are in the process of implementing various programs to increase the supply of energy through both traditional and alternative sources. In order to limit public sector capital requirements for infrastructure, and to prevent accumulation of foreign debt, the ASEAN nations are actively seeking private sector participation in power generation.

In this context, power generation through biomass energy technology has received considerable attention. With the exception of Brunei and Singapore, the other ASEAN countries produce large amounts of agricultural products such as rice, sugarcane, palm oil, coconut and rubber. In addition, Indonesia and Malaysia are major processed-wood exporters. All these agro-based industries generate huge biomass residues, which have been estimated to have the energy equivalent of 25 million tons of oil equivalent (TOE) per annum. It is estimated that only about 50% of these residues are used for heat or power generation, and generally with low efficiencies, since there is no demand for autoproduced energy in excess of the agro-industrial firms' own needs. However, with the recent emphasis by the ASEAN governments in seeking private sector participation in electrical power generation, and improved access for autoproduced electricity to national grids, generation of electricity from biomass and supplying the surplus to the national grid could become economically attractive to certain classes of agro-based firms.

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Wood Wastes Power Plant Technology : An Overview

The Association of South East Asian Nations (ASEAN) comprising the Sultanate of Brunei Darussalam, the Republic of Indonesia, Malaysia, Republic of the Philippines, Republic of Singapore, and Thailand are currently enjoying the largest economic growth rates in the world, resulting in an ever increasing demand for energy and infrastructure. With the exception of Brunei and Singapore, in all the other four countries the demand for energy is expected to surpass the supply. Thus, the governments of these nations are in the process of implementing various programs to increase the supply of energy through both traditional and alternative sources. In order to limit public sector capital requirements for infrastructure, and to prevent accumulation of foreign debt, the ASEAN nations are actively seeking private sector participation in power generation.

In this context, power generation through biomass energy technology has received considerable attention. With the exception of Brunei and Singapore, the other ASEAN countries produce large amounts of agricultural products such as rice, sugarcane, palm oil, coconut and rubber. In addition, Indonesia and Malaysia are major processed-wood exporters. All these agro-based industries generate huge biomass residues, which have been estimated to have the energy equivalent of 25 million tons of oil equivalent (TOE) per annum. It is estimated that only about 50% of these residues are used for heat or power generation, and generally with low efficiencies, since there is no demand for autoproduced energy in excess of the agro-industrial firms' own needs. However, with the recent emphasis by the ASEAN governments in seeking private sector participation in electrical power generation, and improved access for autoproduced electricity to national grids, generation of electricity from biomass and supplying the surplus to the national grid could become economically attractive to certain classes of agro-based firms.

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this criteria will be critical when process technologies are being evaluated.

Energy Intensity

The use of the WWPPT reduces the use of fossil fuels. It is expected that the proposed plant will save approximately 4,950 to 5,560 tons of diesel per annum which may otherwise have to be used to generate electricity through the use of a genset.

Ecological Stability

Girard (1992) points out that the equivalent tons of carbon dioxide (CO_2) emitted per TOE of energy generated after clean burning by different technologies is as follows:

Coal	1.0
Oil	0.8
Gas	0.6
Wood	0.3
Biomass energy residues	0.3

The use of WWPPT and biomass for power generation could thus be said to have a beneficial impact on the environment. It has also been pointed out that the CO_2 generated, by using biomass as energy sources, will be removed later through photosynthesis by the growing of crops and trees. In addition since biomass does not, in general, contain sulphur their burning does not generate toxic and environmentally degrading sulphur dioxide SO_2.

The use of WWPPT thus has beneficial impacts on the environment because it helps to:

- avoid river pollution caused by dumping of wood wastes into the rivers;
- reduce the high pollutant exhausts caused by inefficient incinerators; and
- reduce the CO_2 (carbon dioxide) and SO_2 (sulphur dioxide) emissions normally caused by the use of diesel gensets used as an alternative for electricity generation.

Waste Recycling

WWPPT uses waste produced by timber complexes thereby also reinforcing the beneficial impacts on the environment. The different types of wood wastes that can be used by the WWPPT are:

- sawmill wastes (wet sawdust and wet off-cuts);
- fabrication wastes (dry molding dowels); and
- plywood wastes (wet log ends, wet log core and veneer, dry side cuttings, dry sawdust and dry veneers).

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1.	Using WWPPT (100% load factor, 10% discount rate)	=	0.1017
	Using WWPPT (75% load factor, 10% discount rate)	=	0.1441
2.	Sarawak Electricity Supply Corporation charges (an additional load demand charge is also levied)	=	0.1700

Demonstrated Usefulness

The European manufacturer described in the ASEAN-EC Cogen Reports, apparently has considerable experience in delivering WWPPT and appears to have been active in ASEAN since 1975. No information however is available on how many such installations are in operation throughout the world.

Application of Organizational Capability Compatibility Criteria (OCCC)

Based on the information available in the ASEAN-EC Cogen Programme Reports, details of the assessment of the proposed WWPPT using the OCCC are presented in this section.

Scale of Operation

Based on the capital costs it appears that the WWPPT under discussion is suitable for medium and large companies in the ASEAN region. It may however not be suitable for small scale companies which besides not being able to raise the kind of capital required are unlikely to have scales of operation that will produce the 3,150 tons of wood waste required per month to feed the 2.5 MW power plant.

Labor Intensity

The requirements of labor for operating WWPPT appears to be easily available in the ASEAN region. The type of engineers, operators and skilled laborers required are likely to be obtained without difficulty. Of course specific training may be required to ensure a good understanding and proper usage of the technology.

Durability

The depreciation for the main equipment, as mentioned in the ASEAN-EC Cogen Programme Reports, has been made over a period of 20 years. This high period used may be considered to reflect the durability of the equipment. Considering the nature of the equipment outlined in Table 3 it appears that maintenance will not be difficult and is well within the capabilities of the engineers and technicians in the ASEAN region.

Learnability

Standard operating procedures for operating the plant can be easily learnt. However good plant management practices have to be taught during the training not only with respect to operations but also in maintenance.

State-of-the-Art

It appears that the WWPPT is not currently used extensively in the ASEAN region. The use of this technology promises significant benefits. However enough information is not available in the ASEAN-EC Cogen Programme Reports to assess how this technology being offered by the European supplier rates vis-a-vis WWPPT supplied by Japanese, Korean, Taiwanese or Chinese manufacturers (who have also made significant progress in such technologies) in terms of technical performance and cost.

Interaction

From an organizational perspective the use of WWPPT is beneficial because it complements existing wood-working technologies in the firm and also substitutes inefficient and polluting incinerating units currently in use. Its use is also contingent upon the availability of wood wastes.

Application of Operating Domain Compatibility Criteria (ODCC)

Using the information available in the ASEAN-EC Cogen Programme Reports an assessment of the proposed WWPPT using the ODCC will be carried out in this section.

Supplier Actions

The European company providing the WWPPT appears to have targeted countries in the ASEAN region, especially Malaysia and Indonesia, for selling this technology. This is an advantage for firms in these countries which are interested in adopting the technology because they can expect a much better service from the supplier. Incidentally the supplier also seems to have had experience in the region having operated from Singapore till 1983.

It is also interesting to note that a COGEN subsidy (15% discount on the machinery cost) is available to selected potential buyers. The supplier is also prepared to offer financial facilities - such as soft loans - that other competing suppliers can offer. This is an advantage for the buyer. In addition, buyer credit facilities are offered by some institutions in Europe for the purchase of WWPPT from European firms.

Government Actions

The ASEAN-EC Cogen Programme does not have comprehensive information on the promotional and regulatory measures currently being enforced by the ASEAN governments. However, it appears that the Ministry of Science Technology and Environment of Malaysia is in the process of enforcing pollution prevention due to wood wastes. This may act as an incentive to timber complexes to adopt WWPPT.

Sectoral Effectiveness

This technology contributes directly to the power and industrial sectors by helping to save electricity which could then be used to meet the increasing demand for electricity in industries, where cogeneration possibilities do not exist, and households. In addition, in some instances, the excess power generated could be sold to the national grid thereby strengthening national power generation capacity.

Raw Material Requirement

The WWPPT uses only locally available raw material. However seasonality considerations for raw material supplies could be a negative factor. Deterioration of the wood wastes during storage prior to use, high storage costs due to the bulky nature of wood wastes, and the costs of treatment of the wood wastes prior to use tend to increase costs of raw material storage and preparation.

Import Substitution

In countries like Brunei, Malaysia and Indonesia which produce their own oil, the use of WWPPT does not reduce the importation of oil. However, it releases more oil for export. On the other hand if this technology can be used in countries like Thailand and Philippines there can be savings in terms of oil imports.

Rural Orientation

This criteria may not be of direct relevance to WWPPT. However, it indirectly helps rural households by not adversely affecting their livelihood as discussed below under sociocultural stabilization. Also, energy cogeneration and the supply of excess power to the national grid could enhance rural electrification programs thereby opening up more development opportunities in the rural areas.

Delocalization

WWPPT can be easily diffused into localities where timber complexes are in operation and where the required wood wastes are available.

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Income Disparity Reduction

It is difficult to draw a link between the use of WWPPT and income disparity reduction. However, as pointed out above, under the discussion on rural orientation, the supply of excess power, generated by the wood processing industries through the use of WWPPT, to the national grid could foster rural development.

Sociocultural Stabilization

The use of WWPPT can reduce the pollution caused by dumping vast quantities of wood wastes into rivers. Its use will therefore not adversely affect the livelihoods of the rural folk who earn a living through fresh water fishing and cultivation and may actually benefit them.

Local Ownership

Since WWPPT is not a highly advanced technology, the outright purchase of it will not involve foreign equity participation. However, the manufacture and supply of WWPPT perhaps on a turnkey basis would most probably involve the formation a joint venture between the European supplier and an ASEAN firm. In any case there is likely to be a considerable degree of local ownership.

The Suitability of WWPPT: Some Issues of Relevance

On the whole it appears that, with respect to all the criteria, the proposed WWPPT offered by the European supplier is favorable. However, when several alternative suppliers are available for the supply of WWPPT - for instance from the U.S.A, Japan, Korea, Taiwan or China - then the same analysis has to be carried out for each technology on offer. The results may then be tabulated suitably and the most suitable offer can be selected. Techniques such as the analytical hierarchy process (AHP) of Saaty (1980), or the profile, checklist, scoring or frontier models of Souder (1980) may be used for this purpose.

One of the advantages of the proposed integrated approach is that it facilitates a more comprehensive evaluation of alternative technologies. For instance, the use of diesel gensets to generate power is an option that some wood processing industries may wish to consider in preference to WWPPT. Diesel gensets are superior to WWPPT with respect to the following criteria.

Technological Complexity

Diesel gensets are easy to use. When compared to WWPPT, it needs less space, costs less to install and maintain, and does not require the extensive raw material storage and preparation facilities that WWPPT requires.

Cost

The capital cost of a 2.5 MW WWPPT is higher than a diesel genset. Based on estimates from Shrestha and Bhattarai (1993) it may be said that, in Asia, an equivalent 2.5 MW diesel genset may cost anywhere between US$ 1,800,000 to US$ 2,740,000. The cost would depend on the tariff structures in the country and the bargaining power of the buyer. Using an average value of 1 ECU = US$ 1.25, the cost of the diesel gensets would thus range from 1,440,000 ECU to 2,192,000 ECU. The cost of the 2.5 MW WWPPT discussed in this paper costs 3,125,821 ECU which is significantly higher.

Demonstrated Usefulness

Diesel gensets have been used extensively throughout the world. Their reliability and performance has been well accepted. In terms of demonstrated usefulness, the diesel gensets thus have an advantage over WWPPT.

Scale of Operation

Diesel gensets are available even for small scale companies, unlike WWPPT which is generally viable only for medium and large scale companies. In this regard diesel gensets have an advantage over WWPPT.

Durability

Since diesel gensets have been used extensively for many years, maintenance procedures for it have been well established. In this regard too it has an advantage over WWPPT.

Learnability

Learning to operate a diesel power plant is not difficult. In fact it may be said that standard operating practices with respect to plant operation and maintenance have been well established for diesel gensets than for WWPPT which is relatively new.

Raw Material Requirements

In terms of raw material requirements, there is no seasonality in terms of fuel supply. Also the complexities of storage associated with WWPPT is not there when using diesel gensets. Thus, here too diesel gensets have an advantage over WWPPT.

In the case of criteria such as quality characteristics, labor intensity, state-of-the-art, delocalization, and local ownership, both WWPPT and diesel gensets have similar attributes. With respect to financial criteria such as utility-adjusted price ratios, productivity, and profitability it is not possible to draw firm conclusions due to the non-availability of standard

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data. Market prices vary depending on a variety of factors and the complex analysis needed to compare WWPPT and diesel gensets with respect to these financial criteria is beyond the scope of this paper. However, it may be said that, in general, as the price of diesel increases, WWPPT is likely to become more attractive with respect to these criteria. With respect to criteria such as energy intensity, ecological stability, waste recycling, interaction, supplier actions, government actions, sectoral effectiveness, import substitution, rural orientation, income disparity reduction, and sociocultural stabilization, WWPPT is superior to diesel gensets.

Thus, when WWPPT and diesel gensets are evaluated for appropriateness, the choice decision would depend not only on the criteria used but also on the characteristics of the operating domain. If only technological complexity, quality characteristics, cost, demonstrated usefulness, scale of operation, labor intensity, durability, learnability, state-of-the-art, raw material requirements, delocalization, and local ownership are considered, then a diesel genset would be chosen instead of WWPPT. In a period of falling or stable oil prices, even the inclusion of criteria such as utility-adjusted price ratio, productivity, and profitability is still likely to tilt the scales in favor of diesel gensets. However, if oil prices are increasing, then the latter three criteria may make the choice of WWPPT more attractive. It is important to note that if criteria such as energy intensity, ecological stability, interaction, supplier actions, government actions, sectoral effectiveness, import substitution, rural orientation, income disparity reduction, and sociocultural stabilization are also included, then it is likely that WWPPT would be considered superior to diesel gensets under both the market conditions described above.

Thus, it may be said that the greatest advantage of the proposed integrated approach is its ability to provides a means to escape from the restrictive approaches that have been used in the past to evaluate the suitability of a technology. The proposed approach can also facilitate the incorporation of a wide range of factors that have hitherto received scant attention.

6. Concluding Remarks

The main aim of this session is to deal with the difficult question of technology assessment and choice. Very often discussions on the question of technological choice tend to become complicated with critical issues getting buried under a mass of jargon which means different things to different people. For instance, appropriate technology, is often interpreted in many ways by different analysts.

The primary objective of this session is to provide a simple integrated approach that could place the whole issue of technological assessment and choice in perspective. This approach stresses that "firms in developing countries should choose technologies based on a balanced set of relevant criteria that would reflect the concerns of technologists, managers and government while ensuring that the probability of success and expected returns through the adoption of the chosen technology are enhanced".

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The approach has been illustrated through the use of information on wood waste power plant technology (WWPPT) that has been published by the ASEAN-EC Cogen Programme. It is shown that the WWPPT appears to be a suitable biomass based technology for use in ASEAN countries with a good supply of wood waste.

It must however be pointed out that the problem of technology choice does not end with the selection of a suitable technology. An equally important problem is related to the choice of a suitable technology transfer mechanism that could effectively transfer this technology to the potential user. This aspect, though beyond the scope of this paper, should be a matter of concern to managers in developing countries who hope to acquire technologies from the industrially advanced and newly industrializing countries.

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Table 1: Criteria for Selecting Appropriate Technology

Criteria	Preferred Path
1. Energy intensiveness	Should use less energy
2. Labor intensiveness	Should be in accordance with the humanpower endowment of the country but without leading to inefficiency
3. Cost intensiveness	Affordable
4. Productivity	High
5. Durability	Easy to maintain
6. Learnability	Easy to impart operation and maintenance skills
7. Scale of operation	Suitable for the use of small and medium scale units
8. Sectoral effectiveness	Capable of contributing to more than one economic sector such as (power, agriculture, forestry, industry etc.)
9. Raw material requirements	Ability to use locally available raw material
10.Import substitution	Local resource utilizing
11.Ecological stability	Environmentally friendly
12.Waste recycling	Capable of utilizing waste
13.Rural orientation	Suitable for use in rural areas
14.Delocalization	Capable of being diffused into many localities
15.Income disparity reduction	Capable of reducing income disparity
16.Sociocultural stabilization	Should not have an adverse impact on sociocultural conditions
17.Local ownership	Capable of facilitating local ownership

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Table 2. Proposed Technology Choice Criteria

Criteria	Evaluation Attributes
Technoeconomic Compatibility Criteria (TECC)	
1. Technological complexity	Degree of ease of use
2. Quality characteristics	Degree of contribution towards the improvement of the quality of output
3. Energy intensity	Degree of energy saving
4. Ecological stability	Degree of environmental friendliness
5. Waste recycling	Degree of usage of waste and facilitation of pollution prevention
6. Cost	Size of investment required
7. Profitability	Degree of enhancement of profitability
8. Utility-adjusted price ratio	Comparison with other alternative technologies
9. Productivity	Extent of productivity increase
10.Demonstrated usefulness	Number of firms already using the technology
Organizational Capability Compatibility Criteria (OCCC)	
1. Scale of operation	Suitability for the use of small and medium firms
2. Labor intensity	Degree of use of available labor and skills
3. Durability	Degree of ease of maintenance
4. Learnability	Degree of ease of operation
5. State-of-the-art	State-of-the-art of the technology in comparison to technology existing in the firm
6. Interaction	The type of interaction that the technology will have with other concurrent technologies currently being used by the organization - independent, complementary, contingent or substitute.

Table 2 (continued). Proposed Technology Choice Criteria

Criteria	Evaluation Attributes
Operating Domain Compatibility Criteria (ODCC)	
1. Supplier actions	Degree of facilitation by supplier in terms of market selection, market segmentation, promotional communications, pricing and infrastructure development (after sales service, spare parts supply, troubleshooting etc.)
2. Government actions	Degree of facilitation by the government in terms of infrastructure development, promotional communication and regulation/promotion (fiscal and financial incentives etc.)
3. Sectoral effectiveness	Degree of contribution to other economic sectors
4. Raw material requirements	Degree of use of locally available raw materials
5. Import substitution	Degree of conservation of foreign exchange
6. Rural orientation	Suitability for use in a rural setting
7. Delocalization	Capability of being diffused into many localities
8. Income disparity reduction	Degree of contribution towards reducing income disparity
9. Sociocultural stabilization	Degree of non-adverse impact on sociocultural conditions
10.Local ownership	Degree of facilitation of local ownership

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Table 3. Process Components for the 2.5 MW Wood Wastes Power Plant

System Component		Specifications
1. Wood chipper		30 m^3/h
2. Chips conveyor		
3. Silo and discharging system		240 m^3
4. Conveyor		
5. Fuel distribution and measuring unit		15 m^3
6. Automatic feeding system		5 levels
7. Combustion furnace		
8. Steam boiler	- capacity	19 t/h
	- working pressure (superheated at 300 C)	30 bars
	- design pressure	33 bars
9. Superheater		
10. Deduster		150 mg/Nm^3 (1% ash)
11. Steam turbine	(multistage steam turbine suitable to drive a generator)	
	- specific steam consumption	7.35 kg/kw_e
	- initial steam pressure	30 bars
	- exhaust steam pressure	0.35 bars
12. Generator		2,500 kw
13. Condenser		19,000 kg/h of steam
14. Cooling tower		600 m^3/h
15. High-tension switchgear, control panel and automatic regulation		
16. Chimney		

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TOPIC 9

MANAGING HIGH TECHNOLOGY BUSINESS ALLIANCES

by

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Technology Management Module
Training Course on
"Industrial Exploitation of Indigenous and Aromatic Plants"
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Beijing, China
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1. Introduction

A strategic alliance links specific facets of the businesses of two or more firms. This link is a trading partnership that enhances the effectiveness of the competitive strategies of the participating firms by providing for the mutually beneficial trade of technologies, skills, or products based upon them. An alliance can take a variety of forms. Yoshino and Rangan (1995) define a strategic alliance as possessing simultaneously the following three necessary and sufficient characteristics:

- o The two or more firms that unite to pursue a set of agreed upon goals remain independent subsequent to the formation of the alliance.
- o The partner firms share the benefits of the alliance and control over the performance of assigned tasks.
- o The partner firms contribute on a continuing basis in one or more key strategic areas, e.g., technology, products, and so forth.

Figure 1 shows the form of alliances possible and delineates those that can be called strategic alliances.

This session deals with business alliances with respect to high technology. Thus, it may also be useful to look at what high technology means. The term high technology is usually used to refer to technologies that are sophisticated and complex. Furthermore, high technology development requires advanced R&D efforts, highly skilled engineers and scientists, sophisticated design and manufacturing engineering skills, high capital investment, and world class marketing know-how. In general, the following products are considered high tech products:

- aircraft
- gas turbines
- computers
- nuclear reactors
- microchips
- machine tools
- medical equipment
- precision instruments
- telecommunications equipment
- biotechnology based pharamaceuticals

While the list is not complete, it is nevertheless indicative of the nature of high tech products.

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Unlike earlier forms of international trade, based predominantly on natural resources, high technology is portable. If technological capabilities are high and capital is available, any country can attempt a foray into high technology based production. A good example is Singapore which aims at becoming a high-tech hub of Asia. Japan is an example of a country that has been very successful in transforming its industrial sector to a high technology based system.

In this session we shall attempt to look at strategic alliances in the area of high tech businesses with a view towards understanding how to manage such alliances. The presentation will be made in two parts. The first one will deal with the motivations of the partners while the second will deal with success and failure factors of such alliances.

2. Motivation of Partners

The main motivations for firms to come together to form strategic alliances are as follows:

- To acquire technological complementarily in today's context where increased interaction is required between disciplines and fields of science and technology to come out with competitive products. Good examples are in chemistry and molecular biology; and computers and telecommunications.
- Rapid technological substitution and shortened product life cycles have made it too expensive for one firm to develop a product or process entirely by itself.
- Minimization of uncertainty by supplementing the technological capability of one firm with that of the partner.
- Faster access to market by sharing R&D - design - engineering - production - marketing activities. This also leads to cost reduction.
- Gaining access to new markets by using the partner's marketing channels and also by standardizing technologies and products
- Lack of resources and technological capabilities to undertake a project alone.
- To pre-empt other competitors who may feel reluctant to take on the alliance being forged.

A good understanding of partner motivations is very important when finalizing the details of the alliance.

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3. Success and Failure Factors

It is often assumed that alliances formed between partners who have had very friendly trading relationships in the past will succeed. However, empirical evidence suggests that this is not necessarily true. In this context it may be useful to examine the success and failure factors.

Success Factors

Some of the critical success factors are as follows:

- Shared vision and goal congruity in terms of targets, reinvestment for business expansion, profit distribution and so on.
- Clear benefits for the individual businesses of the partnering firms, rather than only for the alliance. Example: General Motors and Toyota in the U.S.
- Presence of "collaboration champions" in the partnering firms who have the commitment to make the venture work.
- Willingness on the part of the managers to share control with partners.
- The partners must have comparable technological capability and absorptive capacity. Japanese - U.S. alliances have faced difficulties because the American partner has been scared away by the higher learning capacity of the Japanese. Also one partner must not feel that the other is not contributing adequately.
- The partners must be willing to understand and adapt to the work culture of each other.
- Mutual trust!! There is no substitute for this and the partners must conduct themselves in a manner that fosters such trust.

Failure Factors

Some of the important failure factors are:

- Goal incongruence which can lead to an awkward but steady deterioration of commitment on the part of each partner in order to maximize their returns.
- Unplanned leakage of knowledge to one or more partners from the more capable firm.
- Lack of camaraderie among the managers from the different firms and the absence of "champions" with credibility.

- Unwillingness to share control and the desire to dominate the alliance.
- Unwillingness to adapt and understand work cultures, attempts at intimidation, and lack of respect for the partners' managers.
- Changing operating environment which could lead to goal incongruence as in the case of General Motors and Daewoo in Korea.

4. Concluding Remarks

The brief discussion we have had illustrates that the formation and management of strategic alliances can be very difficult. One way to minimize the difficulties would be select the partners carefully. The following guidelines may be of interest.

- Evaluate the strategic vision of the partner in the light of your own.
- Assess how important the alliance is to the partner in relation to the partner's existing business.
- Assess the technological and managerial capability of the partner vis-a-vis your own.
- Assess the partner's cultural adaptability potential.
- Ensure that there will be technological complementarily.
- Assess how successful the potential partner's previous alliances have been.

While these guidelines are merely indicative these could nevertheless provide a basis for partner selection.

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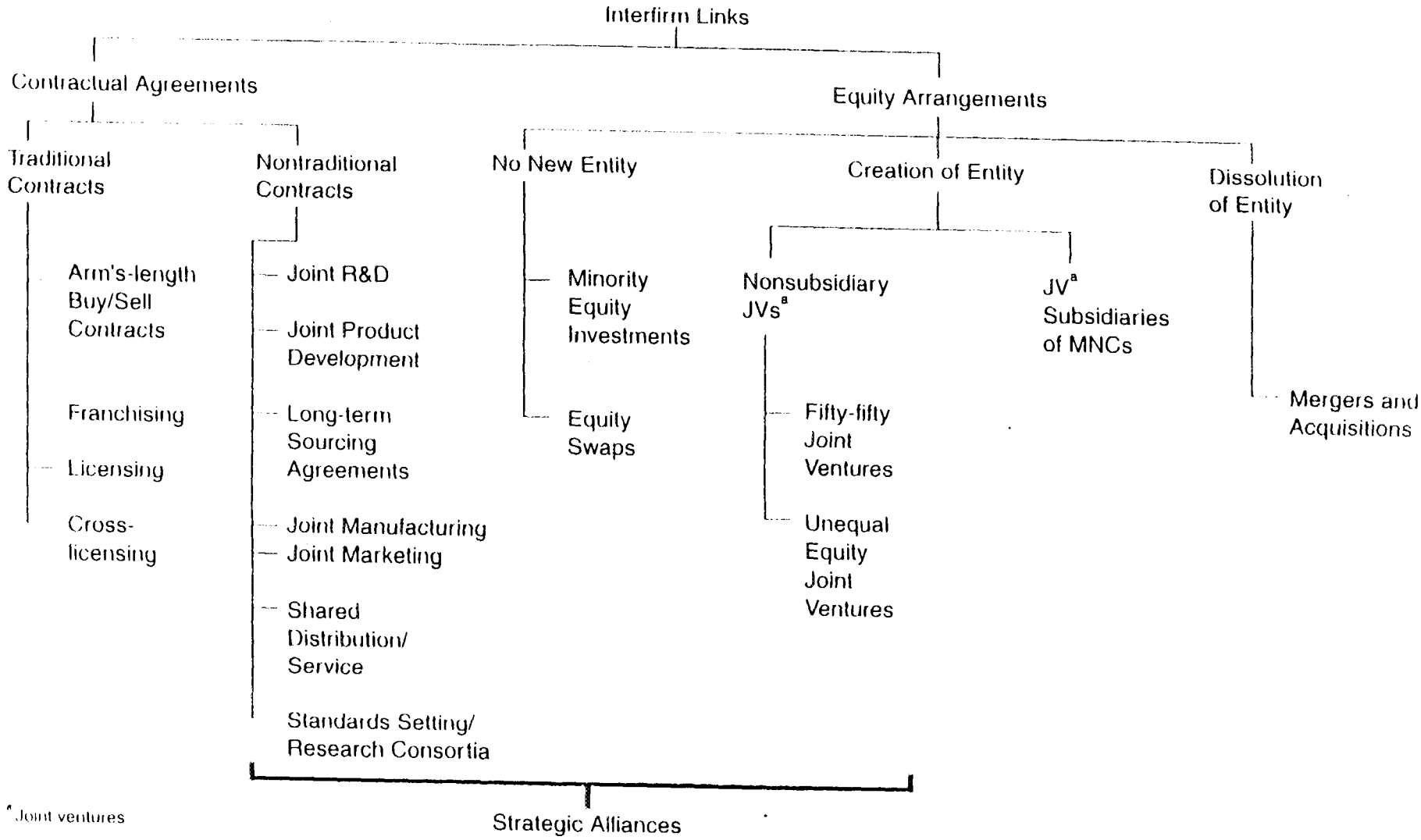
Figure 1
Range of Interfirm Links



[a] Joint ventures

COUNTRY REPORT

TRAINING COURSE ON INDUSTRIAL EXPLOITATION OF INDIGENOUS MEDICINAL AND AROMATIC PLANTS, BEIJING, CHINA, 17 - 27 JUNE 1997

MEDICINAL AND AROMATIC PLANTS RESEARCH IN INDIA

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Early History

Among the ancient civilization, India has been known to be a rich repository of medicinal plants. The *Rigveda* (5000 BC) has recorded 67 medicinal plants, *Yajurveda* - 81, *Atharvaveda* (4500 - 2500 BC) - 290 species. Later *Charak Samhita* (700 BC) and *Sushrut Samhita* (200 BC) have described properties and use of 1100 and 1270 respectively in compounding of drugs and these are still used in the classical formulations in the Ayurvedic system of medicine. *Ayurveda, Sidha, Unani* and tribal folk medicines are the major systems of indigenous medicine. Among these systems Ayurveda is most developed and widely practiced in India. Ayurveda dating back to 1500 - 800 BC has been an integral part of Indian culture. The term comes from the Sanskrit root *Au* (life) and *Veda* (knowledge). As the name implies it is not only the science of treatment of the ill but covers the whole gamut of happy human life, involving the physical, metaphysical and the spiritual aspects. Ayurveda recognizes that besides a balance of body elements one has to have an enlightened state of consciousness, sense organs and mind, if he has to be perfectly healthy. Ayurveda by and large is an experience with nature and unlike in western medicine many of the concepts elude scientific explanation.

India has also a perfumery tradition that dates back to over 5000 years to Indus Valley civilization. Sandalwood oil, rose oil jasmine oil, lemongrass oil and many others were extensively used for the preparation of Indian perfume concentrates, viz. *"Attars"*.

Area and production.

A large majority of medicinal and aromatic plant raw materials are still collected from their wild growth. However, wherever the demand grew large from organized sector of the industry and it could not be met from natural resources, such species have been introduced into agriculture.

Area under cultivation of major medicinal and aromatic plants in India

Name of the crop	Estimated area (ha)	Major use
Psyllium sativum	50,000	Carminative
Cassia senna	10,000	Laxative
Opium poppy	18,000	Nerve stimulant
Solanum viarum	3,000	Spasmolitic, sources of solasidine
Carthamus rosea	3,000	Anti-diebetic, anti-cancer

Mentha Spp.	10,000	Menthol
Cymbopogon flexuoses	20,000	Citral
Cymbopogon winternarus	10,000	Citronellol
Cymbopogon martini	5,000	Geraniol
Apium graveolens	5,000	Digestive, flavouring
Jasminum grandiflora	2,000	Perfumery
Saffron	3,000	Blood purifier, brain stimulant
Vetiveria zizanioides	3,000	Anti-heat, perfumery

India's trade of drug raw materials and phytochemicals

Trade of raw drugs and phytochemicals in the country is about US$ 660 million which is likely to reach US$ 1150 by the year 2000. Despite the diverse nature of crops grown in the country and the existence of a fast growing pharmaceutical sector, the share of India in world trade is quite insignificant considering the large geographical area. However, this is bound to rise rapidly with better research inputs and efficient management of the farm sector.

Trade of aromatic plants and perfumery compounds.

India is the largest producer of sandalwood oil, lemongrass oil, jasmines and tuberose concretes. India holds a major share of the international spice oils and oleoresin market. However, the country's share of international trade of flavours and fragrance is only about 2 %, which is very low. Having indigenously developed most modern processing and manufacturing technology, India is making its presence in the world arena in a big way.

Research infrastructure India for medicinal and aromatic plants.

The research infrastructure in India is fairly large. Indian Council of Agricultural Research (ICAR) with its network of national institutes and State Agricultural Universities deals largely with all aspects of agricultural research on medicinal and aromatic plants while Council of Scientific and Industrial Research (CSIR) and their network of national research institutes conduct research on aspects relating to processing, purification and development of new drugs and phytochemicals. Central Council of Research in Ayurveda and Sidha (CCRAS) in close collaboration with State Department of Indigenous System of Medicine conducts research on the indigenous systems of medicine. Indian Council of Forest Research (ICFR) with its network research institutes also work in this sector. Apart from these Governmental bodies, several other voluntary organisations (NGOs) and Corporate sector conducts research on these crops. All modern analytical tools and facilities are available in almost all leading research institutes.

Medicinal plants in forest eco-system

The forests in India is the principal repository of large number of medicinal and aromatic plants which are largely collected as raw materials for manufacture of drugs and perfumery products. Based on phytogeography, climate and vegetation the forest types are grouped into eight categories

1. Western Himalayas - comprise of subtropical, temperate and alpine vegetation holding about 4800 species - Medicinal plants like *Taxus, Nardostachis, Atropa, Thymus, Swertia* etc. are found here.
2. Eastern Himalayas - It has *Berberis* sp., *Taxus, Cymbopogon* spp. *Valeriana* sp., *Cinnamomum* sp.
3. Assam and North-East India - *Messua* sp., *Hydnocarpus, Alpinia, Smilax* etc. are widely seen here.
4. Semi-arid regions including Thar desert - *Accasia* sp. Ziziphus sp., *Commifora, Aloe* etc. are seen.
5. Gangetic plain - It has medicinal plants like *Cassia fistula, Crataeva nurvala, Tinospora* sp. *Pluchea lanceolata, Aegle marmelos* etc.
6. Western Ghat and Malabar region - The region consists of 4000 species, and 1500 are endemic. *Asoka indica, Piper sp., Cinnamomum thamala, Strynos nux-vomica, Curcuma* spp. etc. are the major medicinal plants.
7. Deccan Peninsula - *Santalum album, Pterocarpus, Phyllanthus emblica, Terminalia sp., Azadirachta* etc. are seen here.
8. Andoman and Nicobar Islands- *Garcinia indica, Termialia bialata* etc. are widely distributed here.

Endangered medicinal and aromatic plants

With the rapid depletion of forests, impairing the availability of raw drugs, Ayurveda, like other systems of herbal medicine has reached a very critical phase. About 50 % of the tropical forests, the treasure house of plant and animal diversity has already been destroyed. In India forest cover is disappearing at an annual rate of 1.5 m hectare every year. What is left at present is only 8 % as against a mandatory 33 % of geographical area. Many valuable medicinal plants are under the verge of extinction. The red data book of India has 427 entries of endangered species of which 28 are considered extinct, 124 endangered, 81 vulnerable, 100 rare and 34 insufficiently known.

Crop improvement

Germplasm assembly and its characteristic lay foundation for crop improvement research. These are now increasingly maintained in field gene banks and long term repositories at several institutes in India. It essentially provides variants in form, content and composition which serve as parent material in making improved varieties. These systematic works on crop improvement by several institutes brought about several new varieties through various methods of breeding, i.e. selection, cross breeding, mutation, biotechnology etc.

List of varieties developed and released for growing medicinal and aromatic plants in India.

Crop	Variety
Plantago ovata (Isabgol)	GI -1, GI- 2, HI - 5
Papaver somniferum (Opium poppy)	JA- 16, IC - 42, UO - 285, NOP - 4, NBRI -3, GS - 24, IS -34
Rauvolfia serpentina	RS -1
Diascoria floribunda	FB (C) - 1, Arka Upahar
Solanum viarum	Arka sanjeevani, Glaxo
Henbane (*Hyocyamus niger*)	IC - 6, Aela
Senna (*Cassia angustifolia*)	ALFT - 2
Glycyrrhiza glabra (Liquorice)	HM - 1
Carthamus rosea (Periwinkle)	WH- 40
Piper longum	Viswam
Lemongrass (*Cymbopogon flexuosus*)	Sugandi, OD-440, OD- 408, Praman, CPK - 25, Kaveri
Palmarosa (*Cymbopogon martinii*)	IW-31245, Thrishna, Jamrosa
Citronella (*Cymbopogon winterianus*)	Manjusha, Mandakini, BIO - 13, Jorlab -2
Japanese Mint (*Mentha arvensis*)	MAS -1, MA-2, HYB -77, EC- 41911
Spear Mint (*M. spicata*)	MSS-1, MSS - 5, PS -1

Crop Management and processing

Though about 1500 species of medicinal and aromatic plants are in use in India, only about 100 species are used in large quantities. For about 50 species, Package of Practices for its cultivation have been developed covering planting, fertilizer management, irrigation, inter-cultivation, weeding, harvesting and post harvest processing. These are published as monographs by various institutes.

Phytochemical studies

Screening of medicinal plants for their active principals and its extraction, purification and its clinical studies are being conducted at various research institutes. Recently, the Central Drug Research Institute, Lucknow have indentified the baccosides responsible for the brain stimulant activity of the herb Baccoppa munneri and now the baccosides are commercially produced and sold in the market as a tablet for increasing memory power.

Problems faced by medicinal and aromatic plants industry

There has been a sudden awakening for Ayurvedic system of medicine in the country mainly due to the side effects of western system of medicines. The system is increasingly being sought after in the developed nations. More and more herbal drugs manufacturers are appearing in the scene. Unlike in the older days when physicians themselves used to collect the herb, prepare and administer the medicine, the new generation of Ayurvedic physicians with prepared drugs in the market, have degenerated into prescription writers without much knowledge of the constituent herb of the drugs they are prescribing. The industry depend on professional plant collectors or traders for their raw drug requirement. Herb collectors and traders unable to meet the increasing demand, adulterate the drugs with other plants, thereby undermining the quality of the drug and the

credibility of the system. The quality control system for crude drug is so vague that the loophole is always exploited by unscrupulous industry.

Activities of the Aromatic and Medicinal Plants Research Station, Odakkali, Kerala

The research centre is a constituent research unit of the Kerala Agricultural University, South India. Apart from other institutions working on medicinal and aromatic plants in the state, we are largely concerned with the development of medicinal and aromatic plants as cultivated crops. We are the foremost research Institute in the country for research on Cymbopogon flexuosus and maintains the largest germplasm on lemongrass with 450 accessions in the world. We are responsible for the transfer of technologies on cultivation, on-farm processing and quality control of aromatic and medicinal plants. A good collection of tropical herb (about 300 species) which are in use in Ayurveda is maintained at the institute. Our major research areas include :-

1. Survey, Collection, Conservation and maintenance of medicinal and aromatic plants of the Western Ghats.
2. Crop improvement of selected MAP
3. Crop management and development of package of practices for its cultivation.
4. Post harvest technology including development of processing, phytochemistry and quality standardization.

Major highlights of research

- Evolved high yielding varieties of lemongrass (OD 19, OD 440, OD 408), palmarosa (ODP 1, ODP -2), vetiver (ODV -3), Cinnamon (ODC- 130), *Piper longum* (Viswam).
- Identified OD-468, a strain of *Cymbopogon gidderba* as the richest source of natural geranyle acetate, a high value perfumery compound
- Isolated a strain belonging to *Cymbopogon parkeri* as an alternate source of geraniol.
- Developed agrotechniques for lemongrass, palmarosa, vetiver, *Ocimum*. *Kaempferia* spp., *Piper longum, Asparagus recemoses, Holostemma* sp., *Plumbago* spp., *Curcuma* spp. etc.
- Standardized post harvest technology including distillation technology, fractional distillation, and storage techniques for essential oils such as lemongrass, palmarosa, vetiver, cinnamon leaf oil, Ocimum etc.
- Involved in conservation and utilization of medicinal and aromatic plants endemic to the Western Ghats of Kerala
- Involved in large scale multiplication and distribution of genuine planting materials of medicinal and aromatic plants for the benefit of farmers.
- Conducts training and extension activities for popularization of medicinal plants cultivation in the state.

INDUSTRIAL UTILISATION OF SPICES IN INDIA

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Country Report

INDUSTRIAL UTILISATION OF SPICES IN INDIA

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India is known for spices since time immemorial. Traders from Portuguese, Dutch, Arab and Britain came to India to purchase black pepper, cloves, cardamom etc. Research in spices and medicinal plants is carried out by various organizations. A few of the Research and Development organizations involved are listed below.

1. Indian Institute of Spices Research under Indian Council of Agricultural Research (ICAR)
2. Central Food Technological Research Institute, Mysore under Council of Scientific and Industrial Research (CSIR)
3. Regional Research Laboratories (CSIR)
4. Spices Board under Ministry of Commerce, Govt. Of India.
5. Central Institute of Medicinal and Aromatic Plants (CSIR)
6. National Research Centre for Medicinal and Aromatic Plants (ICAR)
7. Directorate of Cocoa and Arecanut Development, Ministry of Agriculture, Govt. Of India.
8. All India Coordinated Research Project on Spices (ICAR)

Indian Institute of Spices Research (IISR),Calicut, Kerala is the pioneer institute established by the Indian Council of Agricultural Research (ICAR), New Delhi to research exclusively on the various aspects of spices production. The major spices dealt by the

institute are black pepper, cardamom (small), ginger, turmeric, cinnamon, clove, nutmeg and allspice. The research activities of the Institute are confined to three divisions viz. Crop improvement and Biotechnology, Crop protection and Crop production and post harvest technology. Collection, conservation cataloguing and evaluation of germplasm, Developing improved varieties through selection and breeding, Micro propagation and other modern biotechnological approaches to develop disease planting materials, Developing agro techniques for increased production and sustainable agriculture, Developing Integrated pest and Disease management

Post harvest technology

IISR has a large collection of germplasm in the above mentioned spices. The main programmes in post harvest technology are confined to evaluation of the germplasm for volatile oil, oleoresin, pungent principles and aroma profile.

Black pepper

Pepper is the dried fruit of a perennial climbing vine, *Piper nigrum*. In India pepper flowers during May- June months and it matures in about 6 - 7 months.The small round green berries produced on the spikes are harvested, dried and used for various culinary, Industrial and medicinal applications.During drying the green berries turn brown and then black in colour because of action of enzymes on the polyphenols present in the skin. A yield of about 33 kg of black pepper is obtained from 100 kg of green pepper.

Essential oil : Pepper contains 2 - 5% volatile oil which impart its characteristic spicy odour. The oil is used in food flavouring, pharmaceuticals and perfumery. Garbled pepper gives the

best quality oil. Black pepper oil is made up of monoterpenes (70 - 80 %) and sesquiterpenes (20 - 30 %). About 5% oxygenated compounds influence the overall odour quality of the oil. Major compounds of the oil are pinenes, sabinene, myrcene, limonene and caryophyllene.

Table: Composition of oils from some pepper varieties

Variety	Pinenes	Sabinene Myrcene	Limonene	Caryophyllene
Karimunda	21.1	25.5	25.7	21.0
Chumala	40.7	trace	25.8	33.3
Kuthiravally	46.2	7.1	31.1	10.9
Uthirancotta	34.2	trace	39.6	17.0
CLTP-236	7.3	21.6	7.3	33.4
CLTP-58	7.0	31.0	10.4	34.0

Oleoresin: The total flavour of pepper is obtained by solvent extraction since the pungent factor is non- volatile. Pepper oleoresin contains chiefly volatile oil and piperine the pungent principle. Other pungent compounds in lower concentration are chavicine, piperidine and piperitine.

There are about 69 popular cultivars. The volatile oil content ranged from 2 to 6 %, oleoresin 8 to 18 % and piperine 2 to 6 %. The cultivars with high piperine and oleoresin are

Kottanadan, Kumbhakodi, Kuthiravally and Ceylon. The cultivars with high oil are Balankotta, Kalluvally, Panniyur-I and Karimunda.

White pepper

It is prepared by removing the outer skin of pepper. It is prepared mainly by soaking ripened red berries for 7-10 days in running water and removing the outer skin by trampling. Gas chromatographic evaluation of the essential oils of black and white pepper showed that oil of white pepper is superior over the former.

Among the popular cultivars evaluated for white pepper at IISR , Calicut, Panniyur-I, Valiakaniakkadan and Balankotta are very ideal for the preparation.

Green pepper : Immature green pepper is used for flavouring pickles. Dehydrated green pepper, canned green pepper, Frozen and dehydrated green pepper are also prepared from it.

Cardamom

Cardamom (*Elettaria cardamomum*. M) is well known for its sweet fruity flavour.It is known as the queen of spices. The two major varieties are Malabar and Mysore .The attractive flavour of cardamom is mainly due to the volatile oil present in the seeds. The husk of the pod does not contain any oil but protects the seeds. The oil is used in food flavouring and pharmaceuticals. Cardamom pods contain about 25% husk and 75% seeds. The volatile oil content varies from 5 - 9%. There is distinct variability available in cardamom with regard to its essential oil constituents.The ratio of α- terpinyl

acetate to 1,8- cineole determine the flavour of the oil. Other major constituents of the oil are linalool and linalyl acetate. The germplasm accessions were evaluated for these constituents. Acceessions with high α- terpinyl acetate and low cineole and vice versa were identified at IISR, Calicut.

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Ginger

Ginger is the rhizome of *Zingiber officinale* Rosc, a perennial herbaceous plant native to Southern Asia. Harvesting is carried out in about 8 - 9 months after planting. India produces about 90000 tonnes of green ginger of which about one third is exported as dry ginger or its allied products. Two types of dry ginger are produced in India, bleached and unbleached.

Jamaican ginger has a fine aroma and flavour suitable for soft drinks. Indian ginger is light brown in colour and bold in appearance. It has a characteristic strong, lemon like flavour and is used for blending purposes. Australian ginger is used mainly to prepare preserved ginger.

Ginger oil : The typical pleasing aroma of ginger is due to the essential oil. Most of the varieties contain about 1 - 3 % oil.α,β- zingiberene, ar- curcumene, farnesene and sesquiterpene alcohols are the major constituents of the oil. Oils from ginger having a lemony odour contain up to25 % citral. More than 30 different cultivars are grown in different parts of India . Rio de Janeiro is well known for its pungency, taste and flavour.

Ginger oleoresin : Extracted from ground ginger using acetone, alcohol or ethylene

dichloride. This contains both the essential oil responsible for the aroma and gingerol known for its pungency. Oleoresin content ranges from 4 - 10 %. Germplasm accessions available at IISR, Calicut were categorized based on high oleoresin and gingerol content of oleoresin. A few of the high oleoresin ginger accessions are Rio- de Janeiro, Jugijan, Zahirabad and Maran.

Turmeric

It is the dried rhizome of *Curcuma longa*. L which is famous for its colour and medicinal value. Turneric is consumed mostly in the ground form . Ground turmeric is used in foods to give them an attractive yellow colour and characteristic spicy flavour. It is a major ingredient in curry powders and pickles.

Turmeric oil :It is obtained by distilation of ground turmeric. The oil is pale yellow to orange yellow in colour, with an odour similar to turmeric fingers. More than 50 % of the oil is composed of a mixture of sesquiterpene ketones, known as turmerone and 25 % zingiberene. The yeild of oil ranges from 4 -7 %.

Turmeric pigment : The most valued constituent of turmeric is its yellow pigment, curcumin (di- cinnamoyl methane).The colouring matter is extractable using solvents like ethanol. Alleppey finger turmeric (AFT) is known for its high curcumin. IISR, Calicut has already released four varieties viz., Suguna, Sudharsana, Prabha and Prathiba with more than 6 % curcunin. There are many Industries in India extracting crystalline curcumin from turmeric and exporting to western Countries as a natural colourant.

Studies at the Institute established that curcumin content varies with location, cultural practices and agro climatic conditions. Harvesting turmeric one month before the regular schedule yields more curcumin with a marginal reduction in yield.

Turmeric oleoresin : It is an orange red product consisting of an upper oily layer and lower crystalline layer. Curcumin, the principle colouring matter, constitutes about 1/3 of a good quality of oleoresin.

Cinnamon

It is the inner bark of the stems of the ever green tree, *Cinnamomum zeylanicum.* Harvesting is carried out mainly in the rainy season, which is favourable for easy separation of bark.

Cinnamon bark oil : It is a colourless to light yellow aromatic oil having warm and sweet spicy flavour, characteristic of true cinnamon. Major constituents of the oil are cinnamaldehyde(65 %) and eugenol (10 %).

Cinnamon leaf oil : It is rich in eugenol (83 %). Other constituents are methyl eugenol, cinnamaldehyde, caryophyllene and linalool. Two high quality cinnamon lines with high leaf and bark oil and bark oleoresin are released from IISR, Calicut.

Cassia

Cinnamomum cassia Blume of China, *Cinnamomum loureirii* Nees of Vietnam and

Cinnamomum burmanni Blume of Indonasia constitute the cassia of commerce.

Cassia oil : While cinnamon bark and leaf give oils of different compositions, cassia bark and leaf give oils of the same composition. It has about 90 % cinnamaldehyde. Unlike cinnamon oil,it does not contain any eugenol. Small amounts of cinnamic acid, coumarin etc., are also found in the oil.

Clove

Cloves are the dried unopened flower buds of the evergreen tree *Syzygium aromaticum,* indigenous to Moluccas.

***Oil of Cloves*:** It is one of the most important essential oils being used in the flavouring of a wide variety of food products, pharmaceuticals and toilet goods. The yield of oil is generally is 17-18%. It contains about 90% eugenol, some eugenol acetate and methyl amyl ketone.

***Clove stem and leaf oil*:** Clove stem yield about 5-6% oil containing 85% or more eugenol and leaf gives 1.5-2% oil with 80% eugenol.

Nutmeg

Nutmeg and mace are the dried seed and aril surrounding the seed shell of the fruit of *Myristica fragrans* Houtt an evergreen tree indigenous to the Moluccas .Fruits resemble small peaches. They are fleshy dupes of orange yellow colour which split open along a groove on ripening. The split husk reveals a glossy shell containing the seed, and a net-like crimson aril surrounding the seed coat.

The unshelled nutmegs are dried till the seeds inside rattle on shaking. The seed cover is then cracked open and removed using wooden machines.

The fixed oil of nutmeg, known as nutmeg butter, can be expressed by hydraulic pressure with heating or extracted with solvents. It is an orange butter-like fat containing more than 70% glyceryl myristate.

Oil of nutmeg and mace: The essential oil is a pale yellow liquid with the characteristic odour of nutmeg. The composition of nutmeg oil varies from sample to sample depending upon its origin. Some of the constituents are pinene, linalyl acetate, linalool, safrole, myristicin and elemicin. Myristicin, which is a phenolic ether, is present in the highest boiling fractions of the oil. It is responsible for the physiological effects of nutmeg and mace.

Oleoresins: The spice contains about 30-40% oleoresin. The oleoresin is rich in volatile oil and is supposed to replace about ten times the weight of the spice.

Pimenta or Allspice

It is the dried unripe fruit of the evergreen tree *Pimenta dioica*, indigenous to West Indies. The spice contains on an average 3-3.5% berry oil and 1-1.5% leaf oil. Both the oils are rich in eugenol.

Major Essential oil bearing plants in India are listed below.

Ajowan,basil,camphor,caraway, cardamom, cedarwood, celery, cinnamon, citronella, Celery

sage, clove, coriander, cyperus, davana, dill seed, eucalyptus, fennel, ferula, geranium, ginger,jasmine,juniper,lavender,lemongrass,mint,palmarosa,patchouli, rose mary, sandalwood, tejpat, thyme, vetiver.

A few of the major spice based Industries are listed below

1. Synthite Industrial Chemicals Ltd., Cochin, Kerala , India.

   Manufacturers of oils, oleoresins, curcumin, white pepper, capsaicin, chilli colour etc.

2. SIPPO, Madurai, India.

   Eucalyptus oil, Palmarosa oil, Cinnamon leaf oil, Lemon grass oil etc.

3. Paul & son, Calcutta.

   Aroma chemicals, Essential oils, Fragrances and Flavours.

4. Rajhans Aromatics, Delhi.

   Essential oils, Mentha oils, Aroma chemicals.

5. Devi Group of Industries, Madurai, India.

   Cardamom oil, Cardamom flavours, Ginger oil & oleoresin, Capsicum oleoresion.

INDONESIA

COUNTRY REPORT

DEDIWAN. K

Indonesia is one of the country in South East Asia with about 200 million people in 1995 by growth 2.2% spread over 13,667 islands, sharing 500 language group. Total land area in Indonesia is 1.95 million km^2 with 33% area suitable for agriculture.

Usage of herbal medicine in Indonesia was very popular by term of *Jamu* especially to promote general health and beauty such as to "stay young", "keep breast firm", "improve male virility", "improve married life" or "aid a mother before and after she gives birth". It is estimated that 80% of all Indonesians take some form of *Jamu* daily.

Herbal medicine in Indonesia was found in pharmacies, department stores, street stalls, from door to door vendors, grown in back-yard garden plots or foraged in the forest.

There are three sources of *Jamu* :

1. Preparation from fresh plant materials.
2. Home industries (small holders and family businesses) whose products consist mainly of watery extracts and dried plant materials. These are distributed in simple packaging and in bottles by independent vendors. The vendors carry baskets on their back and sell the medicine, called *Jamu Gendong* (*Jamu* - herbal remedies, *Gendong* - meaning to carry on one's back), door to door.
3. Large scale commercial preparation and distribution (*Jamu* industry) and come in form of pills, powders, teas, tonics, topical oils and creams.

Use of alternative treatment of herbal medicine in Indonesia are:

1. Herbal remedies
2. Health food preparations
3. Diet change

4. Acupuncture
5. Phytopharmaceutical

Research activities on Jamu and medicinal plants are also conducted in several research institutions, such as Indonesia Science Institute, Universities and at R & D Laboratories of ***Jamu*** Industry.

The main objective of current research on Indonesian medicinal plants are :

1. To improve the quality and safety of ***jamu***
2. To search for bioactive natural products
3. To extract, separate and isolate the bioactive principles and try to develope modern medicines from them
4. To obtain high quality raw materials
5. To promote the integration of proven valuable knowledge of herbs into phytomedicine / phytopharmaceutical

There are some problems in developing medicinal plant [1]:

1. Cultivating medicinal plants require skill and knowledge of cropping management
2. Medicinal plants cultivation is still required in order to develop and improve yield and quality of its products
3. In order to standarize of herb, extract and dosage form medicinal dry is required equipment for analyzing (elucidation structure) of active compound
4. Clinical trial of medicinal plant required skill, experience and equipment.

Indonesia has about 300 commercial manufacturers (1996) that produce the herbal medicine and one of those companies is Kimia Farma.

Kimia Farma is one of the government company of Indonesia has 6 factories spread over 5 cities in Indonesia : Jakarta, Bandung (West Java), Semarang (Central of Java), Mojokerto (East Java)

and Medan (North Sumatra), 95 dispensaries and 36 wholesale outlets located in 27 provinces all over Indonesia.

Production of Kimia Farma consist of ethical product, patent medicine, generic medicine, licensed products, raw material (Quinine salts and its derivates, Iodine and its salts, oil and fat), oral contraceptive and CuT 380 A.

As a pharmaceutical industry, Kimia Farma is very concern to the environmental problems. Kimia Farma has the liquid waste processing installation in every production units.

In accordance with the government policy about research and development of traditional medicine, production strategic of Kimia Farma has already been aimed at phytopharmaceutical that is drug from plant material (fresh plants, dried plants or mono substances).

Regulatory items have already been reached for the commercialization of phytopharmaceutical in Kimia Farma consist of :

1. Standardization of preparation using active principles, marker compounds and chromatographic 'fingerprint'. This stage is needed to guarantee preparations containing therapeutically effective doses of active principles, to maintain constant batch composition, to check stability of active principles and avoid adulterations. Standardization of preparation consists of process (plant cultivation, manufacturing of extract/isolate and formulation) and product (plant, extract/isolate and drug) standardization.
2. Toxicology
3. Pharmacology
4. Clinical trials

The herbal medicine that has already produced by Kimia Farma can looked at the enclosed sheet.

LIST OF
MEDICINAL PLANT TO BE DEVELOPED
AS PHYTOMEDICINE
IN KIMIA FARMA

No.	Indication	Name of Plant	Plant part used
1	Anti Diarrhea	a. Jambu Biji (Psidium guajava)	Leaves
		b. Kunyit (Curcuma domestica)	Rhyzoma
2	Astringent	a. Sirih (Piper bettle)	Leaves
		b. Saga (Abrus precatorius)	Leaves
		c. Succus	Root
3	Diuretics	a. Kejibeling (Strobilanthus crispus)	Leaves
		b. Tempuyung (Sonchus arvensis)	Leaves
4	Anti Kheloid	Pegagan (Centella asiatica)	Leaves
5	Anti Cholesterol	Bawang Putih (Allium sativum)	Bulb
6	Lactagogum	Katuk (Sauropus androgynus)	Leaves

APPENDIX : LIST OF MEDICINAL PLANT TO BE DEVELOPED PHYTOMEDICINE (PHYTOPHARMACA)

Anthelmintics

No.	Name of plant	Plant part used
1	Ceguk (Quisqualis indica)	fruit or seed
2	Delima putih (Punica granatum)	root bark
3	Pepaya (Carica papaya)	seeds
4	Labu merah (Curcubita moschata)	seeds
5	Temu giring (Curcuma heyneana)	rhizome
6	*Temu ireng (Curcuma aeroginosa)*	*rhizome*

Anti diabetes

No.	Name of plant	Plant part used
1	Pare (Momordica charantia)	fruit
2	Pulai (Alstonia scholaris)	stem bark
3	Sambiloto (Andrographis paniculata)	leaves

Anti hypertension

No.	Name of plant	Plant part used
1	Bawang putih (Allium sativum)	bulb
2	Ceplukan (Physalis minima)	leaves
3	Keji beling (Sericocalyx crispus)	leaves
4	Pace (Morinda citrifolia)	buah
5	Saledri (Apium graviolens)	whole plant

Diuretics

No	Name of plant	Plant part used
1	Keji beling (Sericocalyx crispus)	leaves
2	Kumis kucing (Orthosiphon aristatus)	leaves
3	Meniran (Phyllanthus niruri)	whole plant
4	Pegagan (Centella asiatica)	whole plant
5	Teki (Cyperus rotundus)	bulb
6	Jungrahab (Baeckea frutescen)	leaves
7	Tempuyung (Sonchus arvensi)	leaves

Liver disorders

No	Name of plant	Plant part used
1	Temulawak (Curcuma xanthorrhiza)	rhizomes
2	Kunyit (Curcuma domestica)	rhizomes
3	Sambiloto (Andrographis paniculata)	leaves

TRAINING COURSE
ON
INDUSTRIAL EXPLOITATION OF INDIGENOUS MEDICINAL AND AROMATIC PLANTS

(Beijing 16 to 28 June 1997)

Country Paper

Boun Hoong Southavong
Research Institute of Medicinal Plants
Ministry of Public Health, Lao PDR

Mr. Chairman,
Ladies and Gentlemen,

On behalf of participant from Laos I would like to bring warm greetings to all participants from friend countries participated in this training course and special greeting to our Chinese friends. Personally, I am very glad that ICS-UNIDO and IMPLAD, Chinese Academy of Medical Sciences and the State Administration of TCMPeople's Republic of China have pay attention to the promotion of the Development of the Industrial Exploitation of Medicinal and Aromatic Plants in Laos and have awarded me a fellowship for training in China. I would like to take this opportunity to express thanks to all above mentioned institutions. I also highly appreciate the initiative in holding this training dedicated to Industrial Exploitation of Indigenous Medicinal and Aromatic Plants .

First of all I would like to briefly introduce our Institute to our colleagues from different counties. The complete name of our Institute is Research Institute of Medicinal Plants, (RIMP). It was founded in 27 April 1976 and belongs to the Ministry of Public Health. It is the only one Institute which is conducting adaptive research on Traditional Lao Medicine (TLM) as well as Medicinal and Aromatic Plants of the entire country. RIMP consists of 5 main Units namely, Administrative bureau, Pharmacognosia laboratory, Phytochemistry laboratory, Processing unit and small pilot plant.

The main tasks of RIMP are as follow:

1- Studies the Utilization of Medicinal and TLM in the country.

2- Preservation of important Traditional Treaties of Traditional Healers by translating old sript on TLM into Lao language, then publishing bookets.

3- Surveying of Medicinal Plants in different provinces and classifying them into systematic botanical order.

4- Transfering the achievements of RIMP's studies to Pharmaceutical Factories

for industrial scale production.

5- Offering Technical support to Provincial Traditional Medicine Stations under the form of Seminars and Short Term Trainings.

6- Contributing in the Human Resources Development. Specially, providing students of the Medical Sciences University, the knowledge in the field of Pharmacognosia and TLM in theory as well as practice.

Work achieved:

In the recent years RIMP has carried out some studies, and had some achievements:

- Establishing the extraction procedures for :

Berberine from Coscinium usitatum Pierre,
l-Tetrahydropalmatine from Stephania rotunda Lour.
Cholate salt from pig's gall bladder
Artocarpine from Artocarpus lakoocha Roxb.
Artemisinine from Artemisia annua L.

- Bringing forth four new medicines for industrial production such as : dry extracts of Leonurus heterophyllus Sweet., Adenosma capitatum Benth. Curcuma longa L. and Eleutherine subaphylla Gagn.

Over the past decade, RIMP had surveyed medicinal plants in several provinces. Dispite the limited coverage and transportation means, the survey revealed that the forests in different provinces of the country are abundant in medicinal plants, including precious plants. Some five hundred of herbarium as well as specimen were collected.

Ongoing works.

At present, the programme of researches of RIMP are focused on antimalarial remedies. As malaria is one of serious diseases in our country and causes mortality at a relatively high percentage, therefore, from 1994 under Sida and WHO's support RIMP has implemented clinical trials of TLM against malaria. Furthermore, by cooprating with Vietnamese related institution we are studying the condition to grow and produce new active compound from plant for healing malaria. The production of Artemisinine from Artemisia annua's leaves has been succesfully carried out in pilot scale.

The resource survey on medicinal and aromatic plants has also been implemented.

Some important and precious plants are taken into account. Found plants were collected and put systematically into plant inventory of RIMP. Especially, we play much attention to antiinflammatory plants.

Future works

Lao is a land-link country with an area of 236,800 Sqkm, covered by 47% of forest area. Many plant species were not exploited for industrial production, these include Medicinal and Aromatic Plants. That's why, to get the plants data, resources survey is still on of important issues of our future activities, this project involved the participation of provincial traditional medicine stations.

Besides of surveying medicinal plants, Traditional Lao treaties will continue to collect from the pagodas and senior Traditional healers in community. These treaties will be selected and published for disseminating to health workers and peoples in rural areas.

Compiling Monographs on Medicinal Plants in Laos which is viewed as guidelines and teaching material on the appropriate use of plants based medicine should be completed and published.

In order to reach the Goal of "Health for All by the Year 2000", as a part of National Drug Policy, a number or simple traditional remedies should be introduced and widely used in PHC system.

Building up an up-to-date analytical laboratory for controlling the quality of herbal medicines is considered as an issue of vital importance.

The exploitation and processing of some medicinal and aromatic plants of economic value should be strengthened.

To attend this important training course, I expected to have opportunity to learn how to develop appropriate methodology as well as technology for improving our research work on TLM for the benefit of people's health. Furthermore, this training provides occasion to all participants have chance to exchange experience to each other which could be important step for intercountry or regional cooperation.

Finally, I would like to take this opportunity to thank the organizers of this training, wish a healthy life to Mr. Chairman and to all delegates and participants.

Thank you for your attention.

MEDICINAL PLANTS IN MALAYSIA

Introduction

Malaysian community consist of three major races namely Malay, Chinese and Indian. Besides that there are also others like Dayak, Iban, Kadazan etc. who live in Sabah and Sarawak (East Malaysia). Each of them has their own traditional ways of using plants and herbs for medicinal use. About 1230 plant species are recorded grown in Malaysia but most of major plants used for the production of medicine are imported which is about RM 85 millions in 1993. It is estimated that in 1992, about RM 73.8 millions are used for pharmaceutical and herbs. Natural products whether from plants, animals or other natural resources are under goverment control (Drugs and Cosmetics Control Act 1984).

Products from these sources are classified as traditional medicine and have to be registered. From the applications for registration, percentage for Malay traditional medicine is about 13%, 68% Chinese, 12% Indian, 12% West Country and 4% homeopathy. About 46% of the applications for registration are from traditional medicine . Now there are about 700 registration holders for traditional medicine and about 400 factory in Malaysia.

Research and Development (R & D) of Traditional Plants in Malaysia

Research activities for medicinal plants were done by universities namely Universiti Kebangsaan Malaysia (UKM), Universiti Sains Malaysia (USM), Universiti Putra Malaysia (UPM) and Universiti Teknologi Malaysia (UTM), Forest Research Institute of Malaysia (FRIM) and Malaysia Agriculture Reseach and Development Institute (MARDI). Among species that has been explored are genus from Calophyllum, Cinnamomum, Eurycoma, Alastonia, Goniathalamus and Uncaria. Very recently, active compound (calonolides) for AIDS virus has been identified from *Calophyllum laniguerum* from Sarawak forest.

For the future of R & D will include this activities :-

1) Documentation of information of medicinal plant in the form of "Materia Medica" from the experices of etnobotany and efnofarmacology.

2) To establish "Centre of Excellance" in the natural product research for example National Biodeversity Centre and National Medicinal Plant Research Centre.

3) To give priority to "problem solving research".

4) Planting of wild medicinal plant from the forest in commercial scale (domestication) and ex-situ conservation.

5) To develop national procedure to control exploitation of plant genetic resources.

Production and Industry

Generally there are 2 types of industry i.e.

1. Backyard (small scale in the village)

- Medicinal plants (roots, leaves, stems and flowers) which were taken from the village or jungle will be sliced and dried up under the sun shine. Some of them will be grounded and some will not and then will be packed in plastic bag. Pack of dried medicinal plant will be stored in normal room temperature in the house.

2. Industry

- All ingredient will be grounded and pack in the form of capsule or others.

Medicinal Plants in Malay Practices

Problems with traditional medicine in Malay practices is that not only one single plant were used for curing or for the health. Normally more that 5 plants were used so we don't know which plant actualy give the effect to the body. The use of plant mixture also varies from one man.

Combinatoin of medicinal plants will be boiled and drink as a tonic or health drink. Some examples of medicinal plant and their uses are shown below :-

1)	*Aneilina lineocatum*	-	family planning
2)	*Musa sp*	-	easy to get pregnancy
3)	*Expirhixanthes cylindrica*	-	easy to get pregnancy
4)	*Lepixanthes longifolia*	-	arbotion
5)	*Goniothalamus scortechinii*	-	arbotion
6)	*Eurycoma longifolia*	-	tonic for man
7)	*Polyathia bullata*	-	tonic for man
8)	*Colens parviflorus*	-	tonic for man
9)	*Smilax myositiflora*	-	tonic for man
10)	*Labisia pothoina*	-	tonic for woman

11)	*Parameria longifolia*	-	tonic for woman
12)	*Rafflesia hesseltii*	-	women affter giving birth (confinement)
13)	*Fibrauea chloroleuca*	-	women affter giving birth (confinement)
14)	*Cinnamomum iners*	-	women affter giving birth (confinement)
15)	*Urea lobata*	-	women affter giving birth (confinement)
16)	*Melastoma malabathricum*	-	women affter giving birth (confinement)
17)	*Helminathostacys Zeylanica*	-	women affter giving birth (confinement)
18)	*Labisia pothoina*	-	women affter giving birth (confinement)
19)	*Vitex negundo*	-	women affter giving birth (confinement)
20)	*Phyllagcithis rotundifolia*	-	women affter giving birth (confinement)
21)	*Kaempferia galanga*	-	women affter giving birth (confinement)
22)	*Morinda elliptica*	-	women affter giving birth (confinement)
23)	*Casia alata*	-	women affter giving birth (confinement)
24)	*Alpinia galanga*	-	women affter giving birth (confinement)
25)	*Curcuma demostica*	-	women affter giving birth (confinement)
26)	*Acorus calamus*	-	women affter giving birth (confinement)
27)	*Vitex pubescens*	-	women affter giving birth (confinement)
28)	*Zingiber officinale*	-	women affter giving birth (confinement)
29)	*Nigella sativa*	-	women affter giving birth (confinement)
30)	*Cuminum cyruinum*	-	women affter giving birth (confinement)
31)	*Alpinia conchigera*	-	women affter giving birth (confinement)
32)	*Jasminum sambac*	-	breast feeding women
33)	*Phyllanthus niruri*	-	breast feeding women
34)	*Eupatorium odoratum*	-	breast feeding women
35)	*Datura metel*	-	breast feeding women
36)	*Lawsonia inermis*	-	breast feeding women
37)	*Andrographis paniculata*	-	diabetes
38)	*Corcorus capsularis*	-	diabetes
39)	*Orthosiphon grandiflorus*	-	high blood preasure
40)	*Tabernaemontana divaricata*	-	cancer
41)	*Hibiscus rosa sinensis*	-	cancer
42)	*Arecha catechu*	-	skin deasease
43)	*Acanthus illeifolius*		
44)	*Cucumis sativus*	-	face
45)	*Persea americana*	-	face
46)	*Citrus aurantifolia*	-	face
47)	*Cocos nucifera*	-	hair
48)	*Parkia speciosa*	-	kidney

"Ulam" (raw vegetables)

In Malay practices, some of the vegatbles will be taken raw or fresh called "ulam". About 80 species of plant were recorded used as "ulam" either fruit, young leaves, flower etc. They belived that ulam has compound for good health. A few examples of ulam are shown below.

1) *Cantella asiatica*
2) *Momordica charantia*
3) *Barringtonia racemosa*
4) *Ocimum basilicum*
5) *Carica papaya*
6) *Cucumis sativa*
7) *Vigna senensis*
8) *Anacardium occidentale*
9) *Cosmus coudatus*
10) *Hydrocotyle americana*
11) *Hydrococotyle sibthorpioides*
12) *Leucaena sp.*
13) *Kaempferia rotunda*
14) *Parkia speciosa*
15) *Onenanther javanica*
16) *Phaeomeria atropurpurea*
17) *Pithecellobium bubalinum*
18) *Pithecellobium jiringa*
19) *Polygonum minus*
20) *Psophocarpus tetragonolbus*

Germplasma Unit in Universiti Putra Malaysia

Under the sixth Malaysian Plan, Universiti Putra Malaysia had allocated RM 1,000,000.00 for the establishment of Germplasma unit with the main function for collecting and planting of plant genetic resources. One of the activity is collection and conservation of medicinal plant. Until now nearly 500 species of medicinal plant has been collected and planted in this unit. Most of the plants were collected from the forest according to the man who practices tradisional medicine. He can identified plant only by vegetative part especially leaf and the aroma. Most of the plants were planted under the shade of old rubber tree. Besides medicinal plants, this unit also conserve fruits such as star fruit, *Eugenia sp.*, rambutan, durian and rare fruit.

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COUNTRY REPORT: MALAYSIA

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MEDICINAL AND AROMATIC PLANTS INDUSTRY IN MALAYSIA

INTRODUCTION

The floral diversity of the Malaysian rainforest of at least 20,000 plant species, 300 fungi and many unknown microorganisms is well known. It is an important source of raw materials for pharmaceutical and industrial applications. Medicinal and aromatic plants from these valuable resources have long been used traditionally as herbal medicines and food by the population which consist of the Malays, Chinese, Indians and various ethnic groups. The plants are sold fresh or dried in the local market. These plants species are usually sourced from the wild. Cultivation of these plants are still very limited.

Although there are many manufactures of herbal medicines in Malaysia, they are mostly small scale and most do not comply Good Manufacturing Practices (GMP). Once GMP practices are enforced and medicinal or herbal products have to be fully registered with the National Pharmaceutical Control Bureau, large amount of capital are required to upgrade production facilities. Under these circumstances, many of these small manufactures will be out of business.

The Malaysian Government is currently enforcing GMP and registration of herbal products. To meet up the new regulation, the local industries found themselves having to upgrade production or modernise facilities. In doing this, many problems have been identified in particular the lack of know-how in modern technologies of processing. Nevertheless, there are companies with large capital, are able to follow through and are now producing herbal products which are now sold in the domestic market as well as for export.

Plant-based products such as herbal medicines and health food are gaining popularity among Malaysians. Imported products ie. ginseng, linzee, alfalfa and jamu are common items in many of the local pharmacies and herbal stores. Based on this scenario, many local industries have now ventured into the production of similar products. However, these companies are dependent on imported raw materials for their products. There is very little effort in producing and processing the raw materials locally. There are

also insufficient R & D efforts especially in the verification of the quality and efficacy of herbal products.

Realizing the lack of raw materials to fit the growing industry, the Government is emphasizing on plantation of aromatic and medicinal plants. Several state lands have been proposed for cultivation of medicinal plants. Research programmes dealing with domestication and agronomic practices have also been proposed. Such activites are also taken up by the private sector and statutory bodies (ie; Nasuha Enteprise, Nona Roguy, Sime Darby, KESEDAR, MARDI). Efforts were also being made in identifying appropriate technologies for large-scale extraction and processing of the plants.

Some examples of common medicinal plant species used as major ingredients in local herbal products are *Eurycoma longifolia, Labisia pumila, Centella asiatica, Cinnamomum* spp. *Curcuma xanthorriza, Andrographis paniculata. Morinda citrifolia, Zingiber zerumbet, Cassia angustifolia* and *Kaempferia galanga.* Aromatic plants such as *Cymbopogon citratus, Polygonum minus, Citrus hystrix, Languas galanga, Cinnamomum zeylanicum, Michelia champaca* and *Cananga odorata* are mainly used in food and personal-care products. The processing and extraction of these plants by the local herbal industries for botanicals or essential oils, is still in infancy and rudimentary.

INSTITUTIONAL BACKGROUND.

The Forest Research Institute Malaysia (FRIM) is a statutory research institution, governed by the Malaysian Forestry Research and Development Board, under the Ministry of Primary Industries. Its main campus is in Kepong, with an additional five field stations located throughout the country. Its mission is to promote the sustainable management and optimal utilisation of forest resources by generating knowledge and technology through research, development and application. FRIM is primarily involved in forestry research, to provide the support for the Forestry Departments, private concession holders, and the vast wood-based industries in the country.

FRIM currently has a total of 503 staff, 163 of whom are researchers. The research in FRIM is organized under 7 divisions. The Natural Forest Division looks into the silviculture and management of a variety of forest types including the hill dipterocarp forests, peat swamp forests and the mangrove forests. The Forest Plantation Division investigates on problems of silviculture and management of plantation forests mainly involves research in areas of tree improvement, nursery and seed and plant propogation. The Enviromental Science Division works in areas of forest bio-diversity, forest biology, plant protection, park management and urban forestry. The Forest Products Division investigates into timber properties, their utilisation, protection, as well as non-wood forest products. The Wood Chemistry Division looks into modification of wood into products, energy from biomass and chemicals from wood. The Medicinal Plants

Division conduct research in the field of medicinal plants especially those from the forests. The research activities in FRIM are further enhanced through collaboration with other agencies and institutions, both local and international.

MEDICINAL PLANTS DIVISION

The Medicinal Plants Division is established in January 1995. It was given the mandate by the Government to coordinate natural products and medicinal plants research in the country. Its main objectives are i) to identify bioactive plant principles which have the potential to be developed as lead compounds in drug research. ii) To assist the local herbal and traditional medicine industries through development of modern techniques in the production of herbal products. iii) To prepare comprehensive ethnobotanical information and guidelines on the propogation of medicinal plants. iv) To upgrade competency of scientists, research capacity and infrastructure through collaboration with other research organisations, either locally or overseas.

Under the Seven Malaysian Plan (RM 7- 1996-2000), the Medicinal Plants Division has adopted a strategy of both short term and long term planning to guide medicinal plant research in Malaysia. The short term plan includes: i) documenting of ethnobotanical and ethnomedical information. ii) establishing standard procedures for the identification of marker compounds and for assesing the safety of medicinal plant for herbal products as part of a collaborative effort within the Malaysia Herbal Monograph Commitee. iii) developing modern processing technologies to convert phytochemicals into high quality and safe herbal products. The long term plan involves research areas with the objective to isolate bioactive components or lead compounds for drug development and to develop biotechnological tools for screening and isolating biological active substances from diverse bioresources.

RESEARCH PROGRAMMES

Research programmes conducted by the Medicinal Plants Division were divided into 5 task areas.

1. Identification of antimicrobial and antiinflammatory principles from selected local plants and fungi.

2. Utilisation of oleoresins and essential oils from selected plants for fragrances, flavours and related products.

3. Utilisation of local plant extracts for the development of herbal and health-care products.

4. Development of bioinsecticide and insect repellent products from extracts of some Malaysian plants.

5. Documentation of medicinal plants and fungi and their associated products in Malaysia.

Most of the projects involved in the programmes were funded by grants under the Intensification of Research in Priority Areas (IRPA) programme or by international organisations. Several local herbal, pharmaceutical and agriculture industries ie. Nona Roguy, Ho Yan Hor, Arjuna, Global Herbs, Sime Darby, KESEDAR, KADA have shown their interest in participating in the medicinal and aromatic plants cultivation, processing, scale-up production and marketing of medicinal and personal-care products.

Presently, FRIM is the lead agency in coordinating a biotechnology partnership programme with MIT(USA). The Malaysia-MIT (USA) biotechnology partnership programmes will mainly focused research on the use of biotechnology for mass propogation of medicinal plants and production of high yield of bioactive metabolites for use in medicinal and nutraceutical products. It is hoped that this programme will strengthen collaborative ties between participating institutions in Malaysia as well as upgrade the various infrastructure and expertise in medicinal plants research.

The chemistry of Mongolian medicinal plants

Ladies and Gentlemen, our colleagues!

I am really happy that I have an opportunity to present a brief information about Mongolia, Mongolian sciences and especially the investigations in the field of chemistry of natural products.

As you know Mongolia is a large landlocked country, measuring 1.5 thousand square km in area - about three times the size of France. The capital and largest city of our country is Ulaanbaatar. The Southern third of Mongolia is dominated by the Gobi Desert. Much of Mongolia covered by grassland. Less than 10% of the land is forested, mostly in the north. Mongolia is also one of the highest countries in the world, with an average elevation of 1580 meters. Mongolia is a land of extremes. So one day you are walking in T-shirt and sandals, the next day you need an overcoat and boots, then the following day it is back to T-shirts. Because of it the flora is pretty interesting and not ordinary.

There are over 2500 species in Mongolian flora among them 700 species of medicinal plants that are used as the constituents of more than 10 thousand prescriptions of Mongolian traditional medicine. Natural products chemistry is one of the main research subjects in Institute of Chemistry and Chemical technology of the Mongolian Academy of Sciences. The investigation of natural products was founded in 1972 in the Laboratory of plant chemistry of our Institute. Our laboratory now has 14 researchers, 3 of them Doctor of Sciences and 4 -- has Ph. degree. Now we are engaging in chemical studies of Mongolian traditional medicinal plants.

One of the more interesting field of our investigation is the study of Mongolian endemic plants. About 250 species of endemic plants grown in Mongolia. More than 300 biologically active compounds such as alkaloids, coumarins, flavonoids, xanthones and lignans were isolated, purified and structurally elucidated from different species of medicinal plants grown in Mongolia by our laboratory. Here you can see the list of medicinal plants studied at our laboratory. About 60 new compounds were found and structurally characterized by means of chemical and spectral analysis . Here in Table 1 you can see the

structure of some new compounds. Some of them have new structural skeleton. There are coumarins and their glycosides, diterpenoid, isoquinoline, quinolizidine and aciklic alkaloids, xantons, iridoids and others. These new compounds were isolated from a small partion of hundreds Mongolian traditional and herbal medicine.

I think It is very interesting that all the new compounds isolated from Mongolian species has a more hydroxy group than the corresponding known compounds. Thus, it is show that the chemical constitution of the plant grown in Mongolia always possess higher oxidized status.

We are also investigating the essential oil of aromatic plants. So the monosesquiterpenes composition of more than 80 species of aromatic plants were studied and about 3 thousand compounds were identified.

Also we collaborate with our pharmacologists in the field of investigating the pharmacological properties of some new compounds, major compounds and crude extracts of Mongolian medicinal plants. For example, thalimonjn a new alkaloid isolated from Thalictrum simplex has an anti virus activity against the virus Herpes.

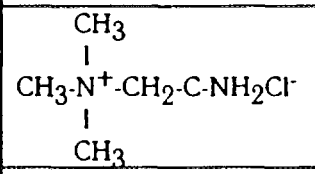
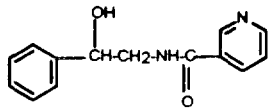
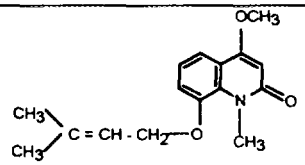
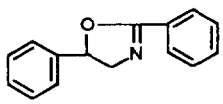
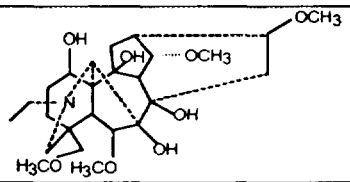
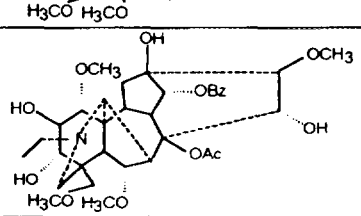
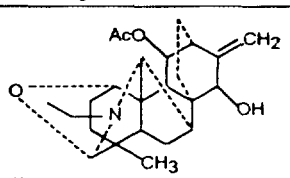
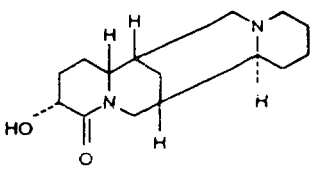
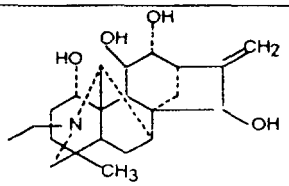
Last time the technology of the preparations "Achillo" from the overgrown part of Achillea asiatica, "Gentihol" from Gentiana barbata, "Halehol" from Halenia corniculata with gall-separating and hepatoprotective activity, "Stellerol" from Stellera chamaejasme with antibacterial activity, 'Salorid' from Salsola laricifolia with immunostimulation activity and others has been elaborated in our laboratory.

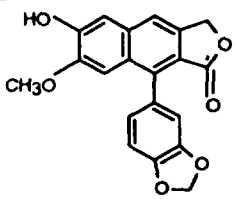
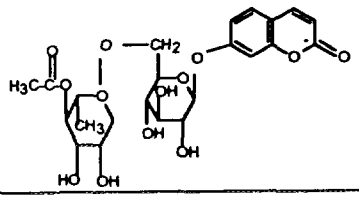
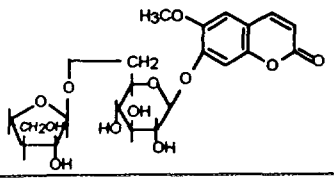
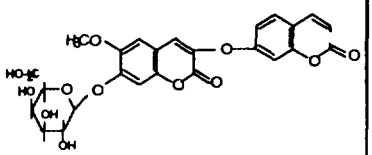
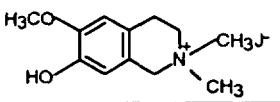
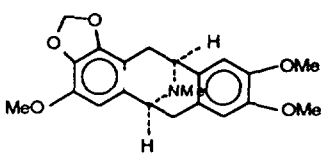
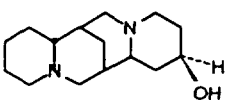
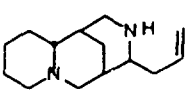
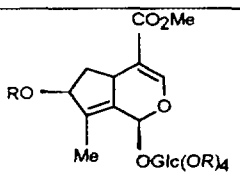
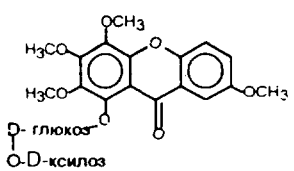
The main compound of Stellera chamaejasme - daphnoretin the bicoumarine has demonstrated an optical bleaching activity. Laboratory and pilot scale processing experiments show that number of quality characteristics of the bleached products was better than those of cashmere and wool bleached by "Uvitex UV-210", optical bleaching agent ("Ciba-Geigi" Switzerland).

At least I want to say that we always will be very happy to collaborate with foreign scientists in such field. Thank you for your attention.

Table 1.

The structures of some new compounds from Mongolian flora.

No	Trivial name(s)	Formula	Structure	Sources
1.	Kalidine	$C_5H_{13}NOCl$		Kalidium gracile
2.	(-)N-nicotinoil-2-phenyl-2-oxyethylamin	$C_{14}H_{14}N_2O_2$		Oxytropis muricata
3.	Daurine	$C_{16}H_{19}NO_3$		Haplophyl. dauricum
4.	Oxytripine	$C_{15}H_{13}NO$		Oxytropis trichophyso
5.	Tursoline	$C_{25}H_{41}NO_8$		Aconitum turczanin.
6.	Altaconitine	$C_{34}H_{47}NO_{12}$		Aconitum altaicum
7.	11-Acetyl-1,19-epoxy-denudatine	$C_{24}H_{33}NO_4$		Aconitum barbatum
8.	(+)3α-hydroxy-lupanine	$C_{15}H_{24}N_2O_2$		Ammopipt. mongolicus
9.	Turpelline	$C_{22}H_{33}NO_4$		Aconitum turczanin.

10.	Daurinol	$C_{20}H_{14}NO_6$		Haplophyl. dauricum
11.	Dauroside A	$C_{23}H_{28}O_{13}$		Haplophyl. dauricum
12.	Lariside	$C_{21}H_{26}O_{13}$		Salsola laricifolia
13.	Chamaejasmoside	$C_{25}H_{22}O_{12}$		Stellera chamaejas.
14.	N-methylcoripalline	$C_{12}H_{18}NO_2I$		Corydalis stricta
15.	(-) - thalimonin	$C_{21}H_{23}NO_5$		Thalictrum simplex
16.	13-epi-hidroxy-spartein	$C_{15}H_{26}N_2O$		Thermopsis mongolica
17.	Desoxyangustifoline	$C_{14}H_{24}N_2$		Thermopsis mongolica
18.	Maijoroside	$C_{12}H_{18}NO_2$		Plantago major
19	1-О-примве-розил-2,3, 4,7-тетра-метокси-ксантон	$C_{28}H_{34}O_{16}$		*Halenia corniculata*

LIST OF STUDIED PLANTS

1. Ferula akitschkensis B. Fedtsch.
2. Artemisia santolinifolia Turcz ex. Bess.
3. Achillea asiatica Serg.
4. Kalidium gracile Fenzl.
5. Salsola laricifolia Turcz et litv.
6. Ephedra sinica Stapf.
7. Ammopiptanthus Mongolicus (Maxim) cherg Fil
8. Oxytropis muricata
9. O. strobilacae Bunge
10. O. trichophyso Bunge
11. Thermopsis lanceolata R.Br.S.
12. Corydalis stricta Steph ex. Fisch
13. Scutellaria baicalensis Georg
14. Peganum harmala L.
15. P. nigellastrum Burge
16. Aconitum altaicum Steinb.
17. A. baicalense Turcz ex. Rapaics
18. A. barbatum pers
19. A. Turczaninowii Worosch
20. A. volubile Pall ex. Koelle
21. Haplophyllum dauricum (L) G.Don fil
22. Stellera chamaejasme L.
23. Bupleurum scorzonerifolium Willd.
24. B. sibiricum Vest.
25. Chiazospermum erectum L.
26. Halenia corniculata
27. Gentiana species
28. Thalictrum species
29. Thermopsis mongolica
30. Hippophae rhamnoides
31. Astragalus species
32. Cistanche deserticola

Herbal Medicne : An answer to primary health care among Filipinos

by

Julita E. Quinto

Department of Horticulture, University of the Philippines ,Los Banos, Laguna , Philippines

Herbal Medicine : An answer to primary health care among Filipinos

Introduction

Researches on herbal medicines are increasing tremendously in the Philippines. Different related studies are conducted on government and non government institutions. Some foreign financial assistance are also made some researches possible.

Through the combined efforts of researches from different sectors, the scientific basis on the use of some Philippine medicinal plants, formulation and recommendations sre established. These medicines from plants which are used for adequate health care are found also cheap, effective and accessible hence herbal medicines are commonly used side by side with synthetic medicines.

Studies on Herbal Medicines

Concerted efforts of different government agencies are devoted to establish scientific basis on the utilization, formulation and recommendation of herbal medicine. Relatively, the National Integrated Research Program on Medicinal Plants (NIRPROMP) , Philippine Council for Health Research and Development recommend ten medicinal plants for primary health care. Thse are:

Vitex negundo L. - for cough, asthma, fever

Mentha x cordifolia Opiz ex Fresen - analgesic

Blumea balsamifera (L.) DC. - diuretic; anti-urolithiasis

Carmona retusa (Vahl) Masam - for gas pain

Quisqualis indica L. - antnelmintic (ascariasis)

Psidium guajava L. - antiseptic; for gingivitis and mouth infection

Cassia alata L. for tinea flava, ringworm, athlete's foot and scabies

Pepperomia pellucida (L.) HBK - for gout and lowers blood uric acid

Allium sativum L. - lowers cholesterol

Momordica charantia L. - for mild diabetes mellitus

From these clinically tested plants., *V. negundo*. *C. retusa* , *B. balsamifera* *M, charantia* are processed and manufactured in tablet form and *C. alata* in ointment form by the Herbal Pharmaceuticala Processing Manufacturing Plant of the Department of Health (DOH) in Tuguegarao, Tacloban, Davao and Cotabato, Philippines. The processing plant manufacture 2,000,000 assorted tablets per month. Different outlets are government hospitals, rural health centers and some barangay or community based drugstores.

The awareness of Filipinos to medicinal plants is augmented by information campaigns. This is made possible through publication of pamphlets, seminars, trainings, radio braodcasts , television programs and others. To mention one, an outreach program for primary health care based in the University of the Philippines Los Banos, where I am a member, promotes the use of medicinal plants likewise teaches preparation of medicines from plants through kitchen technologies since 1975.(See Appendix 1 and 2).

Problems Encountered

1. Short span of shelf life on lagundi syrup

References

Banaynal, E.T. 1997. Personal Communication.

De Padua, L.S. 1996. Kitchen Technologies .

Schwefel, D. and E.D. Palazo.(eds.) 1995. DOH - HAMIS. The federation of the Hamis winners in the Philippines. Manila,Philippines.

Traditional Medicine Program.DOH-Phil.1992. Gabay sa Paggamit ng 10 Halamang Gamot.

Appendix 1

Outreach Program - Medicnal Plants for Primary Health Care

Type — Community based

Institution — Non government Office - University

Site of Project — Los Banos, Laguna

Proponents — Institute of Biological Sciences
c/o Prof. Ludivina S. De Padua
College of Arts and Sciences
UP Los Banos, Laguna,Rgion IV

Objectives

1. To create awareness of the importance of plants in the treatment of common ailments.
2. To help establish a scientific basis for the use of plants in medicine.
3. To help provide adequate health care to the poorer sectors of the population.
4. To disseminate information on the proper utilization of medicinal plants.

Services /Programs Activities

1. training and seminars
2. propagation of herbal plants
3. processing of herbal plants into syrup, ointment, teas, liniment
4. production of manuals

Beneficiaries

1. general public
2. government and non government organizations
3. initially 13 baranggays in Los Banos, Laguna
4. target beneficiaries are low income group

Benefits

1. in general lower cost of medication through use of herbal medicine
2. seedlings
3. IEC materials on use of herbal medicine

Appendix 2

Personnel

2 part time from UPLB

Facilities

Ethnolaboratory

herbal garden

Sources of Funds

1. award money

2. proceeds of sale of medicine and manuals

Herbal preparations

Lagundi syrup	for cough, fever and colds
Ginger lozenges	for sore throat and cough
Ginger tincture	for shallow cuts
Capsicum liniment	for muscular aches and joint pains
Akapulko ointment	for fungal skin infection

Vitex negundo L. - for cough, asthma, fever

Mentha cordifolia Opiz ex Fresen - analgesic

Blumea balsamifera (L.) DC - diuretic; anti-urolithiasis

Carmona retusa (Vahl) Masam - for gas pain

Quisqualis indica L. - anthelmintic (ascariasis)

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Allium sativum L. - lowers cholesterol

Momordica charantia L. - for mild diabetes mellitus

Training Course on Industrial Exploitation of Indigenous Medicinal and Aromatic plants .

17 June to28 June 1997.

Country Report
Sri lanka

Dayangani Ariyaratne
Assistant Director (Drug Research)

Bandaranaike Memorial Ayurvedic Research Institute.

Introduction

The extent to which the indigenous system like Ayurveda rely on "herbal medicine" is well known. Dependence on herbs is socially desirable because it encourages self reliance through appropriate health technology in accordance with the cultural heritage and availability of natural resources. It is economically more advantageous because herbal medicines are less expensive than synthetic drugs. It is now generally accepted that herbal medicines properly prepared and used are free from side effects. This unfortunately is not the case with some of the synthetic drugs. The last mentioned fact has attracted the attention of the scientist and health administrators towards the desirability of using herbal medicines. The interest the World Health Organisation is taken in the development of traditional system of medicine may be partly ascribed to this reason.

Few questions in the field of Ayurveda have, in recent times, attracted greater public attention than the subject of adequate supply of herbal medicines. Over the centuries the practice has been to obtain these herbs from the naturally grown forests, herbaria or home gardens. Forest was the major source of supply of herbs. What ever the source may have been there was always an adequate supply of authentic drugs at almost no cost. This position has changed drastically in recent years.

In predominantly agricultural countries like Srilanka the increasing population is bound to result in a pressure on the limited extent of arable land. Clearing of the jungle for colonisation schemes and chena (slash and burn) cultivation led to the disappearance of much of the forests. This has resulted in the decline of valuable medicinal plant resources.

The indiscriminate exploitation has led to an alarming decrease in the supply of herbs. In case of some others there has been no proper organisation for collection and curing. Two of the well known examples are aralu (Terminalia chebula) and Nelli (Phyllanthus emblica).

Activities of my Institution

Bandaranaike Memorial Ayurvedic Research Institute, Srilanka

The research institute was a specious and valuable building standing on aland of 17 acres. It was on the recommendation of Pandith Shiva Sharma (a well known Ayurvedic physician from India) that the research Institute at Nawinna was set up. It was named in honour of late Mr: S.W.R.D.Bandaranaike . Primeminister of Srilanka.

We are presently engage in production of drugs for research purposes and creating an awareness among the people of the importance in conserving medicinal and aromatic plants.

Also we have the following divisions:

1. Clinical research
2. Literary research
3. Drug research
4. Quality control and standerdization
5. Botany

Current situation and future trends

1. About 144 plant materials are imported from India and neighbouring countries. Ninety one items worth about Rs.32 million were imported in 1994. to Sri-Lanka.

2. There is no systematic growing of medicinal plants by the private sector except in a very few cases like growing of Aloevera for cosmetics,Gloriosa superba for the pods and polpala for export on a very small scale.

3. There are five arboretums maintained by the Department of Ayurveda,in four different climatic zones in the country.

a. Nawinna	- 14 acres
b. Kotte	- 3 acres
c. Bathgoda	- 65 acres
d. Girandurukotte	-150 acres
e. Pattipola	- 25 acres

4. Small herbaria are maintained in district Ayurvedic hospitals.

5. Few Ayurvedic practitioners have their own herbal gardens on very small scales where they grow all what they need.

6. There are 84 private Ayurvedic drug manufacturing units registered under the department of Ayurveda.
   Their products are,

   1. Arishta and assawas (Herbal wines)]
   2. Different types of concentrated decoctions which are called Quathas.
   3. Tinctures and extracts.
   4. Pills
   5. Powders
   6. Medicated oils and ghee
   7. Mineral preparations

7. State owned Ayurvedic drugs Co-operation, established in 1965 is the largest drug production unit which caters to the needs of the government hospitals,central dispensaries and the public.

In large scale preparation of drug it is recommended to educate the manufactures of the importance of exploitation and conservation of medicinal and Aromatic plants for the benefit of the future generations.

Country Report : Thailand

Anan Chaikitwattana
Thai Herbal Products Co., Ltd.
Bangkok, Thailand

part II (cont. Dr. Ratana Teeyapant)

Ladies and Gentlemen,

I would like to report some of the products manufacturing by The Government Pharmaceutical Organization . There are 15 herbal products with the total sales 1 million dollars in 1996, a growth rate of 30% and these will transfer to my company next year after the new factory has been finished.

Thai Herbal Products company is a joint venture company set up between the Government Pharmaceutical Organization and private sectors to produce herbal medicines by the technology transfered from the Government Pharmaceutical Organization. The objectives of the company is to promote the use of indigenous raw materials. This will lead to reduce of imported western drugs and will pave the way for future exports to bring in foreign currencies.

EXAMPLES OF THE HERBAL PRODUCTS

1. SENNA PRODUCTS

Senna

Scientific Name	*Cassia angustifolia* Vahl
Family	Fabaceae (Leguminosae)
Part Used	Dried leaves and dried pods.
Thai Medicinal Uses	Both leaves and pods are used as laxatives. The leaves cause abdominal pain more than the pods.

The Government Pharmaceutical Organization produces Senna laxative in two modern forms. Both are packed in convenient, and easy-to carry packages. They are:

Senna Infusions

Composition	Each bag contains total Sennosides equivalent to 25.0 mg Sennoside B.
Therapeutic Use	Mild laxative
Application	Steep 1 bag of Senna infusion in 1 cup (150 ml) of hot water (70 C) for 10 to 20 minutes.
Dosage	One bag once a day. At bed time or in the morning.
Packing	Each box contains 5 envelopes, each envelope contains 5 bags.

Senna Tablets

Composition	Each tablet of powdered Senna pods contains total Sennaosides equivalent to 7.5 mg Sennoside B.
Therapeutic Use	Mild laxative
Dosage	Adults: 3-4 tablets at bed time. Children age 6-12 years : 1-2 tablets at bed time or in the morning.
Packing	Each envelope contains 10 tablets.

2. MA-WAENG LOZENGE

There are 5 principal ingredients.

2.1 Ma-waeng

Scientific Name	*Solanum trilobatum* Linn.
Family	Solanaceae
Part Use	Dried fruits
Thai Medicinal Use	Mucolytic, antitussive, antipyretic, diuretic, and tonic

2.2 Sacred-Basil

Scientific Name	*Ocimum tenuiflorum* Linn.
Family	Lamiaceae (Labiatae)
Part Used	Dried leaves
Thai Medicinal Uses	Antispasmodic, anti-flatulent, reduces abdominal pain, carminative, expectorant, mucolytic, antiemetic, relieves chronic cough.

2.3 Brazil Wood

Scientific Name	*Caesalpinia bonduc* (Linn.) Roxb.
Family	Fabaceae (Leguminosae)
Part Used	Dried leaves
Thai Medicinal Uses	Carminative, reduces abdominal pain, anti-flatulent, wound healing in the throat.

2.4 Tan-Mon

Scientific Name	*Vernonia elliptica* Dc.
Family	Asteraceae (Compositae)
Part Used	Dried leaves
Thai Medical Uses	Treatment of intestinal ulcers, control of digestion.

2.5 Kha-Min-Oi

Scientific Name	*Curcuma zedoaria* Roxb.
Family	Zingiberaceae
Part Used	Dried rhizomes
Thai Medical Uses	Antipyretic, treat cold feet, expectorant, antiemetic, carminative, anti-diarrhea, and treatment of intestinal ulcers.

Ma-waeng Lozenges

Ma-waeng Lozenges have been tested and found to have no acute toxicity. They have been formulated in a convenient shape and size. Each of the herbal ingredients used has undergone quality control and is standardized to ensure uniformity. Furthermore, lozenges are sterilized and therefore are not contaminated with microorganism. Besides having a highly effective herbal medicine for the market, we are preserving our Thai Traditional pharmacopoeia too.

3. GARLIC

Garlic

Scientific Name	*Allium sativum* L.
Family	Liliaceae
Part Used	Bulbs
Thai Medicinal Uses	Carminative, treatment of ring worm and *Tinea vesicolor*, antitussive, expectorant and stimulates digestive system.

Chofibrin

Composition	350 mg of garlic extract per capsule
Therapeutic Uses	Anti-cholesterol and fibrinolytic
Dosage	Two capsules a day, one after breakfast and one after dinner; or as directed by a physician.
Packing	10 capsules in an aluminum foil pack.

4. PHLAI

Phlai

Scientific Name	*Zingiber cassumunar* Roxb.
Family	Zingiberaceae
Part Use	Mature Rhizome
Thai Medicinal Use	Anti-inflammatory, carminative, anti-diarrheal, and in control menstruation
Plygesal®	Thailand Institute of Scientific and Technological Research formulated the cream using Phlai oil for reducing sprains and bruises. Plygesal is the trade name of this cream which is produced by The Government Pharmaceutical Organization.
Composition	Volatile oil 14% (w/w)
Therapeutic Uses	Anti-inflammatory; reduce soreness, inflamed muscles, bruises and sprains.
Application	Rub and gently massage the cream onto the inflamed area three times a day.

5. TURMERIC

Turmeric

Scientific Name	*Curcuma longa* Linn.
Family	Zingiberaceae
Part Used	Dried rhizomes.
Thai Medicinal Uses	The rhizome of turmeric has been used as bactericide, fungicide, anti-inflammatory and cholagogue. The volatile oil of turmeric has been found to relieve stomachache, discomfort due to excess gas in the stomach and intestine.

Curmin Capsule

Curmin capsule is one of the medicines from the ready-to-use Herbal Medicine Development Project which the Government Pharmaceutical Organization produces by a modern, hygienic process and are sterilized. They are packed in aluminum foil to protect against moisture, and are suitable as a household remedy and convenient to carry.

Therapeutic Uses Carminative, anti-flatulent, and in treatment of dyspepsia (indigestion)

Dosage and Application Two capsules four times a day after meals and before bed time or as prescribe by a physician. Use should be discontinued immediately if there is diarrhea.

6. ALOE VERA

Scientific Name *Aloe vera* (L.) Burn. f.

Family Liliaceae

Part Used Gel from leaves

Aloe Gel

The Government Pharmaceutical Organization has developed Aloe Gel, a clear gel preparation of Aloe vera by using an aseptic technique. Professor Vivat Visutikosol M.D., Ramathibodi Hospital, Mahidol University and his coworkers treated mild burns and scalds with Aloe gel on 13 patients. By examining the size and texture of the burns or scalds with an electron microscope, they showed that the Aloe gel accelerated the healing process.

Composition 85% Aloe gel

Therapeutic Uses Treatment of burns and scalds

Application Apply on the burned and scalded area two to three times a day.

Packing 30 gram per tube.

7. PHAYA YO

Scientific Name	*Clinacanthus nutans* (Burm.f.) Lindau
Family	Acanthaceae
Part Used	Semi-mature leaves
Thai Medicinal	Thai traditional book indicates use of fresh leaves for the treatment of burns, insect bites and itching.

Phaya yo cream

Composition	Phaya Yo cream contains 40 mg extract per gram.
Therapeutic Use	For the treatment of Herpes simplex virus on the skin. This includes initial and recurrent infections on either the reproductive organs or on the lips.
Dosage and Application	Apply around infected area 4 times a day, For 5 consecutive days. If the symptom still appears, the cream can be used five more days.
Precaution	Do not apply around soft tissue eg. Oral and eyes.

8. CITRONELLA

Scientific Name	*Cymbopogon nardus* Linn. , *C. winterianus* Jowitt
Family	Poaceae (Gramineae)
Part Used	Leaves and sheaths
Thai Medicinal Uses	Citronella has been used as an insect repellent for a long period of time.

Mosquito Repellent

Composition	Citronella oil 6% (v/v)
Therapeutic Use	Repel mosquitos for 4-5 hours
Application	Apply directly on arms and legs or open skin.
Precaution	1. Do not apply on children under 6 years old. 2. Do not apply on face or sensitive area.
Packing	30 ml per bottle

These are some of herbal products in Thailand. Another products which were not showed on the slides are Lingzhi or *Ganoderma lucidum* preparations. They are:

1. Lingzhi tablets
2. Instant Lingzhi teas
3. Lingzhi tea
4. Lingzhi slice
5. Lingzhi beverages

Ladies and gentleman, We are now co-ordinating for various joint projects with the Government Pharmaceutical Organization and there will be more than 20 herbal products in 1997.

Thank you for your attention.

Medicinal and Aromatic Plants (MPA) in Thailand

Dr. Ratana Teeyapant
R&D Institute
Government Pharmaceutical Organization
Bangkok, Thailand

Mr. Chairman,

Ladies and Gentlemen,

I would like to take this opportunity to make a brief introduction on the utilization of medicinal and aromatic plants (MAP) in Thailand.

1. General Concept

Thailand is a tropical country with different climate and geographical features in its different regions. It has an abundance of diverse natural resources. The use of medicinal and aromatic plants (MAP) is widespread as traditional or herbal medicine. There are more than 10,000 species of plant in Thailand, of which about 1,400 are listed as indigenous medical and aromatic plants (MAP) in Thai Traditional Materia Medica. Registration of herbal remedies at the Food and Drug Administration lists about 5,000 preparations, which have been studied for possible medical application and used by major parts of population. Even where modern medicine is readily available, they still depend heavily on herbal medicine. National Drug Policies also stress on exploring intensively the therapeutic potential for herbal medicine for safe and efficacious use, especially, in the field of primary health care and attempt to integrate traditional and modern systems of medicine. During the last decade, there has also been a growing interest in herbal medicine as an alternative system of medicine.

2. Trends in the use of herbal medicine

Herbal medicines have two obvious characteristics which are quite far from chemical drugs. One is its long-term use and the other is the use of essentially crude medicines.

Nowadays, the Thai people interest has turned towards natural products because the modern health care is expensive and has undesirable side effects.

Therefore, the use of herbal medicine in Thailand has become a social necessity. Harvesting of medicinal plants from the wild and production of herbal medicine have become viable industries in Thailand. Certain medicinal plants such as cardamons, ginger, curcuma and black pepper constitute important export commodities for Thailand, earning valuable currencies.

A single herb can contain literally hundreds of natural constituent and a prescription includes several hundred natural constituents. It is impossible to attempt to isolate each active ingredient from each herb, particularly in the case of preparations, the time and cost would be tremendous. Although the users could not identify the active compounds responsible for a specific pharmacological effect, but they did know that the plant had specific benificial effect through trial and error. Due to the lack of scientific information regarding the composition of the active ingredients in most herbal preparation, most physician are still reluctanct to prescribe and recommend those formulations to the patients.

3. The Government Pharmaceutical Organization

The Government Pharmaceutical Organization (GPO), which is the state enterprise under the Ministry of Public Health, was established in 1966.

One of the main's functions is manufacturing and producing herbal medicines, in order to substitute modern medicine, according to the policy of Ministry of Public Health. GPO, the centre for the development of plant-based products, undertakes phytochemical research of indigenous plants available in the country such as extraction, characterization of naturally occuring constituents, establishment of reference standards and monitoring of biological activities. The results of the laboratory-scale process can be up-scaled to bulk drug production for manufacturing purposes. All production phases take into consideration the Good Manufacturing Practice (GMP) on manufacture and quality assurance. There are many herbal medicine products, which have been completely researched and manufactured by GPO and will later be reported by Mr. Chaikitwattana.

4. Problems and constraints in research for the development of herbal medicines

The research and development of herbal medicines is impeded by :

1. Lack of scientific data, e.g., data concerning cultivation, proper time for collection, pharmacological and toxicological actions etc.

2. The profile of development is not clear and the principal direction of research and development of herbal medicines is also missing.

3. Limited number of experts available in certain fields.

4. Accessibility of clinical trial. There is little problem in finding physician to use unmodified, medicinal plant derived drugs in clinical study. However, if a drug contains active substances isolated from medicinal plants or by chemical synthesis, physician always hesitate to cooperate in the study.

5. Lack of technology and research equipment for isolation and purification of active ingredients from medicinal plants including technology in organic synthesis, standard production, stability of active substances. In additon, research equipment is very expensive.

5. Recommendation

1. Proper integration of traditional and modern medicine should be encouraged. They should not be competitive but rather supplementary to each other.

2. More active cooperation among countries in the exchange of information on herbal medicine.

3. Standardized methodologies of herbal medicine should be widely disseminated for the effectiveness of their usage.

Ladies and gentleman, there is no doubt that the full and proper use of herbal medicine will make an important and distinct contribution to our efforts to achieve health for all.

Thank you.

ICS-UNIDO TRAINING COURSE ON INDUSTRIAL EXPLOITATION OF MAPs
17-27 JUNE 1996, BEIJING
CHINA

Nguyen Kim Bich
Institute of Materia Medica
SR. Vietnam

First of all, I would like to present some information about my Institute's activities. Institute of Materia Medica (IMM) was set up in 1961, being a National Research Centre for Medicinal and Aromatic Plants(MAP), used in manufacture of Traditional and Modern Medicine. It has the functions and the tasks as follow:

--Carry out the exploitation of medicinal resources, executing the inventory of medicinal material rersources in the whole country.
--Carry out the researches for creation of sources of materials for manufacture of medicine, at the service of Pharmaceutical Industry and TRM, including the acclimatization revitalization, hybrization of new strains with high quality , the Technology of protection, regeneration and preservation of MAP germ plasm.
--Carry out multidisciplinary researches including chemical, pharmacological and clinical studies aiming at confirming the therapeutic value of local medicinal plants and creating new products for the manufacture of medicines, fragrances, cosmetics from MAP.
--Set up specifications for standardization and quality control of raw materials and pharmaceutical products from medicinal plants.
--Study new doses from MAPs to create medicines with high quality.
--Make information for medicinal plants and train post-graduated specialists on phmacognosia master and Ph. D. degrees on pharmacognosia and pharmacology of MAP.
--Establish internal and international scientific cooperation on the research and development of MAP
--Produce certain medicine with high therapeuctic value.

. Number of actual activities:

By the support of UNDP Organization, IMM is equipped pilot production facilities, some kinds of natural products with high therapeutic value had already been produced in the pilot scale, such as Artemisinine, Bidentine, ... these medicine had been produced in industrial scale.

Artemisine is one of antimalarial drugs being the main component of Artenmisia annua L., this one of the most important programme of our Institute which had been carried out from 1991 to 1995. The programme includes the breeding from wild plant condition to cultivated condition. Selecting the best germ plasm, cultivation technology, extraction, purification in laboratory and pilot scale. The production of artimisinine had also been produced in industrial scale.

The Artemisinine content is about 0.7% in the spontaneous plant and can reach 1-1.2% in the cultivated plants of which the yield is about 60-65%. Up to now we have produced one ton of pure Artemisinine, it reaches the great demand of the malarial patients in our country and also export to the other countries.

Bidentine is a traditional drug used for the treatment of hypertension, its active components were found as Triterpenoid saponine, these saponines were extracted from Achyranthes bidentata, having good effect in lowering cholesterol level in the blood.

At the present, we can produce in the processing chaine about 1000,000 capsules of Bidentine per year to supply for patients who are suffered from high cholesterol.

On going works:
IMM is carrying out multidisciplinary researches on some medicnal herbs which can have efficacy on cancer, diabetes, immunology regulation such as :
Stercularia barbata, Lamiaceae,
Papaya carica, Papayaceae,
Hediotis diffusa, Rubiaceae,
Panax pseudoginseng, etc.

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diagrams

ICS—UNIDO Training Course on
Industrial Exploitation of Indigenous Medicinal and Aromatic Plants
17—27 June 1997, Beijing, China

PROCEEDINGS(3)

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Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences

A "drug" is a agent that is used therapeutically to treat disease.

A drug may be defined as any chemical agent and/or biological product or nature product that effects living processes. Many drugs, including digitalis, cocaine, and other alkaloids, are of plant origin. Drugs may also be obtained from animal or mineral sources or microorganisms.

Drug Products

It Means a finished dosage form, for example, a tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.

Drug Substance

It means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to effect the structure or any function of the human body.

Synopsis of Important Principles

1) Drugs act by affecting biochemical or physiological processes in the body. Most drugs act at specific receptors. The action of a drug is characterised by two variables: the magnitude of the response and the concentration required to produce the response.

2) A specific drug acts only at one receptor but may produce multiple effects due to the location of the receptor in various organs. A selective drug acts on one receptor in a particular tissue at concentrations which produce little effect on the receptor in other organs. All drugs have multiple actions and it is usually preferable to use more specific or more selective drugs.

3) Drugs are molecules with characteristic physicochemical and pharmacokinetic properties. Knowledge of these properties helps to predict the behaviour of a drug in the body and is an important guide in the selection of appropriate doses and dosage intervals.

4) The special and simultaneously operating processes in pharmacokinetics are drug absorption, distribution, metabolism (biotransformation) and excretion. The rate at which these processes proceed and consequently the concentration of drug in the body, is influenced by many factors pertaining to the drug and its dosage form, to pathophysiological or genetic variables of the individual patient, and to effects of other drugs taken concurrently.

5) Many drugs are bound to plasma proteins. Changes in the binding of a drug due to drug interactions or diseases such as uraemia or chronic inflammation, affect its distribution and elimination in the body in a way which is predictable from its kinetic properties. When distribution equilibrium is obtained under steady-state conditions, the unbound concentration of pharmacologically active drug should be equal in plasma and in tissues, and at receptor and metabolic (excretory) sites.

6) Individual patients show a wide variation in response to the same dose of many drugs. Much of this variability in drug response between patients can be explained by individual kinetic factors, particularly genetically-determined differences in drug metabolism, and by the effects of intercurrent illness or disease states on pharmacokinetics or tissue response.

7) Drug dosage must be individualised if the desired therapeutic response with minimum side effects is to be obtained. The response to some drugs is better correlated with steady-state plasma concentrations than to dosage.

8) Rational drug prescribing involves a decision on whether or not to use a drug, and if so, selection of a suitable drug and regimen, consideration of compatibility between the drug and patient or any other drugs being given, a legibly written prescription, appropriate instruction of the patient about use of the drug and expectations from treatment and follow-up.

藥品之要件

外觀特性 EXTERNAL PROPERTIES

含量準確 ACCURACY

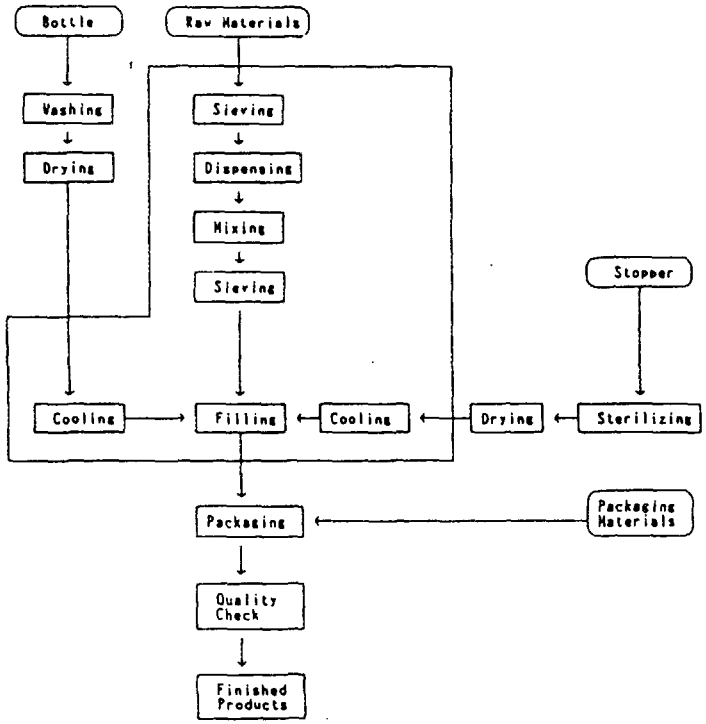
純度 PURITY

均勻度 HOMOGENEITY

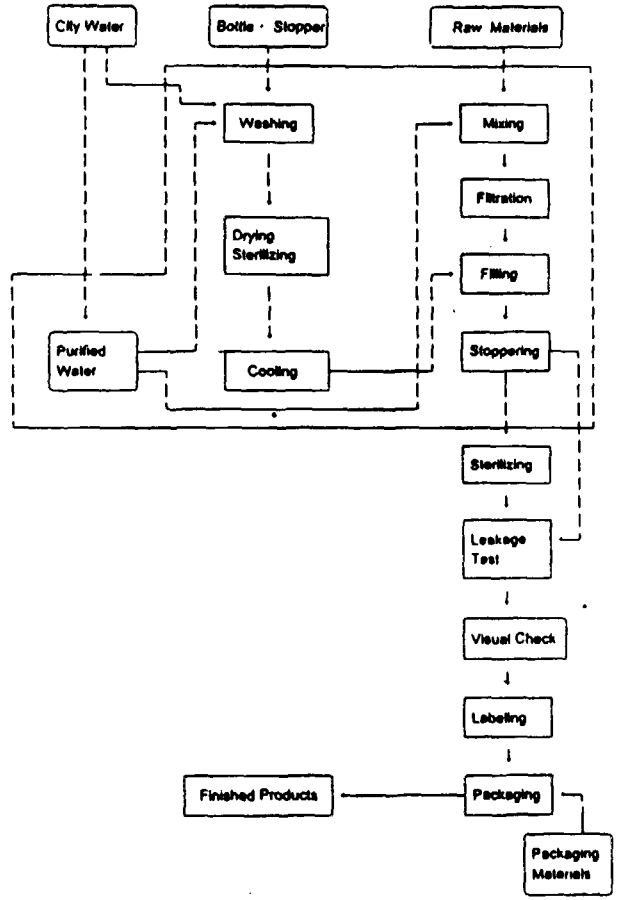
安定性 STABILITY

釋出特性 RELEASE CHARACTERISTICS

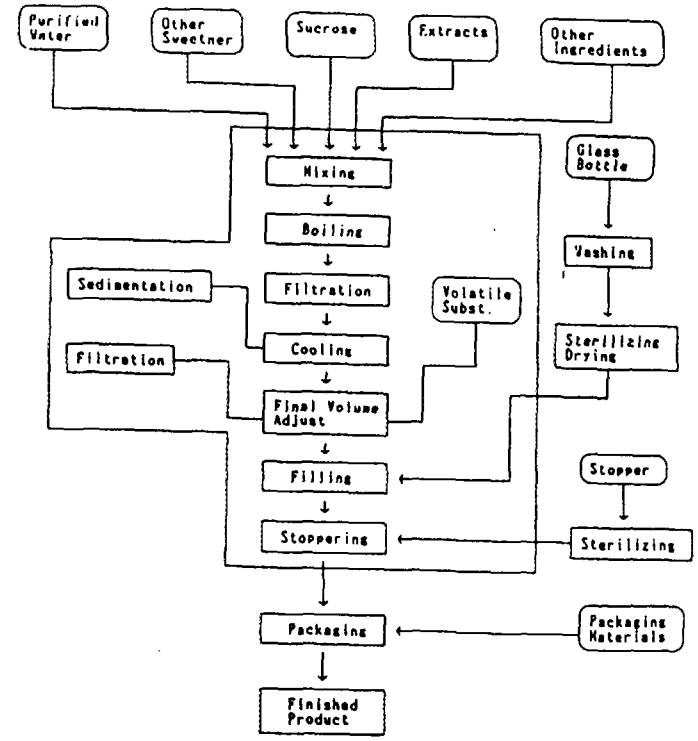
POWDERS



Oral Liquids



SYRUPS



QUALITY ASSURANCE OF PHARMACEUTICS

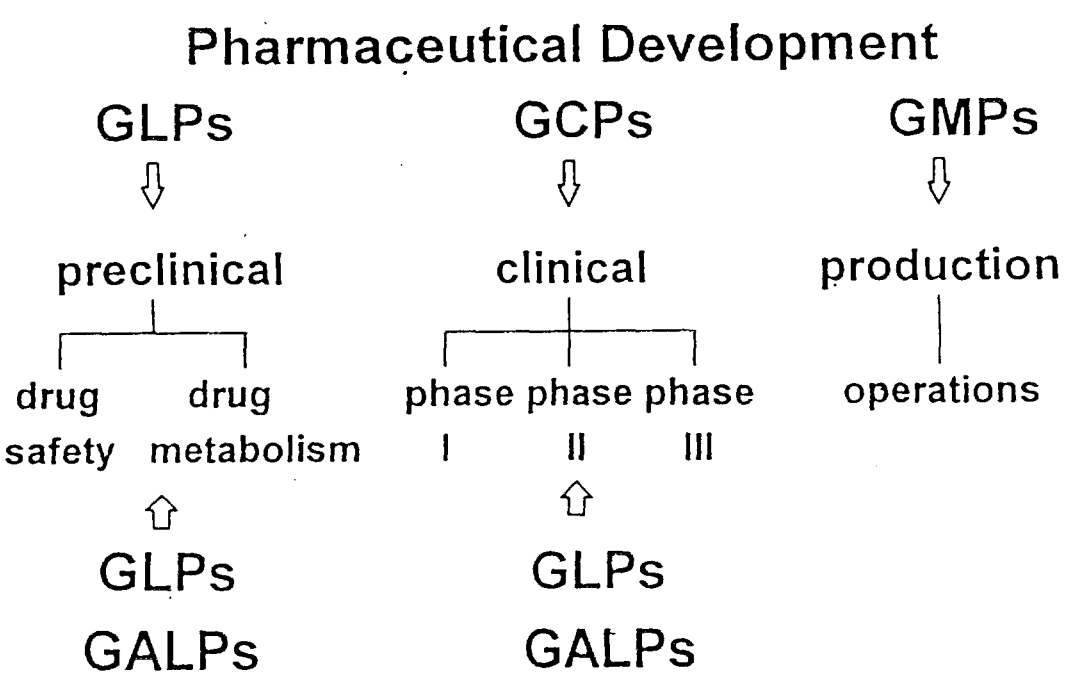
GLP: Good Laboratory Practice

GMP: Good Manufacturing Practice

GCP: Good Clinical Practice

GALP: Good Analytical/Automated Laboratory Practice

R&D QUALITY ASSURANCE COMPLIANCE



WORLD HEALTH ORGANIZATION

Good Practices for the Manufacture and Quality Control of Drugs

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be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

9.2 *Items for self-inspection*

Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel
(b) premises including personnel facilities
(c) maintenance of buildings and equipment
(d) storage of starting materials and finished products
(e) equipment
(f) production and in-process controls
(g) quality control
(h) documentation
(i) sanitation and hygiene
(j) validation and revalidation programmes
(k) calibration of instruments or measurement systems
(l) recall procedures
(m) complaints management
(n) labels control
(o) results of previous self-inspections and any corrective steps taken.

9.3 *Self-inspection team*

Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

9.4 *Frequency of self-inspection*

The frequency at which self-inspections are conducted may depend on company requirements.

9.5 *Self-inspection report*

A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results
(b) evaluation and conclusions
(c) recommended corrective actions.

9.6 *Follow-up action*

The company management should evaluate both the self-inspection report and the corrective actions as necessary.

9.7 *Quality audit*

It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 8, "Contract production and analysis").

9.8 *Suppliers' audits*

The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

9.9 Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards for active pharmaceutical ingredients (see section 18).

10. PERSONNEL

10.1 *Principle.* The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded as written descriptions. All personnel should be aware of the principles of GMP that affect them.

10.2 *General*

The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

10.3 The manufacturer should have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.

10.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

10.5 Steps should be taken to prevent unauthorized people from entering production, storage, and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

10.6 *Key personnel*

Key personnel include the head of production, the head of quality control, the head of sales/distribution, and the authorized person(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

10.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of (a) chemistry (analytical or organic) or biochemistry, (b) chemical engineering, (c) microbiology, (d) pharmaceutical sciences and technology, (e) pharmacology and toxicology, (f) physiology, or (g) other related sciences. They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

10.8 The heads of the production and quality control departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

(a) the authorization of written procedures and other documents including amendments;
(b) the monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of quality assurance;
(f) the approval and monitoring of suppliers of materials;
(g) the approval and monitoring of contract manufacturers;
(h) the designation and monitoring of storage conditions for materials and products;
(i) the retention of records;
(j) the monitoring of compliance with GMP requirements;
(k) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

10.9 The head of the production department generally has the following responsibilities:

(a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
(b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
(c) to ensure that the product records are evaluated and signed by a designated person before they are made available to the quality control department;
(d) to check the maintenance of the department, premises, and equipment;
(e) to ensure that the appropriate process validation and calibrations of control equipment are performed and recorded and the reports made available;
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

10.10 The head of the quality control department generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;
(d) to approve sampling instructions, specifications, test methods, and other quality control procedures;
(e) to approve and monitor analyses carried out under contract;
(f) to check the maintenance of the department, premises and equipment;
(g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control department are summarized in section 3.2.

10.11 *Training*

The manufacturer should provide training in accordance with a written programme for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

10.12 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.

10.13 Personnel working in areas where contamination is a hazard, e.g., clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, should be given specific training.

10.14 The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

10.15 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

10.16 *Personal hygiene*

All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

10.17 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from the production department together with the authorized person from the quality control department.

(h) Sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

3.3 The quality control department as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

3.4 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

3.5 Quality control personnel must have access to production areas of sampling and investigation as appropriate.

4. SANITATION AND HYGIENE

4.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *hygiene* please refer to section 10, "Personnel", and for *sanitation* to section 11, "Premises".)

5. VALIDATION

5.1 Validation studies are an essential part of GMP and should be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of processing, testing, and cleaning procedures.

5.2 *Process validation*
Critical processes should be validated, prospectively or retrospectively.

5.3 When any new master formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.4 Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process, should be validated.

6. COMPLAINTS

6.1 *Principle.* All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

6.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.

6.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

6.4 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the study of such problems.

6.5 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

6.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

6.7 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

6.8 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

6.9 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

7. PRODUCT RECALLS

7.1 *Principle.* There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

7.2 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of the sales and marketing organization. If this person is different from the authorized person, the latter should be made aware of any recall operation.

7.3 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of the hospital or pharmacy.

7.4 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

7.5 The distribution records should be readily available to the person(s) responsible for recalls, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

7.6 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

7.7 The effectiveness of the arrangements for recalls should be evaluated from time to time.

7.8 An instruction should be included to store recalled products in a secure segregated area while their fate is decided.

8. CONTRACT PRODUCTION AND ANALYSIS

8.1 *Principle.* Contract production and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. There must be a written contract between the contract giver and the contract accepter which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility.

8.2 *General*
All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

8.3 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.4 The contract should permit the contract giver to audit the facilities of the contract accepter.

8.5 In the case of contract analysis, the final approval for release must be given by the authorized person(s).

8.6 *The contract giver*
8.6 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

8.7 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.

8.8 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person(s).

8.9 *The contract accepter*
The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

8.10 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

8.11 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

8.12 *The contract*
A contract should be drawn up between the contract giver and the contract accepter that specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

8.13 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

8.14 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

8.15 Manufacturing, analytical, and distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

8.16 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.

9. SELF-INSPECTION AND QUALITY AUDITS

9.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
Self-inspections should be performed routinely, and may

Recovery (or blending). The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

Reprocessing. The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Returned Product. Finished product sent back to the manufacturer.

Specification. A document described in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Standard Operating Procedure (SOP). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

System. A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation. The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

PART ONE. QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS

In the drug industry at large, quality management is defined[1] as the aspect of management function that determines and implements the "quality policy", i.e., the overall intentions and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

- an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes, and resources; and
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

In drug manufacture and supply the terminology may differ. In particular, the term "quality system" is rarely used, and it is "quality assurance" that usually embraces such elements as organizational structure, procedures, and processes.

The concepts of quality assurance, GMP, and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

[1] This definition conforms with that contained in International Standard ISO 9000.

1. QUALITY ASSURANCE

1.1 *Principle.* "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

(a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP)[2] and good clinical practice (GCP);

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) managerial responsibilities are clearly specified in job descriptions;

(d) arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;

(f) the finished product is correctly processed and checked, according to the defined procedures;

(g) pharmaceutical products are not sold or supplied before the authorized persons (see also section 10.6) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;

(h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;

(i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

[2] This is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment. It is different from that described in "Good Laboratory Practices in governmental drug control laboratories" in the Thirtieth Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 748, 1987, Annex 1).

2. GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS (GMP)

2.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production, that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers. Under GMP:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(b) critical steps of manufacturing processes and any significant changes made to the processes are validated;

(c) all necessary facilities are provided, including:
  (i) appropriately qualified and trained personnel;
  (ii) adequate premises and space;
  (iii) suitable equipment and services;
  (iv) correct materials, containers, and labels;
  (v) approved procedures and instructions;
  (vi) suitable storage and transport; and
  (vii) adequate personnel, laboratories, and equipment for in-process controls under the responsibility of the production management;

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;

(e) operators are trained to carry out procedures correctly;

(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality;

(i) a system is available to recall any batch of product from sale or supply;

(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent recurrence.

3. QUALITY CONTROL

3.1 Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

3.2 Each holder of a manufacturing authorization should have a quality control department.[3] The independence of quality control from production is considered fundamental. The quality control department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

(a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.

(b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.

(c) Test methods must be validated.

(d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting, and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.

(e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.

(f) Records must be made of the results of inspecting and testing materials and intermediate, bulk, and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

(g) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the

[3] Except for a holder performing only a fraction of the manufacturing process under a contract (see section 8).

INTRODUCTORY NOTE

The first World Health Organization (WHO) draft text on good manufacturing practices (GMP) was prepared at the request of the Twentieth World Health Assembly (resolution WHA20.34) in 1967 by a group of consultants. It was subsequently submitted to the Twenty-first World Health Assembly under the title "Draft requirements for good manufacturing practice in the manufacture and quality control of drugs and pharmaceutical specialties" and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published as an annex to its twenty-second report *(1)*. The text was further reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

When the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in resolution WHA22.50 (1969), it accepted at the same time the GMP text as an integral part of the Scheme. The revised versions of both the Certification Scheme and the GMP text were adopted in resolution WHA28.65 in 1975. Since then, the Certification Scheme has been extended to include certification of:

- veterinary products administered to food-producing animals;
- starting materials for use in dosage forms, when they are subject to control by legislation in the exporting Member State and in the importing Member State; and
- information on safety and efficacy (resolution WHA41.18, 1988).

The GMP text, however, has not been revised since 1975.

Considerable developments have occurred in GMP in the intervening years, and important national and international documents including new revisions have appeared, such as:

- *Guide to Good Pharmaceutical Manufacturing Practice 1983*. London, Her Majesty's Stationery Office, 1983 ("Orange Guide"). [Superseded by the 1992 EEC guide.]
- *Bonnes Pratiques de Fabrication et de Production Pharmaceutiques*. Paris, Ministère des Affaires Sociales et de la Solidarité Nationale, Secretariat d'Etat charge de la Santé. Direction de la Pharmacie et du Médicament, 1985. [Superseded by the 1992 EEC guide.]
- ASEAN Good Manufacturing Practices Guidelines, 2nd ed. Association of South East Asian Nation, 1988.
- *Good Manufacturing Practice for Medicinal Products in the European Community*. Commission of the European Communities, 1992.
- *Guide to Good Manufacturing Practice for Pharmaceutical Products*. Convention for the Mutual Recognition of Inspection in Respect of the Manufacture of Pharmaceutical Products (PIC), 1992.

New types of guidelines have appeared in recent years: GMP texts applicable to the manufacture of bulk pharmaceutical chemicals as opposed to the manufacture of formulations of dosage forms (PIC guidelines, 1987; various national documents). Another important development in the industry at large is the appearance of the guidelines of the International Organization for Standardization (ISO), specifically the ISO 9000 to 9004 standards for quality systems (1987 rev. 1990). These developments, together with plans to expand and revise the Certification Scheme call for the revision of the WHO GMP text.

The revised draft requirements for GMP are presented in three parts. Part One, "Quality management in the drug industry: philosophy and essential elements", outlines the general concepts of quality assurance as well as the principal components or subsystems of GMP, which are joint responsibilities of the top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials, and documentation.

Part Two, "Good practices in production and quality control", provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of quality assurance.

Part Three contains two supplementary guidelines, but it is an open-ended section, and it is anticipated that further guidelines will be developed in the future, e.g., for biological products, materials for clinical trials, and validation.

The provisions in this guide are fully consonant with those in the above-mentioned documents published by the EEC and PIC.

GENERAL CONSIDERATIONS

Licensed pharmaceutical products should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government drug inspectors, as well as for production and quality control personnel in the industry.

The guide is applicable to all large-scale operations for the production in drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of clinical trials supplies.

The good practices outlined below are to be considered general guidelines[1] and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance should be validated. Parts One and Two of this guide are not intended to cover the production of active pharmaceutical ingredients for which specific requirements are presented in section 18. Nor does the guide as a whole cover safety aspects for the personnel engaged in manufacture; those are governed by national legislation. However, the manufacturer must assure the safety of workers. Nonproprietary names for pharmaceutical substances designated by WHO should be used when available, together with designated names.

GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meaning in other contexts.

Active Pharmaceutical Ingredient. A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

[1] The word "should" in the text means a strong recommendation.

Airlock. An enclosed space with two or more doors, which is interposed between two or more rooms, e.g., of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.

Authorized Person. A person responsible for the release of batches of finished product for sale. In certain countries the batch documentation of a batch of finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

Batch (or lot). A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number). A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Batch Numbering System. Standard operation procedure describing the details of the batch numbering.

Batch Records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bulk Product. Any product that has completed all processing stages up to, but not including, final packaging.

Calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area. An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Consignment (or delivery). The quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Critical Process. A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Finished Product. A product that has undergone all stages of production, including packaging in its final container and labelling.

In-process Control. Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate Product. Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume Parenterals. Sterile solutions for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture. All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products, and the related controls.

Manufacturer. A company that carries out at least one step of manufacture.

Marketing Authorization (product license, registration certificate). A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling, and shelf-life.

Master Formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Packaging. All operations including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging Material. Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product. Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Processing Instructions. See master formula.

Production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Quality Assurance. See Part One.

Quality Control. See Part One.

Quarantine. The status of starting or packaging material, intermediate, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Reconciliation. A comparison, making allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

10.18 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

10.19 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment, or personnel) that they consider may adversely affect the products.

10.20 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

10.21 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

10.22 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material, and personal medicines should not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

10.23 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees – e.g., contractor's employees, visitors, senior managers, and inspectors.

11. PREMISES

11.1 ***Principle.*** Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

11.2 ***General***

Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

11.3 Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation.

11.4 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures.

11.5 Electrical supply, lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

11.7 ***Ancillary areas***

Rest and refreshment rooms should be separate from other areas.

11.8 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

11.9 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

11.10 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

11.11 ***Storage areas***

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned, or recalled products.

11.12 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity) these should be provided, checked, and monitored.

11.13 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

11.14 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

11.15 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

11.16 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

11.17 Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

11.18 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

11.19 ***Weighing areas (may belong to either storage or production areas)***

The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

11.20 ***Production areas***

In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain other products, such as some antibiotics, hormones, cytotoxic substances, highly active pharmaceutical products, and non-pharmaceutical products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not normally be allowed in premises used for the manufacture of pharmaceutical products. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.

11.21 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

11.22 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

11.23 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

11.24 Pipework, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

11.25 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

11.26 Production areas should be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

11.27 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

11.28 Production areas should be well lit, particularly where visual on-line controls are carried out.

11.29 ***Quality control area***

Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

11.30 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), and records.

11.31 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

11.32 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors, or where it is necessary to isolate the instruments.

12. EQUIPMENT

12.1 ***Principle.*** Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

12.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

12.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

12.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

12.6 Production equipment should be designed, located, and maintained to serve its intended purpose.

12.7 Production equipment should be designed so that it can be easily and thoroughly cleaned on a scheduled basis.

12.8 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.

12.9 Washing and cleaning equipment should be chosen and used so as not to be a source of contamination.

12.10 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

12.11 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

13. MATERIALS

13.1 ***Principle.*** The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (active, auxiliary, packaging). Special attention should be given to the materials as such.

13.2 ***General***

All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

13.3 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-in, first-out rule.

13.4 *Starting materials*[1]
The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

13.5 Starting materials should be purchased only from suppliers named in the relevant specification and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling, and packaging requirements as well as complaints and rejection procedures, are discussed between the manufacturer and the supplier.

13.6 For each consignment, the containers should be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

13.7 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed data.

13.8 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

13.9 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing, and release.

13.10 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference where applicable;
(b) the batch number(s) given by the supplier and on receipt by the manufacturer, if any;
(c) where appropriate, the status of the contents (e.g., on quarantine, on test, released, rejected, returned, recalled);
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerized storage systems are used, not all of the above information need be in a legible form on the label.

13.11 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

13.12 Only starting materials released by the quality control department and within their shelf-life should be used.

13.13 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

13.14 Each dispensed material and its weight or volume should be independently checked and the check recorded.

13.15 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

13.16 *Packaging Materials*
The purchase, handling, and control of primary and printed packaging materials shall be as for starting materials.

13.17 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

13.18 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

13.19 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

13.20 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the packaging instructions.

13.21 *Intermediate and bulk products*
Intermediate and bulk products should be kept under appropriate conditions.

13.22 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

13.23 *Finished products*
Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

13.24 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 16, "Good practices in quality control".

13.25 *Rejected and recovered materials*
Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved by authorized personnel and recorded.

13.26 The reprocessing of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number.

13.27 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

13.28 The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

13.29 *Recalled products*
Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

13.30 *Returned goods*
Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; they may be considered for resale, relabelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

13.31 *Reagents and culture media*
All reagents and culture media should be recorded upon receipt or preparation.

13.32 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

13.33 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

13.34 *Reference Standards*
Reference standards may be available in the form of official reference standards. Reference standards prepared by the producer should be tested, released, and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

13.35 Official reference standards should be used only for the purpose described in the appropriate monograph.

13.36 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. All in-house reference standards should be based on official reference standards, when available.

13.37 All reference standards should be stored and used in a manner that will not adversely affect their quality.

13.38 *Waste materials*
Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

13.39 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

13.40 *Miscellaneous*
Rodenticides, insecticides, fumigating agents, and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials, or finished products.

14. DOCUMENTATION

14.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

14.2 *General*
Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

14.3 Documents should be approved, signed, and dated by appropriate authorized persons. No document should be changed without authorization.

14.4 Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

14.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

14.6 Where documents require the entry of data, these entries should be clear, legible, and indelible. Sufficient space should be provided for such entries.

14.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

14.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.

[1] Please refer also to Part Three, section 18.

14.9 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

14.10 *Documents required*

Labels

Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example: quarantined, accepted, rejected, or clean).

14.11 All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;
(b) a list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight, or volume;
(c) the batch number assigned by the manufacturer;
(d) the expiry date in an uncoded form;
(e) any special storage conditions or handling precautions that may be necessary;
(f) directions for use, and warnings and precautions that may be necessary; and
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

14.12 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

14.13 *Specifications and testing procedures*

Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routing testing.

14.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents, and reagents (e.g., acids and bases) used in production should be included.

14.15 Each specification should be approved and maintained by the quality control unit. Specifications for starting materials, intermediates, and bulk and finished products are referred to in sections 14.18-14.21.

14.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

14.17 Pharmacopoeias, reference standards, reference spectra, and other reference materials should be available in the quality control laboratory.

14.18 *Specifications for starting and packaging materials*

Specifications for starting and primary or printed packaging materials should provide, if applicable, a description of the material including:

(a) the designated name (if applicable, the International Nonproprietary Name) and internal code reference;
(b) the reference, if any, to a pharmacopoeial monograph; and
(c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

(a) the supplier and the original producer of the materials;
(b) a specimen of printed materials;
(c) directions for sampling and testing, or a reference to procedures;
(d) storage conditions and precautions;
(e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for critical and major physical defects as well as for the correctness of identity markings.

14.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

14.20 *Specifications for intermediate and bulk products*

Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

14.21 *Specifications for finished products*

Specifications for finished products should include:

(a) the designated name of the product and the code reference where applicable;
(b) the designated name(s) of the active ingredient(s) (if applicable, the International Nonproprietary Name(s));
(c) the formula or a reference to the formula;
(d) a description of the dosage form and package details;
(e) directions for sampling and testing or a reference to procedures;
(f) the qualitative and quantitative requirements, with acceptance limits;
(g) the storage conditions and precautions, where applicable; and
(h) the shelf-life.

14.22 *Master formulae*

A formally authorized master formula should exist for each product and batch size to be manufactured.

14.23 The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product, and size;
(c) a list of all starting materials to be used (if applicable, with the International Nonproprietary Names), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
(e) a statement of the processing location and the principal equipment to be used;
(f) the methods, or reference to the methods, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing;
(g) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
(h) the instructions for any in-process controls with their limits;
(i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
(j) any special precautions to be observed.

14.25 *Packaging instructions*

Formally authorized packaging instructions should exist for each product, pack size, and type. These should normally include, or make reference to:

(a) the name of the product;
(b) a description of its pharmaceutical form, strength and method of application where applicable;
(c) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
(d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications for each packaging material;
(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(h) details of in-process controls with instructions for sampling and acceptance limits.

14.26 *Batch processing records*

A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors.

14.27 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

14.28 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) the name of the product;
(b) the number of the batch being manufactured;
(c) dates and times of commencement, of significant intermediate stages, and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing);
(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

14.29 *Batch packaging records*

A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

14.30 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

14.31 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) the name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained, and the reconciliation;
(b) the date(s) and time(s) of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;

(d) the initials of the operators of the different significant steps;
(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting;
(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

14.32 *Standard operating procedures (SOPs) and records*
There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

14.33 The records of the receipts should include:
(a) the name of the material on the delivery note and the containers;
(b) the "in-house" name and/or code of material if different from (a);
(c) the date of receipt;
(d) the supplier's name and, if possible, manufacturer's name;
(e) the manufacturer's batch or reference number;
(f) the total quantity, and number of containers received;
(g) the batch number assigned after receipt;
(h) any relevant comment (e.g., state of the containers).

14.34 There should be standard operating procedures for the internal labelling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

14.35 Standard operating procedures should be available for eachinstrument and piece of equipment and placed in close proximity to the equipment.

14.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

14.37 The sampling instructions should include:
(a) the method of sampling and the sampling plan;
(b) the equipment to be used;
(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(d) the amount(s) of sample(s) to be taken;
(e) instructions for any required subdivision of the sample;
(f) the type of sample containers to be used, and whether they are for aseptic sampling or for normal sampling;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

14.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

14.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

14.40 The standard operating procedure for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

14.41 Batch-number allocation should be immediately recorded, e.g., in a logbook. The record should include date of allocation, product identity and size of batch.

14.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

14.43 Analysis records should include at least the following data:
(a) the name of the material or product and, where applicable, dosage form;
(b) the batch number and, where appropriate, the manufacturer and/or supplier;
(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and references to any specifications (limits);
(e) dates of testing;
(f) the initials of the persons who performed the testing;
(g) the initials of the persons who verified the testing and the calculations, where appropriate;
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

14.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

14.45 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

14.46 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:
(a) equipment assembly and validation;
(b) analytical apparatus and calibration;
(c) maintenance, cleaning, and sanitization;
(d) personnel matters including qualification, training, clothing, and hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls;
(i) returns.

14.47 Logbooks should be kept with major and critical equipment and should record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

14.48 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

14.49 There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used and facilities to be cleaned. Such written procedures should be followed.

PART TWO. GOOD PRACTICES IN PRODUCTION AND QUALITY CONTROL

15. GOOD PRACTICES IN PRODUCTION[1]

15.1 ***Principle.*** Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

15.2 ***General***
All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

15.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

15.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

15.5 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

15.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and the batch number. Where applicable, this indication should also mention the stage of production.

15.7 Access to production premises should be restricted to authorized personnel.

15.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

15.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

15.10 ***Prevention of cross-contamination and bacterial contamination in production***
When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust.

15.11 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

15.12 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:
(a) production in segregated areas (which may be required for products such as penicillins, live bacterial preparations and certain other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
(b) providing appropriate airlocks, pressure differentials, and air extraction;
(c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(d) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
(f) using a "closed-system" of production;
(g) testing for residues;
(h) using cleanliness status labels on equipment.

15.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

15.14 Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

15.15 ***Processing operations: intermediate and bulk products***
Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels, or documents not required for the current operation.

15.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

15.17 Means should be instituted of indicating failures of equipment or of services (e.g., water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. Production equipment should be cleaned according to detailed written procedures and stored only under clean and dry conditions.

15.18 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

15.19 Any significant deviation from the expected yield should be recorded and investigated.

[1] For the manufacturer of sterile products please refer to Part Three, section 17 for the manufacture of active pharmaceutical ingredients (bulk drug substances) please refer to Part Three, section 18.

15.20 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

15.21 Pipes used for conveying distilled or deionized water and, where appropriate, other water-pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

15.22 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated.

15.23 Repair and maintenance operations should not present any hazard to the quality of the products.

15.24 *Packaging operations*

When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

15.25 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used and not required for the current operation. The line clearance should be performed according to an appropriate checklist and recorded.

15.26 The name and batch number of the product being handled should be displayed at each packaging station or line.

15.27 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

15.28 The correct performance of any printing (for example of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

15.29 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

15.30 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

15.31 On-line control of the product during packaging should include at least checks on:

(a) the general appearance of the packages;
(b) whether the packages are complete;
(c) whether the correct products and packaging materials are used;
(d) whether any overprinting is correct;
(e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

15.32 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation, and approval by authorized personnel. A detailed record should be kept of this operation.

15.33 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

15.34 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

16. GOOD PRACTICES IN QUALITY CONTROL

16.1 *Principle.* Quality control is concerned with sampling, specifications, and testing as well as with the organization, documentation, and release procedures that ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental.[1]

16.2 *Control of starting materials and intermediate, bulk, and finished products*

All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

16.3 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

16.4 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

16.5 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

16.6 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

16.7 Each sample container should bear a label indicating:

(a) the name of the sampled material;
(b) the batch or lot number;
(c) the number of the container from which the sample has been taken;
(d) the signature of the person who has taken the sample; and
(e) the date of sampling.

16.8 *Test requirements*

Starting and packaging materials

Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.

16.9 An identity test should be conducted on a sample from each container of starting material (see also section 13.11).

16.10 Each batch (lot) of printed packaging materials must be examined following receipt.

16.11 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 9.8 and 9.9) and through on-site audits of the supplier's capabilities. (This does not affect section 16.9). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

(a) identification of the issuing supplier, signature of the competent official, and statement of his or her qualifications;
(b) the name and batch number of the material tested;
(c) a statement of specifications and methods used; and
(d) a statement of test results obtained and the date of testing.

In-process control

16.12 In-process control records should be maintained and form a part of the batch records (see section 15.2).

Finished products

16.13 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

16.14 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

16.15 *Production record review*[1]

Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

16.16 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

16.17 *Stability studies*

The quality control department should evaluate the quality and stability of finished pharmaceutical products, and when necessary, of starting materials and intermediate products.

16.18 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

16.19 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

(a) a complete description of the drug involved in the study;
(b) the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
(c) provision for the inclusion of a sufficient number of batches;
(d) the testing schedule for each drug;
(e) provision for special storage conditions;
(f) provision for adequate sample retention; and
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

16.20 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

PART THREE. SUPPORTING AND SUPPLEMENTARY GUIDELINES

17. STERILE PHARMACEUTICAL PRODUCTS

Explanation

These guidelines do not replace any of the sections in Parts One and Two but stress specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate, and pyrogen contamination.

17.1 *General*

The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for goods. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of an appropriate efficiency.

17.2 The various operations of component preparation (such as containers and closures), product preparation, filling, and sterilization should be carried out in separate areas within the clean area.

[1] Please refer also to Part One, section 3.

[1] Also known as batch review.

17. Clean areas for the production of sterile products are classified according to the required characteristics of the air, in grades A, B, C, and D (see Table 1).

Table 1
Air classification system for manufacture of sterile products

Grade	Maximum number of particles permitted per m^3 0.5-5μm	>5μm	Maximum number of viable microorganisms permitted per m^3
A (Laminar-airflow workstation)	3 500	none	less than 1
B	3 500	none	5
C	350 000	2 000	100
D	3 500 000	20 000	500

To obtain air of the required characteristics, methods specified by the national authorities should be used. It should be noted that:

- Laminar-airflow systems should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow but precise air speeds will depend on the type of equipment.
- In order to reach the B, C, and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good airflow pattern and appropriate HEPA (high-efficiency particulate air) filters.
- Low values for contaminants are reliable only when a large number of air samples are taken.
- The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209E (1992) as follows: Class 100 (grades A and B), Class 10 000 (grade C), and Class 100 000 (grade D).

It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

17.4 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 17.5 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions given in Table 1 should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions should also be achieved throughout the background environment if no personnel are present in the processing area, and if the standards fall for any reason it should be possible to recover the conditions after a short "clean-up" period. The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of manufactured products. When such techniques are used, the recommendations in these supplementary guidelines, particularly those relating to air quality and monitoring, still apply, with appropriate interpretations of the terms "workstation" and "environment".

17.5 *Manufacture of sterile preparations*

Manufacturing operations are here divided into three categories: first, those in which the preparation is sealed in its final container and terminally sterilized; second, those in which the preparation is sterilized by filtration; and third, those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced from sterile starting materials in an aseptic way. Area grades as specified in sections 17.5.1-17.5.3, must be selected by the manufacturer on the basis of validation runs (e.g., sterile media fills).

17.5.1 *Terminally sterilized products*

Solutions should generally be prepared in a grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels. For parenterals, filling should be done in a laminar-airflow workstation (grade A) in a grade C environment. The preparation of other sterile products, e.g., ointments, creams, suspensions, and emulsions, and filling of containers should generally be done in a grade C environment before terminal sterilization.

17.5.2 *Sterile filtered products*

The handling of starting materials and the preparation of solutions should be done in a grade C environment. These activities could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a grade A or B area with a grade B or C background respectively.

17.5.3 *Other sterile products prepared from sterile starting materials in an aseptic way*

The handling of starting materials and all further processing should be done in a grade A or B area with a grade B or C background respectively.

17.6 *Personnel*

Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside the areas as far as possible.

17.7 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g., building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

17.8 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

17.9 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

17.10 Outdoor clothing should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure.

17.11 The clothing and its quality has to be adapted to the process and the workplace, and worn in such a way as to protect the product from contamination.

17.12 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.

17.13 Clothing should be appropriate to the air grade of the area where the personnel will be working. The description of clothing required for each grade is given below.

Grade D: The hair and, where appropriate, beard should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C: The hair and, where appropriate, beard should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

Grade B: Headgear should totally enclose the hair and, where appropriate, beard; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn; trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

17.14 For every worker in a grade B room, clean sterilized protective garments should be provided at each work session, or at least once a day if monitoring results justify it. Gloves should be regularly disinfected during operations, and masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

17.15 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

17.16 *Premises*

All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas should be designed so that all operations can be observed from outside.

17.17 In clean areas, all exposed surfaces should be smooth, impervious, and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

17.18 To reduce the accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards, and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

17.19 False ceilings should be sealed to prevent contamination from the space above them.

17.20 Pipes and ducts should be installed so that they do not create recesses that are difficult to clean.

17.21 Sinks and drains should be avoided wherever possible and should be excluded from areas where aseptic operations are carried out. Where installed they should be designed, located, and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps with air breaks to prevent back-flow. Any floor channel should be open and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

17.22 Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, so minimizing microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

17.23 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

17.24 *Equipment*

A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified if it becomes necessary to contain materials such as pathogenic, highly toxic, radioactive, or live viral or bacterial materials. Decontamination facilities and the treatment of air leaving a clean area may be necessary for some operations.

17.25 It should be demonstrated that airflow patterns do not present a contamination risk, for example care should be taken to ensure that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

17.26 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should

be fitted between areas where this difference is important and the pressure difference should be regularly recorded.

17.27 Consideration should be given to restricting unnecessary access to critical filling areas, e.g., grade A filling zones, by the use of a physical barrier.

17.28 A conveyor belt should not pass through a partition between a clean area B and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g., in a sterilizing tunnel).

17.29 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

17.30 As far as possible, equipment fittings and services should designed and installed so that operations, maintenance, and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be resterilized after complete reassembly wherever possible.

17.31 When equipment maintenance is carried out within the clean area clean instruments and tools should be used, and the area should be cleaned and disinfected where appropriate before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

17.32 All equipment, including sterilizers, air-filtration systems, and water-treatment systems including stills, should be subject to planned maintenance, validation, and monitoring; its approved use following maintenance work should be documented.

17.33 Water-treatment plants should be designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored, and distributed in a manner that prevents microbial growth — for example, by constant circulation at 80°C or not more than 4°C.

17.34 *Sanitation*

The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with a written programme approved by the quality control department. Where disinfectants are used, more than one type should be employed, with periodic alterations. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

17.35 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should not be stored for long periods unless sterilized. Partly emptied containers should not be topped up.

17.36 Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

17.37 Clean areas should be monitored at planned intervals during operations by means of microbial counts of air and surfaces; where aseptic operations are performed, monitoring should be frequent to ensure that the environment is within specifications. The results of monitoring should be considered when batches are assessed for approval. Air particulate quality should also be evaluated on a regular basis. Additional monitoring is sometimes desirable even when there are no production operations, e.g., after validation of systems, cleaning, and fumigation.

17.38 *Processing*

Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

17.39 Preparations containing live microbiological organisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines of dead organisms or of bacterial extracts may be dispensed into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.

17.40 The use of nutrient media that support microbial growth in trials to simulate aseptic operations (sterile media fills, "broth fills") is a valuable part of overall validation of an aseptic process. Such trials should have the following characteristics:

(a) They should simulate as closely as possible actual operations, taking into account such factors as complexity of operations, number of personnel working, and length of time.

(b) The medium or media selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment.

(c) They should include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected.

It is recommended that at least 3000 units of production be included in each broth-fill trial. The target should be zero growth and anything above 0.1% of units contaminated should be considered unacceptable. Any contamination should be investigated. Broth fills should be repeated at regular intervals, and whenever a significant alteration in the product, premises, equipment, or process warrants revalidation.

17.41 Care should be taken that validations do not harm the processes.

17.42 Water sources, water-treatment equipment, and treated water should be monitored regularly for chemicals, biological contamination, and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.

17.43 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

17.44 Microbiological contamination of starting materials should be minimal, and the "bioburden" should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

17.45 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

17.46 Components, bulk-product containers, and equipment should be handled after the final cleaning process in such a way that they are not recontaminated. The stage of processing of components, bulk-product containers, and equipment should be properly identified.

17.47 The interval between the washing and drying and the sterilization of components, bulk-product containers, and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

17.48 The time between the start of the preparation of a solution and sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

17.49 Any gas that is used to purge a solution or blanket a product should pass through a sterilizing filter.

17.50 The microbiological contamination of products ("bioburden") should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g., by hydrophobic microbial air filters.

17.51 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures that achieve the same end of not introducing contamination (e.g., triple wrapping) may be acceptable in some circumstances.

17.52 The efficacy of any new processing procedure should be validated, and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

17.53 *Sterilization*

Sterilization can be achieved by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling of sterile final containers, or by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

17.54 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

17.55 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated. This work should be repeated at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

17.56 Biological indicators should be considered only as an additional method for monitoring the sterilization. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.

17.57 There should be a clear means of differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, sterile.

17.58 *Sterilization by heat*

Each heat sterilization cycle should be recorded by appropriate equipment with suitable accuracy and precision, e.g., on a time/temperature chart with a suitably large scale. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

17.59 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.

17.60 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

17.61 *Sterilization by moist heat*

Sterilization by moist heat is suitable only for water-wettable materials and aqueous solutions. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be

regular leak tests on the chamber when a vacuum phase is part of the cycle.

17.62 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but prevents recontamination after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

17.63 Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level that could cause contamination of the product or equipment.

17.64 *Sterilization by dry heat*
The process used for sterilization by dry heat should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied, it should be passed through a microorganism-retaining filter. Where this process of sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation.

17.65 *Sterilization by radiation*
Radiation sterilization is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

17.66 If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of section 17.65 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g., for the right dose) should also be specified.

17.67 During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

17.68 Validation procedures should ensure that consideration is given to the effect of variations in the density of the packages.

17.69 Handling procedures should prevent any mix-up between irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

17.70 The total radiation dose should be administered within a predetermined time span.

17.71 *Sterilization by ethylene oxide*
Various gases and fumigants may be used for sterilization. Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material. These limits should be incorporated into the specifications.

17.72 Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

17.73 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

17.74 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

17.75 Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.

17.76 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature, and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded throughout the cycle on a chart. The records should form part of the batch record.

17.77 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to fall to the defined level. This process should be validated.

17.78 *Filtration of pharmaceutical products that cannot be sterilized in their final container*
Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22μm (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

17.79 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

17.80 Filters that shed fibres should not be used. The use of asbestos-containing filters should be absolutely excluded.

17.81 The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately after each use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this should be noted and investigated. Results of these checks should be recorded in the batch record.

17.82 The same filter should not be used for more than one working day unless such use has been validated.

17.83 The filter should not affect the product by removal of ingredients from it or by release of substances into it.

17.84 ***Finishing of sterile products***
Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

17.85 Containers sealed under vacuum should be sampled and the samples tested for maintenance of that vacuum after an appropriate predetermined period.

17.86 Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals.

17.87 ***Quality control***
Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

(a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

(b) for products that have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

17.88 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured and can be interpreted only in conjunction with the environmental and batch processing records.

17.89 Batches failing an initial sterility test should not be released on the basis of a second test unless an investigation into the type of organism found, and into the environmental and batch processing records involved, show that the original test was invalid.

17.90 For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by the marketing authorization on the finished product. When a sample fails a test, the cause of failure should be investigated and remedial action taken where necessary.

18. GOOD MANUFACTURING PRACTICES FOR ACTIVE PHARMACEUTICAL INGREDIENTS (BULK DRUG SUBSTANCES)

Explanation
Since there are fundamental distinctions between the production of bulk active pharmaceutical ingredients and the formulation of finished pharmaceutical products, the strict application of GMP as set forth in the main part of this guide is not always practical or necessary. The present supplementary guidelines outline procedures and practices that manufacturers should employ to ensure that the methods, facilities, and controls used for the production of active pharmaceutical ingredients are operated or managed so that such products have the quality and purity appropriate for their use in finished pharmaceutical products.

18.1 *General considerations*
In the manufacture of active pharmaceutical ingredients, overall control is essential to ensure high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be used to save life or to restore or promote health.

18.2 Recommended practices for the manufacture of active pharmaceutical ingredients are set out below. Adherence to these practices, complementing the various control tests carried out from the beginning to the end of the production cycle, will contribute substantially to the production of consistently uniform batches of high-quality active pharmaceutical ingredients.

18.3 The manufacturer must assume responsibility for the quality of the active pharmaceutical ingredients produced. The manufacturer alone can avoid mistakes and prevent mishaps by exercising adequate care in both production and control procedures. Full evidence of compliance with GMP should be given from the step from which the processes or the starting materials used have a critical influence on the quality of the active pharmaceutical ingredient. This step should be determined in each individual case by agreement between the competent authority and the manufacturer.

18.4 The good practices outlined below should be considered general guides; whenever necessary, they may be adapted to meet individual needs provided the established standards of quality of the active pharmaceutical ingredients are still achieved. The good practices are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of active pharmaceutical ingredients.

18.5 Sometimes several firms cooperate in the production (including packaging and labelling) of an active pharmaceutical ingredient. It may also happen that a finished, packed, and labelled active pharmaceutical ingredient is repacked and/or relabelled and given a new designation. Since such procedures constitute part of a manufacturing operation, they should be subject to the relevant guidelines set out below.

18.6 The practices outlined below are intended to apply to active pharmaceutical ingredients for both human and veterinary preparations.

18.7 *Personnel*
Each firm should employ personnel with the necessary qualifications and competence for the production and quality control of active pharmaceutical ingredients. There should be an adequate number of staff with appropriate education, technical knowledge, and practical experience related to the job they perform.

18.8 The firm should have a defined organization represented in a chart. Individual responsibilities should be laid down in written instructions, to ensure that there are no gaps or overlaps. The responsibilities placed on any one individual should not be so extensive as to incur any risk to quality.

18.9 Staff at all levels should be adequately trained for the tasks and responsibilities assigned to them.

18.10 Measures should be taken to ensure that no person affected by a disease in a communicable form or having open lesions on the exposed surface of the body is engaged in any production step involving direct contact with the active pharmaceutical ingredients.

18.11 *Premises*
Premises, including areas containing open tanks, should be of suitable construction. They should provide a suitable environment for manufacturing operations and should be adequately adapted to and of a sufficient size for their intended use. The premises should not contribute to actual or potential mix-ups or contamination of the active pharmaceutical ingredients. The arrangement should provide for a logical work flow.

18.12 For special purposes, such as the production of sterile products and of certain antibiotics, hormones, and cytostatic substances, separate specifically designed enclosed areas with completely separate air-handling systems should be provided.

18.13 To maintain hygienic working conditions, the premises should include facilities for changing clothes, washing, and toilet purposes as well as for eating, drinking, and smoking.

18.14 *Equipment*
Manufacturing equipment should be designed, constructed, located, and maintained in such a way as to:
(a) be suitable for its intended use;
(b) facilitate thorough cleaning;
(c) minimize the risk of contamination of products and containers during production; and
(d) facilitate efficient and, if applicable, validated and reliable operation.

18.15 Production and testing equipment should be cleaned, sterilized when necessary, used, and maintained in accordance with specific written instructions. Before production of another product is started, multi-purpose equipment used should be thoroughly cleaned and checked for cleanliness. Appropriate records of such procedures should be maintained.

18.16 If necessary, equipment used for production and testing should have been shown to be capable of carrying out the processes for which it is intended.

18.17 Process-monitoring systems should be available where necessary. Measuring, recording, and control equipment should be calibrated and checked at suitable intervals by appropriate methods. Appropriate records of such tests should be maintained.

18.18 Defective equipment should be labelled immediately as defective and repaired or removed as soon as possible. Technical maintenance and repair should be documented.

18.19 *Sanitation*
Written sanitation programmes should be available. These should include validated cleaning procedures for premises and equipment, a quality standard for water, instructions for hygiene when manufacturing and handling goods, and instructions relating to the health, hygienic practices, and clothing of personnel and the disposal procedures for waste materials and unusable residues.

18.20 These programmes should be implemented; they should regularly be brought to the attention of the personnel involved and emphasized during continued staff training.

18.21 Protective garments and other protective items appropriate to the processes being carried out should be worn.

18.22 Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

18.23 *Documentation*
Master formulae
Written instructions covering each stage of production, storage, and quality control should be available, and they should be updated whenever necessary.

18.24 There should be a master formula setting out in writing the starting materials and packaging materials (quality and quantity), as well as detailed production and quality control procedures for each active pharmaceutical ingredient. Wherever possible, the master formula should be prepared for standard batch sizes.

18.25 Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated.

18.26 Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.

18.27 In certain circumstances, for example in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula.

18.28 *Batch documentation*
A batch manufacturing record should be completed during the production of each batch of intermediate products and of active pharmaceutical ingredients. It should contain the relevant parts of the master formula and should include the following:
(a) the name of the product (if applicable, the International Nonproprietary Name) or stage and the size and number of the batch;
(b) the dates of the different stages of production;
(c) production details, including reference to the main equipment used and yields;
(d) the batch or reference number (or analytical control number), if any, of starting materials used in the production;
(e) a record of the in-process controls followed and the results obtained;
(f) details of, and signed authorization for, any deviation from the master formula (any unplanned deviation being subject to investigation in relation to product quality);
(g) any recovered materials, and procedures applied;
(h) the initials of the operators and signature of the person responsible for the production operations and the date of signature;
(i) all analytical records relating to the batch, or a reference that will permit their retrieval;
(j) a decision for the release or rejection of the batch with the date and signature of the person responsible for the decision;
(k) the production record review (see section 16.15).

18.29 Where circumstances require the use of contract production and control facilities, this fact should be stated in the batch record.

18.30 Data may be recorded by electronic data-processing systems or by photographic or by other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means, and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

18.31 *Retention of records and reference samples*
Records should be kept in such a way that activities concerning the production and quality control of active pharmaceutical ingredients are traceable.

18.32 Records and reference samples of the active pharmaceutical ingredients, and where necessary of intermediate products, should be retained at least one year beyond the expiry date of the finished product or for a specified period if there is no expiry date.

18.33 *Production*
Processing procedures
Processing should be carried out in accordance with the master formula.

18.34 Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the procedures applied should be validated.

18.35 Processing should be supervised and performed by competent persons.

18.36 During processing, vessels, containers, and significant equipment should be unambiguously labelled or identified with the name of the product and the batch number.

18.37 Information on the daily activities in each processing department should be available in addition to the batch documentation.

18.38 *Starting materials*
Starting materials should be received, quarantined, sampled, identified, examined for compliance with established specifications, released or rejected, stored, labelled, and dispensed in accordance with written instructions.

18.39 Some starting materials may not be tested for compliance because of the hazards involved (e.g., phosphorus pentachloride and dimethyl sulfate). This is acceptable when a batch certificate of analysis is available from the vendor and when there is a reason based on safety or other valid considerations.

18.40 *Intermediate products*
Intermediate products should, where necessary, be tested in accordance with the specifications and should be conspicuously labelled/identified and properly stored.

18.41 *Active pharmaceutical ingredients*
Each batch of finished active pharmaceutical ingredient must meet established specifications for quality, purity, identity, and potency, including, where applicable, specifications for tests and limits for residues of solvents and other reactants.

18.42 For the production of sterile active pharmaceutical ingredients, section 17 ("Sterile pharmaceutical products") may be applicable to the steps at which the process may have a critical influence on the quality attributes of the finished pharmaceutical product.

18.43 *Packaging*
Care should be exercised when packaging materials are selected for active pharmaceutical ingredients. The materials should have no detrimental effect on the substance, and should give adequate protection against external influences and potential contamination. Suitable written specifications should be available.

18.44 Attention should be directed at all stages to the prevention of packaging errors. Sound procedures must be employed to protect the quality of the product when it is packaged and to ensure that the correct labels are applied to the containers.

18.45 The containers should be conspicuously marked with the following information:
(a) the name of the product;
(b) its quality, if specified;
(c) the batch number;
(d) the expiry or retest date, if specified;
(e) warnings, if required;
(f) storage conditions, if specified; and
(g) the names of the manufacturer and the supplier.

18.46 Quality control
Every manufacturer should have an independent quality control unit, the head of which is directly responsible to the management of the firm. The principal duties of the quality control unit are listed below.
(a) It should approve:

(i) specifications and testing methods for starting materials, intermediate products and, if required, packaging materials and active pharmaceutical ingredients;
(ii) sampling procedures;
(iii) instructions regarding sanitation and hygiene;
(iv) reprocessing procedures for rejected batches or recovered materials;
(v) other instructions related to the quality of the product.

(b) It should be responsible for the release or rejection of starting materials, active pharmaceutical ingredients, packaging materials, and, if required, intermediate products.

(c) It should ensure that the stability of active pharmaceutical ingredients is monitored.

(d) It should be responsible for the investigation of complaints related to the quality of active pharmaceutical ingredients.

18.47 Every manufacturer should have access to a control laboratory. The laboratory should be staffed and fully equipped for performing all quality control tests required. The tests should be performed in accordance with written and validated procedures. Instruments should be calibrated at suitable intervals and reagents should be of appropriate quality.

18.48 Where circumstances require the use of outside laboratories, this fact should be stated in the analytical records.

18.49 *Stability studies*
A written stability-testing programme should be established for active pharmaceutical ingredients. Stability-indicating methods should used.

18.50 Samples should be stored in suitable containers and in simulated market containers at room temperature or the recommended temperature and under stress conditions.

18.51 Expiry dates do not usually need to be set for active pharmaceutical ingredients. If testing does not indicate a reasonable shelf-life, e.g., two years or more under anticipated storage conditions, then the product can be labelled with an appropriate arbitrary expiry date and should be retested on or before that date.

18.52 *Self-inspection and quality audits*
In order to maintain strict adherence to GMP and to all manufacturing procedures and prescribed controls, it is advisable for a firm to designate an expert or a team of experts to conduct regular independent inspections of its overall production and control procedures. Such experts should be as independent as possible in their inspection of production and control procedures.

18.53 Self-inspections and audits (see section 9) should be recorded.

18.54 *Storage*
Active pharmaceutical ingredients should be stored under conditions established by the manufacturer on the basis of stability studies.

18.55 Records should be maintained on the distribution of each batch of an active pharmaceutical ingredient in order to facilitate the recall of the batch if necessary, according to written procedures.

18.56 *Complaints and defects*
The manufacturer should maintain written instructions for dealing with complaints and defects concerning the quality of active pharmaceutical ingredients.

18.57 All necessary action should be taken promptly, the complaints thoroughly investigated, and all facts recorded.

18.58 The manufacturer should have a system to allow review of all products that may have been affected by a repetitive error or a failure in the procedures of the firm.

18.59 *Rejected materials*
The manufacturer should maintain written instructions concerning the handling of rejected materials, whether starting materials, intermediate products, packaging materials, or active pharmaceutical ingredients. Rejected materials should be conspicuously identified as such and stored in a controlled manner pending destruction, reprocessing, or return to the supplier.

Regulations for Manufacturing Control and Quality Control of Ethical Extract Products in Kampo Medicine (Oriental Medicine) Formulations

(Self-Imposed regulations of Japan Kampo-Medicine Manufacturers Association: JKMA)

Chapter 1 General Provisions

<Purpose>

The purpose of the Regulations is to assure quality of ethical extract products in Kampo medicine formulations by establishing requirements for the manufacturing control and quality control, mainly of raw material crude drugs, in the manufacturing process for such products, and in conformity with the Regulations for Manufacturing Control and Quality Control of Drugs (hereinafter referred to as "GMP Regulations").

<Scope of application>

The Regulations shall apply to any manufacturing plant for ethical extract products in Kampo medicine formulations and to that for extracts for such products.

<Definitions>

The definitions contained in the Japanese Pharmacopoeia (JP), Standards for Non-pharmacopoeial Crude Drugs (Non-JP Crude Drug Standards) and the GMP Regulations shall be applicable to the general terms used in these Regulations. The following definitions of terms apply to these Regulations:

"Extract for Kampo medicine formulations" means an extract used as raw material for prescription extract products in Kampo medicine formulations.

"Designed quality" means a quality as described in the letter of manufacturing (import) approval of an extract for Kampo medicine formulations established in accordance with the standard decoctions stipulated in "Requirements for Prescription Extract Products in Kampo Medicine Formulations" [PAB/ERD-2 Notification No. 120 (May 31, 1985)].

"Indicator ingredient" means an ingredient used as an indicator for the assurance of the equivalence of the extract for Kampo medicine formulations and finished product to the standard decoction.

"Self-determined ingredient" means an ingredient, other than the indicator ingredient, determined quantitatively by the manufacturer at his own discretion.

<Crude drug (or herbal material) control manager>

The manufacturer of the extract for Kampo medicine formulations, as stipulated in the GMP Regulations, shall designate a manufacturing control manager and a quality control manager under the product security pharmacist, and a crude drug control manager under the quality control manager.

The quality control manager may be at the same time the crude drug control manager.

1) The crude drug control manager shall have the following qualifications:
   (1) Having professional knowledge on crude drugs and an ability to form a qualitative judgment of crude drugs.
   (2) Having abundant knowledge from practical experience on the treatment of raw material crude drugs.
2) In order to provide practical quality assurance of raw material crude drugs, the crude drug control manager shall perform the following duties by himself, or if necessary, by a designated person.
   (1) Method of sampling of raw material crude drugs.
   (2) In the process of the analysis and testing of raw material crude drugs, evaluation of the results of differentiation (including differentiation of morphological quality)
   (3) Education and training of personnel handling raw material crude drugs.
   (4) Miscellaneous duties for the quality assurance of raw material crude drugs.

Chapter 2 Quality Assurance of Raw Material Crude Drugs

For the quality assurance of raw material crude drugs, there shall be the drug product standard code, manufacturing control standard code and quality control standard code, describing necessary matters in the light of JP, non-JP Crude Drug Standards, other official standards, related official notifications and the latest scientific levels, as well as the following matters:

<Drug product standard code>

1) Specifications and test method
   (1) For a crude drug containing an indicator ingredient and a self-determined ingredient, a method of determination and content limit of such ingredients shall be settled.
   (2) Grading test of cut crude drugs.
   (3) Differentiation test.
   (4) Any test deemed necessary in the light of related official notifications and the latest levels of science and technology, on a full understanding of the concept of the original text of Kampo medicine.
2) Requirements in the commission of cutting processing of crude drugs
   In addition to "Requirements for Commissioned Manufacture of Drugs etc." (PAB Notification No. 234, March 12, 1986), the following requirements shall be taken into consideration:
   (1) Before commissioning, the quality of whole crude drugs shall be assured on commissioning person's responsibility.

B) Standards for receipt of cut and powder crude drugs shall be established, and analysis and testing of such products shall be performed accordingly upon their receipt.

(B) Intermediate materials and drug products

A) Quality of Intermediate materials and drug products

The method and standard to confirm ingredients or characteristics shall be described in the light of the latest scientific levels in addition to specifications and test method prescribed in the approval letter for the quality assurance of intermediate materials and drug products.

(2) Manufacturing methods and procedures

(A) Manufacturing methods and procedures

The requirements that should be added to manufacturing methods and procedures prescribed in the approval letter shall be described for the quality assurance of intermediate materials and Drug products because crude drugs are used as raw materials.

Chapter 3 Manufacturing Control Standard Code

The following items shall be additionally described in Manufacturing Control Standard Code.

(1) Storage of raw material crude drugs

(A) Requirements for Storage

A) Lot control

The lot control shall be kept, in principle, by the unit of receipt, and if necessary, the unit of receipt shall be devided into two or more lots.

B) Storage control

Requirements for facilities, methods and conditions of storage shall be established, where appropriate, for prevention of contamination, deterioration due to fungi, invasion of insects and rodents, etc.

(2) Control in the manufacturing process

(A) Check and Records in each manufacturing process

A) Preparation of Raw material crude drugs

When Raw material crude drugs in two or more lots are mixed, the lot numbers, amounts, as well as the composition (amounts of raw materials) shall be records.

When a previously mixed crude drug is used as raw material, a new lot number shall be assigned.

B) Confirmation of Raw material crude drugs

Manufacturing control manager or a designated person shall open the package of Raw material crude drugs and confirm properties etc. when they are used in the manufacture.

(C) Prevention of contamination

Chapter 4 Quality Control Standard Code

The following items shall be additionally described in Quality Control Standard Code.

(1) Quality control

(A) Sampling method

An appropriate method of sampling for the analysis and testing shall be established for each crude drug in consideration of its characteristic and shape in accordance with General Rules for Crude Drugs and General Test method (the Tests for Crude Drugs) of JP.

(B) Re analysis and retesting

Raw material crude drugs shall be stored in conformity with the standards of re analysis and retesting established for that purpose in consideration of the properties of the crude drugs.

(C) Retention of reserve samples of extract for Kampo medicine and Crude drug

Chapter 5 Manufacturing Hygiene Control Standard Code

The following matters shall be described in Manufacturing Hygiene Control Standard Code.

(1) Manufacturing Hygiene control

(A) Hygiene control of working personnel

(B) Hygiene control of manufacturing room, facilities and utensils

Chapter 6 Contract etc. between Manufacturer of Bulk Products and Manufacturer of Finished Products

(1) Contract

(A) Confirmation of the approval letter

(B) Manufacturing control of bulk products

The confirmation method of the conditions of the manufacturing control shall be required.

(C) Quality control of bulk products

A) The confirmation of specification and testing method shall be prescribed

B) The confirmation of the test results shall be required.

(D) Transportation of bulk products

A) Quality and form of containers and packaging materials shall be confirmed.

B) Consideration shall be given for prevention of deterioration of bulk products during transportation.

(2) Miscellaneous

(A) Liaison Manager

In preparation for doubt aroused about the quality of the product, a liaison manager shall be designed on both sides that are manufacturer of bulk products and manufacturer of finished products for the maintenance of close communication.

Chapter 7 Analysis and Testing of Finished Products

The quality assurance of finished products shall be maintained not only by the specifications and the analysis and testing described in the approval letter, but also by the method and requirement of quality control specially established in the latest scientific levels.

At the same time, efforts should be made for the development of new evaluation method including measure for biological contamination.

Chapter 8 Archiving and Practical Use of Each Records

All of the records shall be retained for 3 years after the date of preparation of the record.

Each records shall be appropriately arranged and retained, and used for quality assurance of raw material crude drugs and, Proprietary Kampo medicine and Crude drug formulations.

Regulations for Manufacturing Control and Quality Control of Proprietary Kampo Medicine and Crude Drug Formulations

(Self-imposed regulations of Japan Kampo-Medicine Manufacturers Association:JKMA)

Chapter 1 General Provisions

(1) Purpose

The purpose of this regulation is to assure quality of Proprietary Kampo medicine and Crude drug formulations by establishing additional requirements for the manufacturing control and quality control as well as in conformity with "the Regulations for Manufacturing Control and Quality Control of Drugs (hereinafter referred to as "GMP Regulations")" taking into account that crude drugs are used as raw materials.

(2) Scope of application

This Regulation shall apply to any manufacturing plants for Proprietary Kampo medicine and Crude drug formulations.

(3) Definitions

The definitions contained in the Japanese Pharmacopoeia (JP), Standards for Non pharmacopoeial Crude Drugs (Non JP Crude Drug Standards) and the GMP Regulations shall be applicable to the terms used in this Regulation. The following terms in particular shall apply to these Regulations.

(A) Raw material crude drugs

"Raw material crude drugs" means crude drug used in the manufacture of Proprietary Kampo medicine and Crude drug formulations.

(B) "Bulk product" means the product used in the formulation of processed raw material crude drugs.

(4) Crude drug control manager

The manufacturer of Proprietary Kampo medicine and Crude drug formulations (except for the manufacturer that do not use raw material crude drugs for their productions) shall designate a crude drug control manager under the quality control manager.

The quality control manager may be at the same time the crude drug control manager.

(A) Qualifications of crude drug control manager

The crude control manager shall have the following qualifications.

A) Having professional knowledge on crude drugs and an ability to form a qualitative judgment of crude drugs

B) Having appropriate knowledge from practical experience on the treatment of raw material crude drugs

(B) Duties of crude drug control manager

In order to provide practical quality assurance of raw material crude drugs, the crude drug control manager shall perform the following duties by himself, or if necessary, by a designated person.

A) Method of sampling of raw material curde drug.

B) In the process of the analysis and testing of raw material crude drugs , evaluation of the results of differentiation (including differentiation of morphological quality).

C) Education and training of personnel handling raw material crude drugs.

D) Miscellaneous duties for the quality assurance of raw material crude drugs

Chapter 2 Drug Product Standard Code

The following items shall be additionally described in Drug Product Standard Code

(1) Specifications and test method of the starting materials, intermediate materials and drug products

(A) Starting materials

A) Quality Assurance of raw Material Crude Drugs

The method and standard to confirm ingredients or characteristics shall be described in the light of the latest scientific levels for the quality assurance of raw material crude drugs.

B) Grading test and Differentiation test of raw material crude drugs

C) Requirements in the commission of cutting and powder cutting processing of raw material crude drugs

In addition to "Requirements for Commissioned Manufacture of Drugs, etc." (Pharmaceutical Affairs Bureau Notification No 234, March 12, 1986), the following requirements shall be taken into consideration

a) Before commissioning, the quality of raw material crude drugs shall be assured on commissioning person's responsibility

(2) Standards for receipt of cut crude drugs shall be established, and analysis and testing of such products shall be performed accordingly upon their receipt.

3) Requirements in purchasing cut crude drugs

When cut crude drugs are received, the quality of whole crude drugs shall be assured on the basis of the results of analysis and testing of whole crude drugs submitted by the supplier.

<Manufacturing control standard code>

1) Lot control (of whole land cut crude drugs)

The lot control shall be kept, in principle, by the unit of receipt. It shall also be kept by the place of production, packaging form, appearance, etc. of the crude drug, and, if necessary, the crude drug shall be controlled for each lot.

2) Storage control

(1) Appropriate standards for facilities, methods and conditions of storage shall be established and followed for prevention of contamination and deterioration due to fungi, insects, rodents, etc.

(2) Fumigation shall be performed according to JP General Rules for Crude Drugs.

The record of fumigation shall be retained for three years.

<Quality control standard code>

1) Method of sampling

An appropriate method of sampling for the analysis and testing shall be established for each crude drug in consideration of its conditions such as the place of production, appearance, distribution and packaging form.

2) Re-analysis and retesting

Raw material crude drugs (whole and cut), when stored for a long period, shall be stored in conformity with the standards of re-analysis and retesting established for that purpose in consideration of the properties of the crude drugs.

3) Retention of reserve samples of crude drugs

The reserve samples of crude drugs consisting of at least twice the quantity necessary for the analysis and testing required shall be retained for each lot under appropriate conditions for three years after the date of manufacture of the extract for Kampo medicine formulations.

4) The records shall be accumulated and kept in good order for the quality assurance of crude drugs.

Chapter 3 Manufacturing Control and Quality Control in the Manufacturing Process of Extract for Kampo Medicine Formulations

With good understanding of original texts of Kampo medicine, facilities for stable manufacture of extracts for Kampo medicine formulations equivalent to the designed quality described in the letter of manufacturing (import) approval shall be established; manufacturing conditions and methods fulfilling that purpose shall be devised; and the quality of the extract shall be assured in the light of the designed quality by a scientific evaluation.

In order to attain the above purposes, the drug product standard code, manufacturing control standard code, manufacturing hygiene control standard code, and quality control standard code shall be prepared, describing the following information:

<Drug product standard code>

1) Manufacturing method and process for each product

"Method and process" in the above include the following information:

Standard charge-in quantity, extraction condition, concentration and drying conditions, sieving, mixing conditions, storage conditions.

2) Amount and rate of yield in each manufacturing process

(1) The range of the amount and rate of yield shall be given in consideration of raw material crude drugs and the production scale.

(2) The assurance of designed quality of the manufactured extract for Kampo medicine formulations shall be verified.

3) Specifications and test method for the extract for Kampo medicine formulations

<Manufacturing control standard code>

1) Manufacturing control

(1) Control of solvents for extraction.

(2) Prevention of contamination.

(3) Regulations for routine control and regular control.

(4) Other matters concerning manufacturing control.

2) Requirements for a change in facilities, manufacturing method, etc.

(1) Confirmation of designed quality.

(2) Measures to be taken after confirmation and evaluation.

<Manufacturing hygiene control standard code>

1) Manufacturing hygiene control

(1) Hygiene control of working personnel

(2) Hygiene control of manufacturing room, facilities and utensils

<Quality control standard code>

1) Retention of reserve samples of extract for Kampo medicine formulations

The reserve samples consisting of at least twice the quantity necessary for the analysis and testing required shall be retained for each lot under appropriate conditions for three years after the date of manufacture.

Chapter 4 Record of Manufacturing Process of Extract for Kampo Medicine Formulations

A record describing clearly the manufacturing control, manufacturing hygiene control and quality control shall be maintained, and it shall be retained for three years after the date of manufacture of the finished product with use of the extract. The matters to be recorded shall be selected in consideration of the matters required in the GMP Regulations; and the following matters shall be added:

1) Lot number and amount of raw materials

When raw material crude drugs in two or more lots are mixed, the lot numbers, amounts, as well as the composition (amounts of raw materials) shall be recorded.

When a previously mixed crude drug is used as raw material, a new lot number shall be assigned.

2) Recording matters in the manufacturing process of extract for Kampo medicine formulations
   (1) Weighing process
   (2) Extraction process

   Number of the extracting machine, charge in quantity, amount of solvent for extraction, time for raising temperature, extraction temperature, extraction time.
   (3) Concentration process

   Number of the concentrating machine, concentration temperature, concentration time.
   (4) Drying process

   Number of the drying machines, drying temperature, drying time, amount of dried extract.
   (5) Other recording matters in each process

Chapter 5 Contract Between Manufacturer of Extract for Kampo Medicine Formulations and Manufacturer of Finished Product

In the case where the manufacturer of an extract for Kampo medicine formulations is not at the same time the manufacturer of the finished product, the manufacturers shall conclude a contract beforehand for supply and receipt of the extract, and establish standards concerning the following matters, so that the quality assurance of the extract is maintained.

1) Confirmation of the letter of approval of the extract
2) Manufacturing control of the extract

   Confirmation of the conditions of the manufacturing control.
3) Quality control of the extract
   (1) Presentation of the test method and establishment of the standards for supply and receipt.
   (2) Confirmation of the test results.
4) Transportation of the extract
   (1) Quality and form of containers and packaging materials.
   (2) Consideration shall be given for prevention of deterioration of the extract during transportation.
5) Supply and receipt of the extract
   (1) Record of supply and receipt shall be maintained by lot.
   (2) The manufacturer of the extract, when supplying the extract, shall attach the manufacturing process record of the extract after consultation with the manufacturer of finished product.

6) The manufacturer of finished product shall confirm, when necessary, records concerning manufacturing control, manufacturing hygiene control and quality control submitted by the manufacturer of the extract.
7) In preparation for doubt aroused about the quality, a liaison manager (in the quality control unit) shall be designated on both sides for the maintenance of close communication.
8) Records shall be retained for three years.

Chapter 6 Manufacturing Control and Quality Control of the Process of Preparation of Finished Products

In the process of preparation of finished products, the GMP Regulations and the Regulations for Buildings and Facilities for Pharmacies etc. shall be followed. At the same time, in consideration of the fact that the extract for Kampo medicine formulations is a rich nutritive source for microorganisms, manufacturing control shall be maintained with special attention being paid to the prevention of microbial contamination.

Chapter 7 Analysis and Testing of Finished Products

The quality assurance of finished products shall be maintained not only by the specifications and the analysis and testing described in the letter of approval, but also by the guidelines specially established in the light of the latest scientific level. At the same time, efforts should be made for the development of new evaluation method.

1) The tests required in addition to the specifications and analysis and testing in the letter of approval may include the following:
   (1) A quantitative test of ingredients under control other than ingredients conforming to the specifications for approval.
   (2) Microbiological test.
   (3) Physical test.
   (4) Other test.

Chapter 8 Complaints

As stipulated in the GMP Regulations, an appropriate measure shall be taken quickly upon receipt of a complaint. The manufacturer of the prescription extract product in Kampo medicine formulations shall investigate not only into his manufacturing plant, but also into the manufacturer of the extract for Kampo medicine formulations used and raw material crude drugs and the trader of the crude drugs, and take appropriate measures accordingly.

The record of complaints shall be retained for three years after the date of preparation of the record.

Chapter 9 Imported Products

Imported products shall be subject to the same regulations as those for the domestic products so that their designed quality is assured.

人事 Personnel

企業領導人 Chairman

部門負責人 Key Personnel (responsible staff)

生產 Production

品質管制(質量管理) Quality Control

專職

不得互兼

培訓 Training

廠房 Premises

生產環境

流程

合理佈局

防蟲、鼠、鳥 .....

房屋內墻局： 光滑、清洗、消毒、弧角

暗管

照明：＞ 300 Lux

溫度

相對濕度

下水道

清淨度

設備 Equipment

易清洗、消毒、維護保養

防塵、防止交叉污染

考慮安全

依製造順序排列

滅菌監測、定期驗證

純水、注射用水：循環、貯罐保濕

定期保養、修理、驗證

記錄

衛生 Personnel Hygiene

健康檢查

訂衛生管理制度

清潔規程

工作服

生產操作人員不得化妝、佩飾

異常現象報告上級

原物料、中間品、成品

購、用之管理制度

貯存場所適當、合理

待驗區 Quarantine Area

抽驗區避免污染

毒劇藥之管理及貯存

貯存期

退貨管理

包裝及貼籤

包裝品之管理制度

包裝指示 Packaging Instructions

批次包裝記錄 Batch Packaging Records

標籤管理 Label Control

生產管理

管理制度

原、物料規格及檢驗方法

批、批號

產品生產管理文件

產品質量管理文件

設備管理制度

生產記錄

標準作業程序

Standard Operating Practice, S.O.P.

設備管理制度

部門衛生管理制度

防止污染和混淆

清場記錄

質量管理

質量管理部門直屬企業負責人

職責

自檢 Self-Inspection

組織

記錄

銷售記錄

用戶意見及怨訴

A comparison of major engineering cleanroom classes in the world

	Country and Standard				
	USA 209D	*Britain BS 5295*	*Australia AS 1386*	*France AFNOR X44101*	*W Germany VDI 2083*
Date of issue	*1988*	*1989*	*1989*	*1981*	*1990*
					0
		C	0.035		1
	1				2
	10	D	0.35		3
	100	E or F	3.5	4000	4
	1000	G or H	35		5
	10 000	J	350	400 000	6
	100 000	K	3500	4 000 000	7
		L			

表 2.1.1.1 医药工业洁净厂房空气洁净度等级

洁净级别	尘粒数/M³		活微生物数/M³	
	≥0.5μm	≥5μm	沉降菌	浮游菌
100 级	≤3500	0	≤1	≤5
10000 级	≤350000	≤2000	≤3	≤100
100000 级	≤3500000	≤20000	≤10	≤500
大于 100000 级	≤35000000	≤200000	暂缺	暂缺

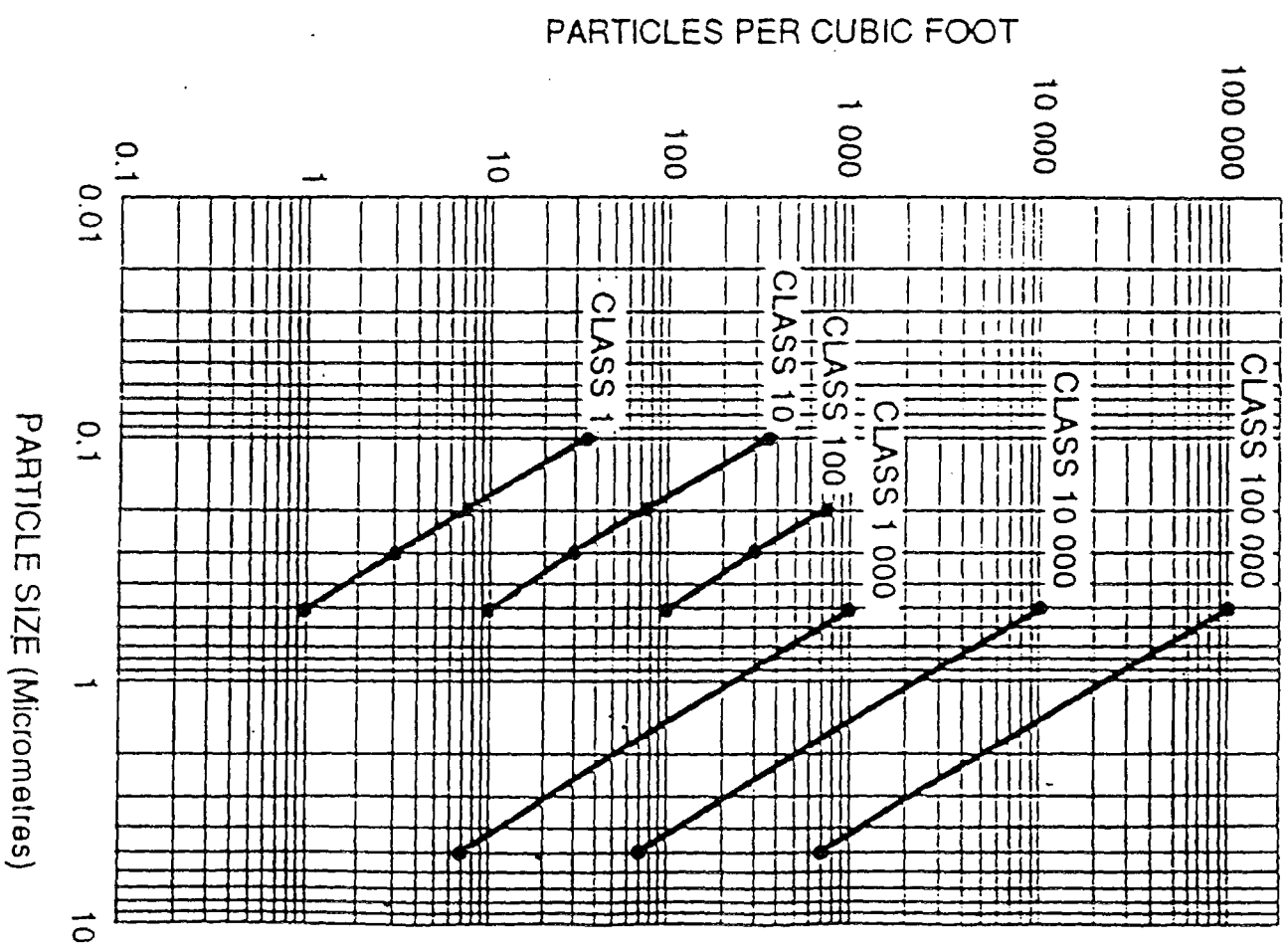
* 如国家有新规定时，按新规定执行。有条件的企业也可实施更高的标准。

注 1、测状态以静态为据。

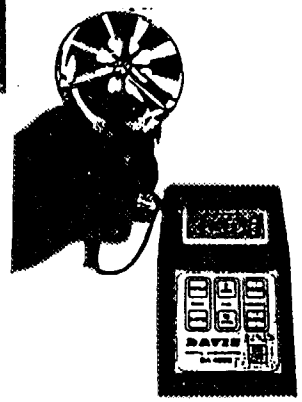
Federal Standard 209D class limits in particles per cubic foot, of size equal to or greater than particle size shown

Class	*Measured particle size (μm)*				
	0.1	*0.2*	*0.3*	*0.5*	*5.0*
1	35	7.5	3	1	NA
10	350	75	30	10	NA
100	NA	750	300	100	NA
1000	NA	NA	NA	1000	7
10 000	NA	NA	NA	10 000	70
100 000	NA	NA	NA	100 000	700

NA = Not applicable



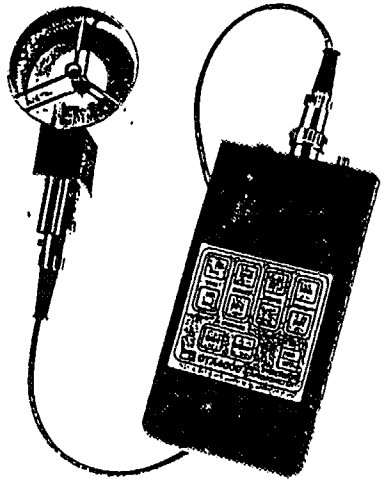
Davis Portable Air Velocity Kit



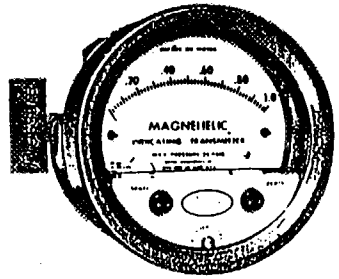
Air Velocity / Volume System

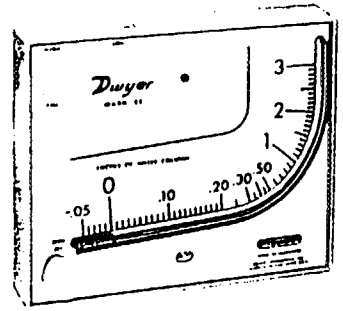
A Complete System For Digital Measurement Of:

- Air Velocity
- Air Volume
- Temperature
- Relative Humidity

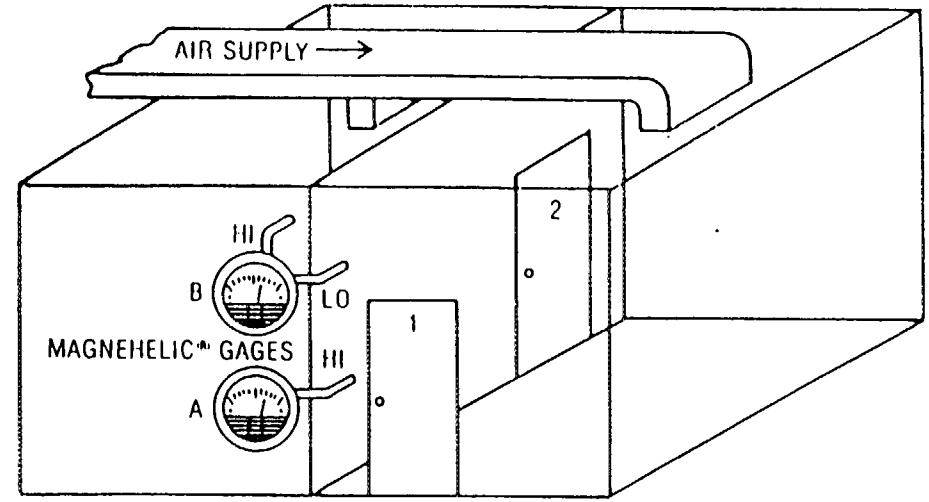


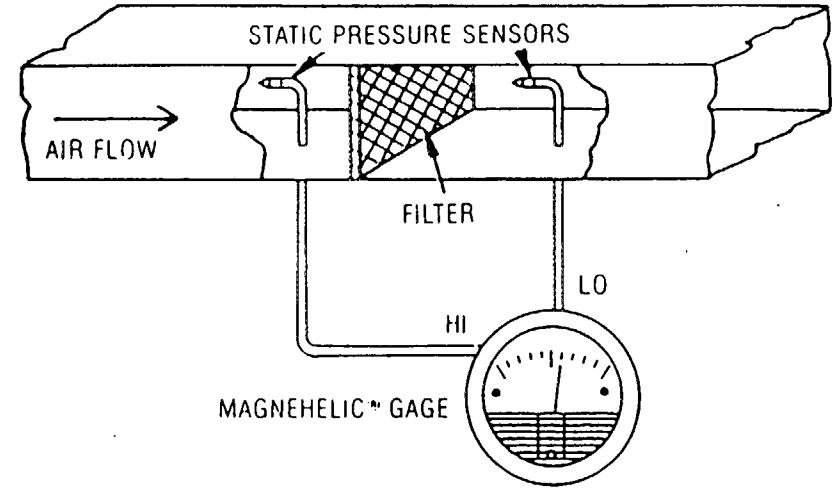
Differential Pressure Transmitter





Mark II molded plastic air filter gage.





Product Master File

1. Copy of Certificate Issue by Government Authorities
2. Name, Dosage Form, Strength (or Potency) & Code Nos.
3. Complete Formulation, Unit Content, Lot Requirement
4. Raw Material's Specification and Control Procedures
5. Fixed Lot Size & Raw Materials Requirement per Lot
6. Lot Manufacturing Record
7. Theoratical Yield & Control Range
8. Theoratical and Actual Yields in Different Steps
9. In-Process's Specification & Control Procedures
10. Product's specification & Control Procedures
11. Packing Material's specification & Control Procedures
12. Packaging Instruction and Methods
13. Samples of Printed Packaging Material
14. Procedure of Special Method or Manufacturing Process
15. Procedure of Special Analytical Method
16. Storage Condition of In-Process and Finished Product
17. Written By, Approved By, & Date
18. Revised Records

RAW MATERIAL SPECIFICATION

1. Name
2. Code No.
3. Physical and Chemical Properties
4. Potency, Requirements and Limitations
5. Method of Packing
6. Storage Requirement
7. Notice and Precaution
8. Sampling Method and Quantity
9. Quantity of House Samples and Packaging Method
10. Re-evaluation Date Required
11. Written By, Approved By, and Date
12. Revision Records and Date

Specifications of Packaging Material

1. Name
2. Code No.
3. Materials
4. Shape, Size and Drawing
5. Description
6. Test Items and Specification
7. Packing Method
8. Storage Condition
9. Notice and Precaution
10. Sampling Method & Quantity
11. Quantity of House Sample
12. Written By, Approved By, and Date
13. Revision Records and Date

WRITEN PROCEDURES & RECORDS REQUIREMENT

ENVIROMENTAL SANITATIONS	PROCEDURE	RECORDS
Plant Layout	x	
Dust-Removal Systems Cleaning Procedures	x	x
Waste Disposal Procedures	x	
Waste Water Analysis Procedures	x	x
BUILDING & FACILITIES		
Area, Building Sanitation Procedures	x	x
Departmental Cleaning Procedures	x	x
Sanitation Check List		x
Rodent & Insect Control Program	x	x
Air Classification, Filtration, and Handling Program	x	
Air Particulate Counting Procedures	x	x
Water Chiller Operating Procedures	x	
Air Handling Unit Operating Procedures	x	
Dehumidifier Operating Procedures	x	
Temperature Records		x
Relative Humidity Records		x
Positive Pressure Differential Checking Records		x
Organic Solvents and Gases Storage Program	x	
Lockers, Lavatory and Rest Facilities Sanitation Program	x	x
Boiler Operating Procedures	x	
Boiler Maintenance Program	x	x
Water Treatment Procedures	x	x
Water-Still Operating Procedures	x	x
Container Cleaning Procedures	x	x
Container Sterilization Procedures	x	x
Microbial Enviromental Monitoring Program	x	x

	PROCEDURE	RECORDS
UV Light Maintenance Procedures	x	x
Aseptic Area Cleaning & Sterilization Procedures	x	x
Laminar Flow Operating Procedures	x	
Laminar Flow Validation Procedures	x	x
HEPA Filter Installation, Operating and Maintenance Programs	x	x
HVAC Qualification Program	x	x
EQUIPMENTS		
Equipment Operating Procedures	x	
Equipment Cleaning Procedures	x	x
Equipment Sterilization Procedures	x	x
Equipment Calibration Procedures	x	x
Equipment Qualification Program	x	x
Weighing Equipment Operating Procedures	x	
Weighing Equipment Calibration Procedures	x	x
Reagent and Test Solution Handling Procedures	x	
Standard Solution Preparing Records		x
Reference Standards Handling Program	x	x
Working Standards Handling Records	x	x
Control Bacteria References Handling Procedures	x	x
ORGANIZATION & PERSONNEL		
Organization chart		x
Key Staffs Qualifications and Experience		x
Job Description and Personnel Responsibility	x	
Job Training Program	x	x
GMP Training Program	x	x
Aseptic Technics Training Program	x	x

	PROCEDURE	RECORDS
Industrial Safety Training Porgram	x	x
Personnel Good Sanitation Practice	x	x
Uniforms Handling Procedures	x	
Medical Examination Program	x	x
Medical Assessment of Employees Program	x	x

RAW MATERIALS, PRIMARY CONTAINERS & CLOSURES

Raw Material Specifications	x	
Raw Material Laboratory Control Procedures	x	
Raw Material Receiving Procedures	x	x
Raw Material Storage Procedures	x	x
Raw Material Sampling Procedures	x	x
Raw Material Physical Inspection Procedures	x	x
Raw Material Approved or Rejection Procedures	x	x
Raw Material Lot No. Registered Records		x
Raw Material Re-evaluation Record		x
Supplier and Vendor Approval Procedures	x	x
Reserve Sample Handling Procedures	x	x
Material Lot Identification Procedures	x	x
Narcotics and Poisons Handling Program	x	x
Statistical Sampling Procedures	x	
Laboratory Analytical Requisition		x
Analytical Reprot		x
Inventory Handling Procedures	x	x
Rejected Material Handling Procedures	x	x

	PROCEDURE	RECORDS

PRODUCTION CONTROL

Product Master File	x	
Raw Material Requirement Sheets		x
Raw Material Requisition Per Lot		x
Product Specifications	x	
Product Laboratory Control Procedures	x	
Master Manufacturing Instructions	x	x
Department Operating Procedures	x	x
Equipment Log and Identification Program	x	x
Lot Manufacturing Records		x
Raw Material Dispensing and Checking Procedures	x	x
In-Process Sampling Procedures	x	x
Production Order		x
Machine-Hour Records		x
Man-Hour Records		x
Manufacturing Schedule Sheet		x
Yield/Accountability Determination and Limits Setting Procedures	x	x
Re-Working/Tailing Handling Procedures	x	x
Scag Handling Procedures	x	x
Process Validation Program	x	x
In-Process Inspection Procedures	x	x
Aseptic Manufacturing Procedures	x	
Procedures of Validating Sterilization Process	x	x
Procedures of Validating Aseptic Filling Process	x	x

	PROCEDURE	RECORDS
PACKAGING & LABEL CONTROL		
Packaging Materials Specifications	x	
Packaging Materials Laboratory Control Procedure	x	
Packaging Materials Storage Procedures	x	x
Packaging Materials Sampling Procedures	x	x
Packaging Materials Physical Inspection Procedures	x	x
Packaging Materials Approval or Rejection Procedures	x	x
Packaging Materials Lot No. Registed Record		x
Packaging Materials Lot and Identification Procedures	x	x
Printed Label or Carton Storage Procedures	x	
Printed Label or Carton Destroyed Procedure	x	x
Lot No. Printing and Checking Procedures	x	x
Packaging Order	x	
Master Packaging Instruction	x	
Lot Packaging Instruction and Records	x	x
Printed Lable Issuing Procedures	x	x
Packaging Line Inspection Procedures	x	x
Finished Products Inspection Procedures	x	x
Expiration Dating Manual	x	
Lot No. and Expiration Dating Records		x
STORAGE & DISTRIBUTION		
Finished Products Storage Procedures	x	
Finished Products Inventory Records		x
Finished Products Distribution Procedures	x	x
Shipping/Packing List		x
Merchandise Recall Procedures	x	x
Narcotics and Poisons Handling Program	x	x

	PROCEDURE	RECORDS
QUALITY CONTROL		
Laboratory Operating Procedures	x	x
Instrument Operating Procedures	x	x
Instruemnt Using Records		x
Instrument Calibration Procedures	x	x
Instrument Maintenance Procedures	x	x
Finished Products Stability Testing Procedures	x	x
New Products Stability Testing Procedures	x	x
Procedures of Review of Standard Operating Written Procedures	x	x
Procedures of Records Review	x	x
Reserve Sample Retaining Procedures	x	x
Reserve Sample Review Programs	x	x
Procedures for the Housing, Feeding, Handling and Care of Animals	x	x
Penicillin Cross-Contamination Detection Procedures	x	x
Antibiotic Cross-Contamination Detection Procedures	x	x
Clean Validation Program	x	x
RECORDS & REPORTS		
Record Retention Program	x	
Product Quality Review Program	x	x
Process Validation Program	x	x
Lot Manufacturing Record		x
Lot No. Printed Label Specimens Sheet and Sampling Record		x
Raw Materials and In-Process Identification Tag Retaining Records		x
Equipment Identification Tag Retaining Records		x
Container Identity Tag Retaining Records		x
Laboratory Test Reports		x
Calculation Sheets		x
Instrument Graph, Chart, and/or Spectra Records		x
Microbiological Test Reports		x
Animal Test Reports		x

	PROCEDURE	RECORDS
Yield Investigation Program	x	x
Analytical Statistical Control Charts		x
In-Process X-$\bar{R}$ Charts		x
Lot Review Programs	x	x

CONPLAINT, AND RETURNED GOODS

Procedures of Handling Product Complaints	x	x
Procedures of Handling Return Goods	x	x
Procedures of Re-Packing Process	x	x

標準作業程序

內　容

目　的　Purpose

範　圍　Scope

職　責　Responsibilities

器　物　Materials

手　續　Procedures

標準作業程序

S　O　P

名稱　Title, Subject

編號　No.

頁數　Page ____ of ____

生效日期　Effective Date

承續日期　Supersedes Date

頒佈部門　Issued By

使用部門　Departments

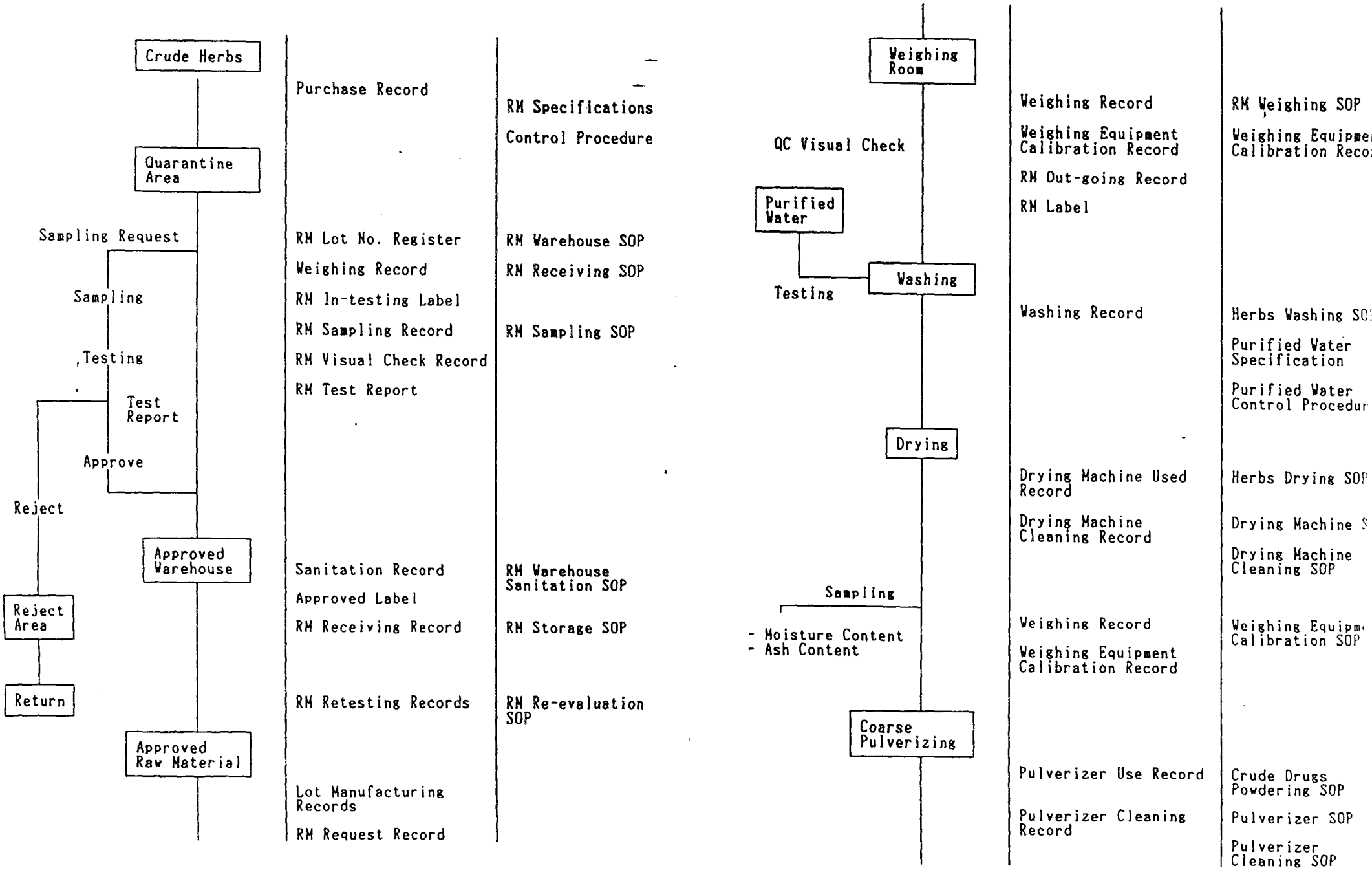
擬訂人　Prepared By

核准人　Approval

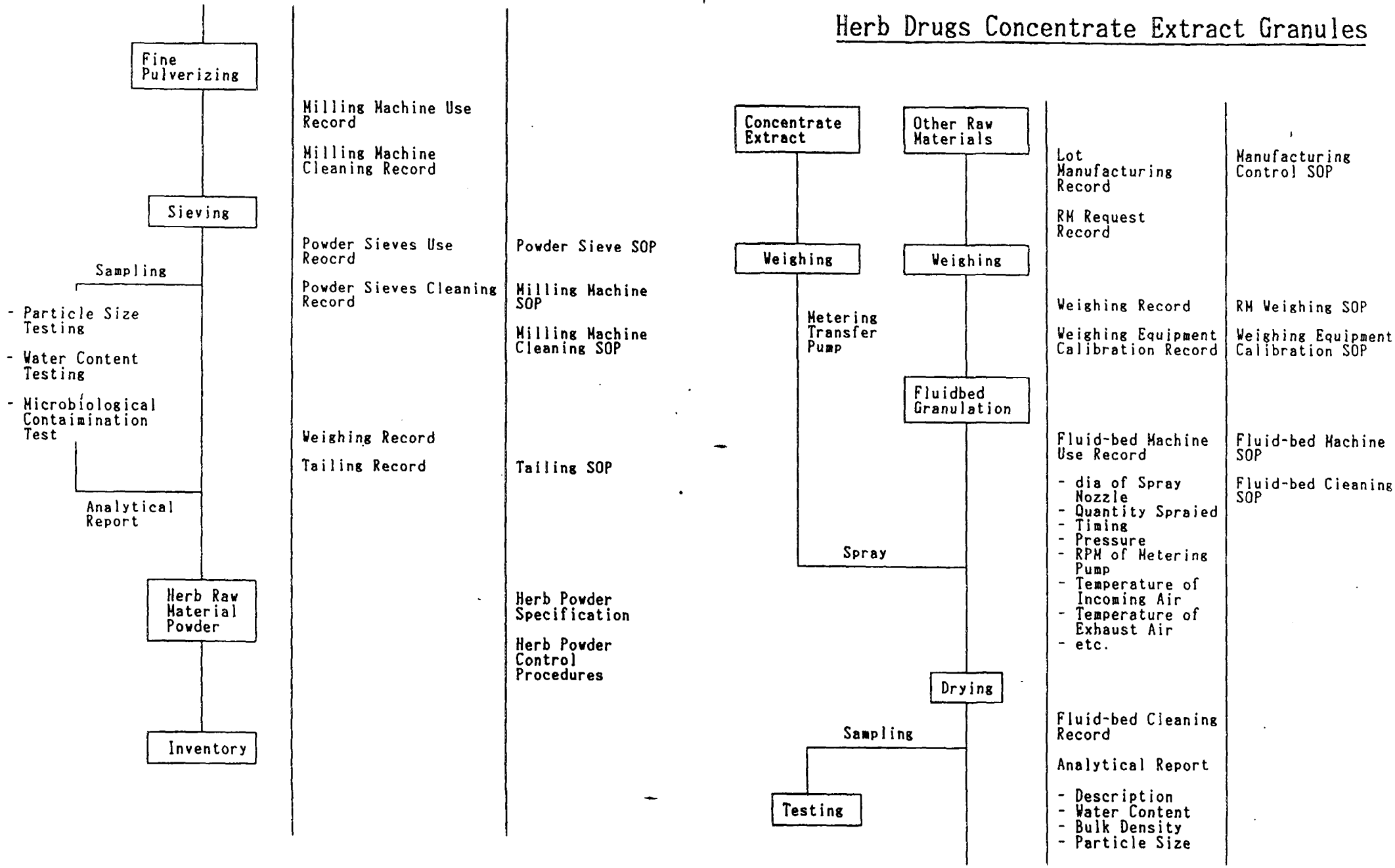
內容　Content

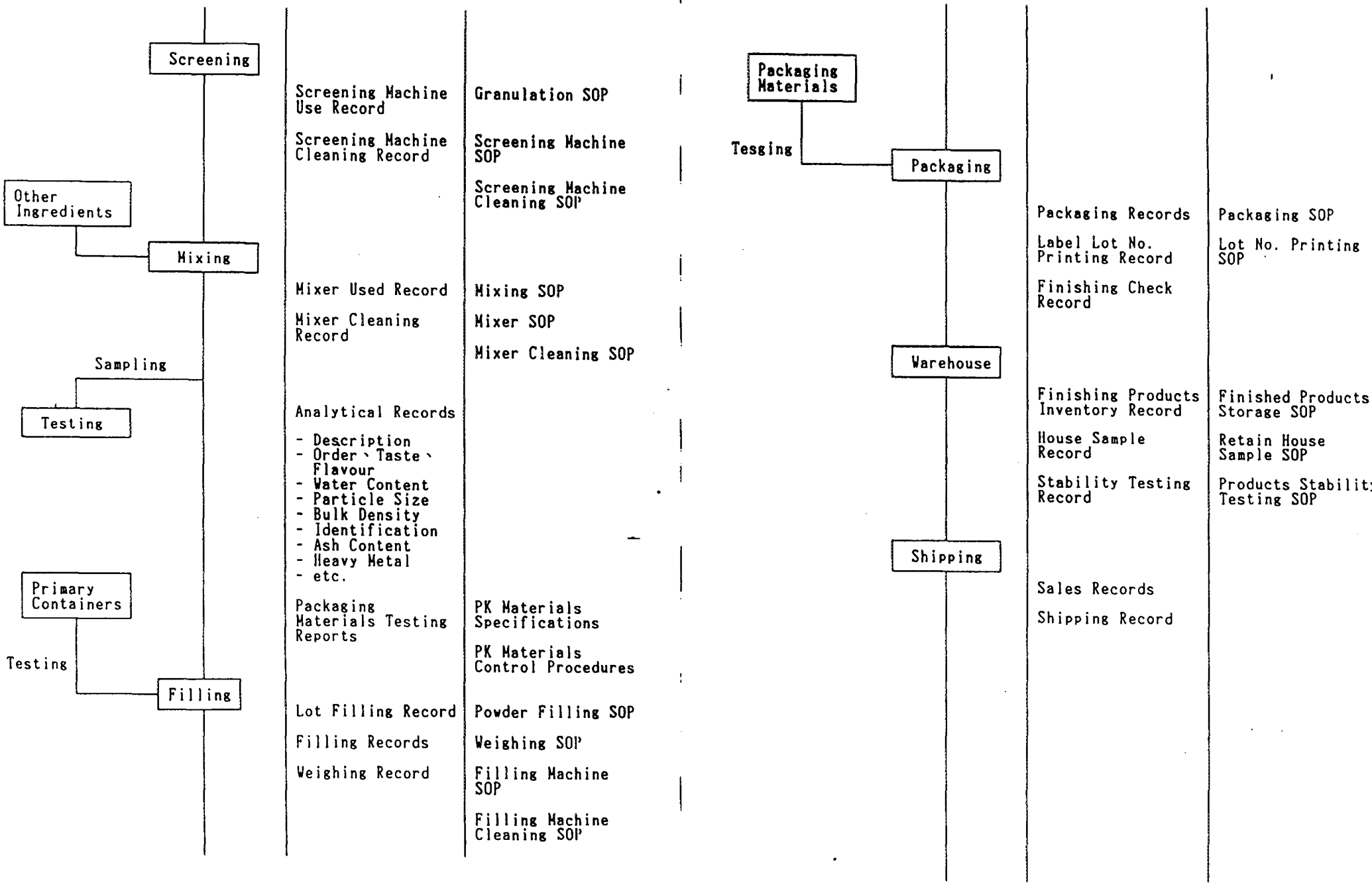
修訂記錄　Change History

HERB POWDER


Crude Herbs
Purchase Record
RM Specifications
Control Procedure
Quarantine Area
Sampling Request
RM Lot No. Register
RM Warehouse SOP
Weighing Record
RM Receiving SOP
Sampling
RM In-testing Label
RM Sampling Record
RM Sampling SOP
Testing
RM Visual Check Record
RM Test Report
Test Report
Approve
Reject
Approved Warehouse
Sanitation Record
RM Warehouse Sanitation SOP
Approved Label
Reject Area
RM Receiving Record
RM Storage SOP
Return
RM Retesting Records
RM Re-evaluation SOP
Approved Raw Material
Lot Manufacturing Records
RM Request Record
Weighing Room
Weighing Record
RM Weighing SOP
Weighing Equipment Calibration Record
Weighing Equipmer Calibration Recor
QC Visual Check
RM Out-going Record
RM Label
Purified Water
Washing
Testing
Washing Record
Herbs Washing SO
Purified Water Specification
Purified Water Control Procedur
Drying
Drying Machine Used Record
Herbs Drying SOP
Drying Machine Cleaning Record
Drying Machine S
Drying Machine Cleaning SOP
Sampling
- Moisture Content
- Ash Content
Weighing Record
Weighing Equipm Calibration SOP
Weighing Equipment Calibration Record
Coarse Pulverizing
Pulverizer Use Record
Crude Drugs Powdering SOP
Pulverizer Cleaning Record
Pulverizer SOP
Pulverizer Cleaning SOP

Herb Drugs Concentrate Extract Granules




Screening
Other Ingredients
Mixing
Sampling
Testing
Primary Containers
Testing
Filling
Packaging Materials
Tesging
Packaging
Warehouse
Shipping
Screening Machine Use Record
Granulation SOP
Screening Machine Cleaning Record
Screening Machine SOP
Screening Machine Cleaning SOP
Mixer Used Record
Mixing SOP
Mixer Cleaning Record
Mixer SOP
Mixer Cleaning SOP
Analytical Records
- Description
- Order、Taste、Flavour
- Water Content
- Particle Size
- Bulk Density
- Identification
- Ash Content
- Heavy Metal
- etc.
Packaging Materials Testing Reports
PK Materials Specifications
PK Materials Control Procedures
Lot Filling Record
Powder Filling SOP
Filling Records
Weighing SOP
Weighing Record
Filling Machine SOP
Filling Machine Cleaning SOP
Packaging Records
Packaging SOP
Label Lot No. Printing Record
Lot No. Printing SOP
Finishing Check Record
Finishing Products Inventory Record
Finished Products Storage SOP
House Sample Record
Retain House Sample SOP
Stability Testing Record
Products Stability Testing SOP
Sales Records
Shipping Record

6.3 Control limits can be classified by two types: alert and action levels. If the system exceeds the alert limits, the excursion is investigated and the system is adjusted back into an acceptable state. If the system exceeds action limits, QA evaluation is required.

7.0 RECORDS

7.1 Individual Instrument History

Each instrument has a history recording the repairs, calibrations and adjustments, including input/out results at the calibration points performed on the instrument, and the dates thereof.

7.2 Tagging

The instrument may additionally be tagged with the device identification, current status of calibration, identification of the person who performed the calibration, and the next calibration date and location.

- May be color coded
- Tag may be for location and not for a particular instrument, just enter a new serial number without changing the tag number.

7.3 Accuracy Limits

7.3.1 Critical vs. Non Critical

Critical instruments must be identified and should be calibrated on a regular schedule consistent with its application.

Non critical instruments should be identified and may be calibrated on an as needed basis. Annotation on the tag is usually the only record utilized.

7.4 Calibration Schedules

Established a published schedule for calibration for all calibrated devices.

7.5 System Record Retention

Establish a system in place to ensure orderly retention or records.

7.6 Archival Policies

Establish a policy that states where records are to be kept and how they are stored.

CALIBRATION 校正

Demonstrating that a measuring device produces results within specified limits of those produced by a reference standard device over an appropriate range of measurements. This process results in corrections that may be applied if maximum accuracy is required.

VALIDATION 確效

Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

確效、確認、驗證

Process Step	Control Variables	Measured Responses
Preblending	Blending Time rpm Load Size Order of Addition	Blend Uniformity
Granulating	Load Size Amount of Granulating Agent Solvent Addition Rate rpm Granulation Time	Density
Drying	Initial Temperature Load Size Drying Temperature Program Air Flow Program Drying Time Cooling Time	Density Moisture Content Yield
Sizing	Screen Type Screen Size Feed Rate	Granule Size Dist. Loose Density Packed Density
Blending	Load Size rmp Blending Time	Blend Uniformity Flow Characteristics
Tableting	Compression Rate Granule Feed Rate Precompression Force Compression Force	Weight Variation Friability Hardness Thickness Disintegration Time Dissolution Dosage Form Uniformity

Typical variable and responses - granulated product.

Factors Affecting Validation

1. Raw Materials and Components
2. Product Design
3. Process Design
4. Equipment
5. Support Systems
6. In-Process Controls
7. Sampling Method
8. Analytical Testing Methodology
9. Product Specifications
10. Personnel Practices

INSTALLATION QUALIFICATION (IQ)

Documented verification that all key aspects of the installation adhere to the appropriate codes and approved design intentions and that manufacturers recommendations are duly considered.

OPERATIONAL QUALIFICATION (OQ)

Documented verifications that the system or subsystem performs as intended throughout all anticipated operating ranges.

PERFORMANCE QUALIFICATION (PQ)

Documented verification of the appropriateness of critical process parameters, operating ranges and system reproducibility over an appropriate time period.

THE VALIDATION PROCESS

1. Setting standards for quality attributes and operating parameters.
2. Defining the systems and subsystems suitable to produce the desired quality attribute and operating parameter.
3. Select/design equipment, controls and monitoring technologies.

Protocol

Approve

4. Installation Qualification (IQ)
   - Instrument calibration
   - Verify accuracy of drawings/manuals
   - Installation testing

5. Operational Qualification (OQ)
   - Tests to show system is operating as required
   - Set alert and action levels

   (This phase may overlap with step 6)

6. Performance Qualification

- Confirm the appropriateness of the critical process parameters and operating range

- System reproducibility is demonstrated over an appropriate time period or repeat runs

7.Validation Maintenance Program (Life Cycle Validation)

Review and update programs or procedures

- Change Control of Equipment and Systems
- Monitoring Programs
- Preventative maintenance
- Re-calibration
- Operating procedure
- Cleaning
- Training (where appropriate)

8.Validation Report

9.Annual System/Equipment Review

Validation Protocol Outline

I. Environmental Control
- HEPA filter installation and integrity testing
- Particular matter monitoring
- Air velocity profiles
- Differential pressure balancing
- Air change rate
- Temperature and Humidity control
- Microbial monitoring
- Cleaning, Maintenance and Operating procedures
- Instrument calibration

II. Sterilization Processes

A. Steam Sterilizers
- Thermocouple calibration
- Instrument calibration
- Jacket temperature profile
- Heat distribution study
- Heat penetration study
- Microbiological challenge with B. Stearothermophilus
- Cleaning, Maintenance, and Operating procedures

B. Dry Heat Sterilizers
- Thermocouple calibration
- Instrument calibration
- Heat distribution study
- Heat penetration study
- Microbiological challenge with B. Subtilis and E. Coli endotoxin

C. Filtration
- Physical integrity testing
- Pyrogen testing of effluent
- Particulate matter testing of effluent
- Extractables testing of effluent
- Chemical compatibility with product
- Flow rate evaluation with product
- Audit of Filter Manufacturer
- Microbial challenge testing

III. Water Systems
- Sanitization and Passivation procedures
- Equipment and instrument calibration
- U.S.P. W.F.I. testing
- Particulate matter profile
- Cleaning, Maintenance and Operating procedures

IV. Component Processing
- Bioburden reduction
- Particulate matter reduction
- Pyrogen reduction

V. Aseptic Filling Processes
- Media fill procedure
- Container/Closure integrity

VI. Equipment Processing
- Preventative maintenance program
- Cleaning, Maintenance and Operating procedures
- Cleaning procedure validation

VII. Service Systems

A. Compressed Air
- Dew point
- Hydrocarbon testing
- Microbial profile

B. Nitrogen
- Microbial profile

C. Clean Steam
- Sanitization and Passivation procedures
- U.S.P. W.F.I. test on condensate at all use points
- Cleaning, Maintenance and Operating Procedures

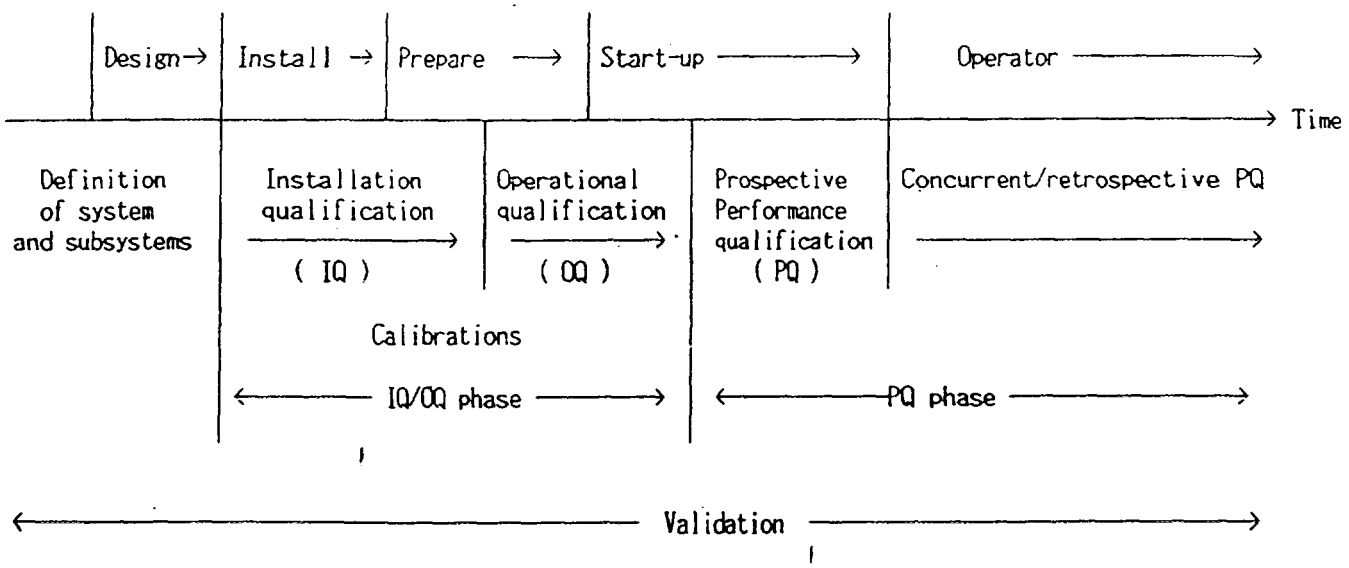
VIII. Solution Preparation and Delivery Systems
- Bioburden
- Particulate matter profile
- Cleaning procedures
- Sterilization procedures for tanks and lines

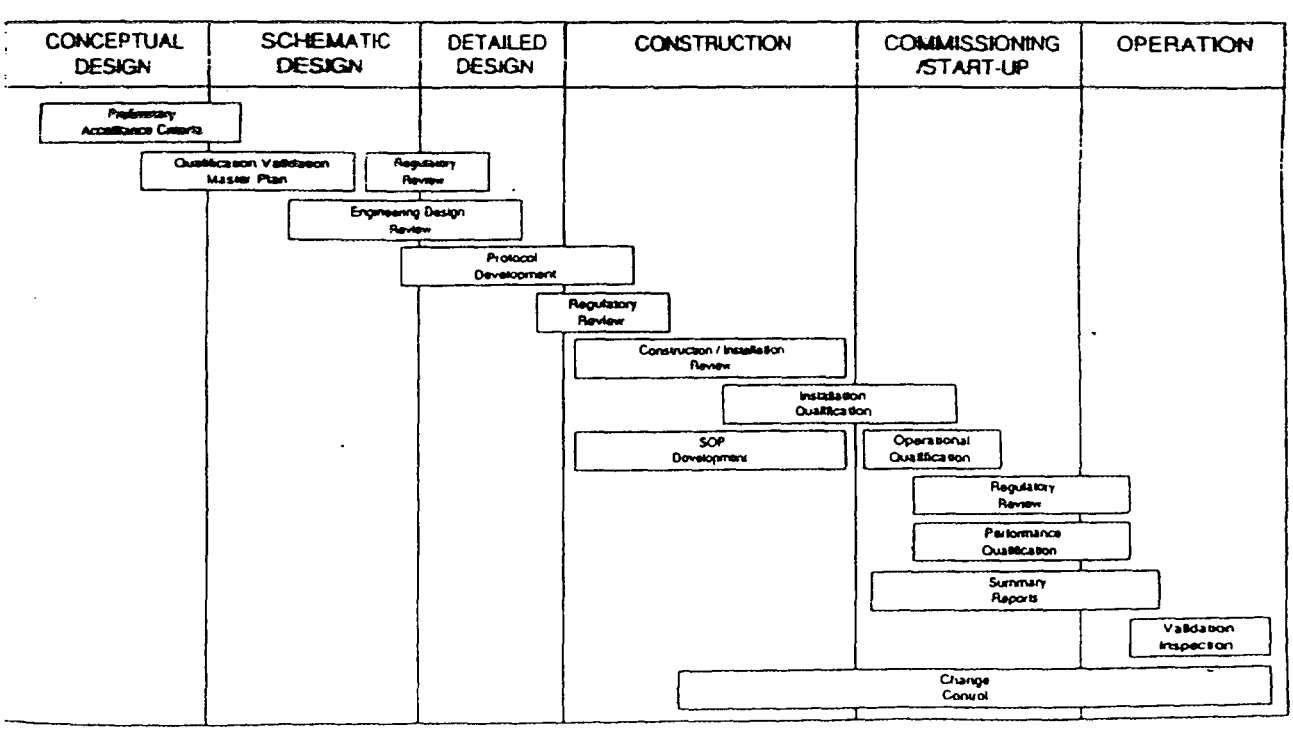
IX. Working Direction, S.O.P. and Documentation System Revision

X. Inspection Procedures

XI. Personnel Training

The Validation time line





JACOBS

Process Validation

Systems		Manufacturing	Designed	
Equipments		Processing		
Computers	for	Packaging	are Installed	to meet Requirements
Processes		Labelling		
Facilities		Storing	Operated	
Instrumentation		Testing		
		Controlling	Maintained	

Studies and Associated Activities will be Performed, Documedted, and kept current

to provide

Product Quality Assurance

Outline for Process Validation Program

Objective	Proving or demonstrating that the process works
Types of validation	Prospective, concurrent, retrospective, revalidation
Typical processes	Chemical, pharmaceutical, fabrication, packaging, sterilization
Definition of process	Flow diagram, equipment/materials, in-process, finished product
Definition of process output	Potency, yield, physical parameters
Definition of test methods	Methods, equipment, calibration, traceability, precision, and accuracy
Analysis of process	Critical modules and variables defined by process capability design and testing program
Control limits of critical variables	Defined by process capability design and testing program
Preparation of validation protocol	Facility, equipment, process, product number of validation trials and type, sampling frequency, type, size tests to be performed, method, criteria definition of successful validation
Organizing for validation trials	Responsibility, authority
Planning validation trials	Timetable and PERT chart, availability, material acquisition and disposal
Validation trials	Supervision/administration, process documentation
Validation findings	Data summary, data analysis, conclusions
Final report and recommendations	Process validated, further trials, requires more process capability design and testing

CLEANING VALIDATION

To establish documented evidence that the specified cleaning procedure, when followed, will reduce chemical, microbiological and detergent residues to a level at, or below acceptable limits.

分析方法確認之考慮因素

ACCURACY	準確度
LIMIT OF DETECTION	測定下限
LIMIT OF QUANTITATION	定量下限
LINERARITY	線性
PRECISION	精確度
RANGE	範圍
RUGGEDNESS	變異不定性
SELECTIVITY	選擇性

CLEANING VALIDATION PLAN

(EQUIPMENT CLEANING PROCESS)

-Update General Cleaning Procedure
-Validate Cleaning Procedure using Worst-Case Scenerio(Difficult Chemical/Difficult Equipment designwise.)
-Develop Cleaning Process Validation Protocol which should be used in Each Product/Each Equipment case.This should be linked with concurrent Process-Validation of New Products.

CLEANING PROCEDURE

-INTERACTING COMPONENTS:
-Surface
-Residues
-Cleaning Vehicle

-CHEMISTRY INVOLVED:
-Solvation
-Detergency
-Chemical Reaction

-CLEANING TECHNIQUES:
-Manual(Wipe/Mop On)
-Pressure Spray
-Soaking
-Ultrasonic Immersion
-CIP

-FACTORS AFFECTING CLEANING PROCESS:
-Conc.of Surfactant
-Action(Physical Force Used)
-Temperature
-Contact Time

-EVALUATION OF CLEANING:
-Inspection
-Sampling
-Residual Testing(Limits)

CLEANING VALIDATION

(Agenda)

Parts of A Cleaning Validation Program

Validating a cleaning procedure including a clear clea procedure that describes:

- What to clean
- When to clean
- How to clean
- With what
- Standards of cleanliness
- Testing
- Documentation

Consider making use of check sheets for the operator t document work as it is performed

Other procedures and programs to support cleaning:

- Developing a validated test method
- Training program
- Routine monitoring
- Selection and qualification of cleaning agents

Establishing limits

- Visual
- Chemical test of active
- Detergent
- Micro

Protocol

- Selecting product or products for cleaning validat

Annual review

Presentation test method validation?

CLEANING VALIDATION PROGRAM

- Know the Objective
- Set the Cleaning Methods
- Set Your Sampling Plan
- Validate the Test Methods.
- Set Your Criteria
- Document Thoroughly

- Know the Objective
  - To establish documented evidence that the specif cleaning procedure, when followed, will reduce chemical, microbiological and detergent residues level at, or below acceptable limits.
- Set the Cleaning Method
  - Procedures
  - Materials
  - Training
  - Documentation
- Set Your Sampling Plan
  - Number of Samples
  - Location of Samples
  - Method of Collection
  - Materials for Collection

- Validate The Test Methods
  - Required for all Residues Including Detergent
  - Must have Sufficient Sensitivity, Specificity
  - May be Simple Methods
  - Also Validate Sample Collection Methods
- Set Your Criteria
  - Based on Biological Activity/Toxicity
  - Consider Non-Homogeneous Contamination
  - Include Chemical, Microbial and Detergent Residues
  - Define Denominator for "Parts Per" Limits
  - Include Visual Criteria where Possible
- Document Thoroughly
  - Protocol and Report
  - Include Assumptions and Justifications
  - Assure Appropriate Reviews and Approvals

CLEANING VALIDATION PROGRAM

- Change Control
- Training
- Ongoing Monitoring
- SOP's

- Change Control
  - For Procedures
  - For Equipment Modification
  - For Materials
  - Tie into Revalidation Evaluation

- Training
  - Necessary to Assure Adherence to Procedure
  - Basic to Assure Intended Endpoint
  - Should be Documented

- Ongoing Monitoring
  - Don't "Set and Forget"
  - Establish Periodic Monitoring
  - Review Procedures, Results and Training Annually

- Sop's Should Cover
  - Cleaning Procedure
  - Change Control/Revalidation Requirements
  - Training Documentation
  - Periodic Monitoring

MEDICINAL PLANT COLLECTION

FROM WILD SOURCE	:	CENTELLA, EUPHORBIA
FROM CULTIVATED SOURCE	:	SENNA, PLANTAGO, DIGITALIS
BY SKILLED WORKERS	:	CINCHONA, BELLADONNA, DIGITALIS
BY UNSKILLED WORKERS	:	IPECAC, SENNA, CARDAMOM
SEASONAL VARIATIONS	:	IN WINTER RHUBARB CONTAINS ANTHRANOLS BUT IN SUMMER OXIDATION TO ANTHRAQUINONES
ONTOGENETIC VARITOINS	:	VARIATIONS OF SECONDARY METABOLITES
WHEN TO COLLECT PLANT PARTS	:	LEAVES, FLOWERS, BARKS, UNDERGROUND PARTS

Irrespective of the type of crude drug and the area of collection, there cannot be two opinions that the drugs are collected suitably when they contain maximum concentration of the active constituents the advantage of existing environmental conditions is also taken into consideration while collecting the crude drugs.

the drugs which consist the leaf of the flowering tops of the plant are collected at stage of maturity e.g. Senna, digitalis, vinca, belladonna etc. whole leaves of aloe are collected when they are sufficiently thick.

WHEN TO COLLECT PLANT PARTS

* Leaves are collected as the flowers are beginning to open.
* Flowers just before these are fully expanded. or Just before pollination e.g. saffron, chamomile, clove buds
* Underground organs as the aerial parts die down. Roots in spring when before the vegetative process stops
  Rhizomes when the store simple reserve food material.
* Barks are collected after a period of damp weather. in Spring or early Summer when the cambium is active as it is easy to detach them from the stem.
* Gums, Gum resins collected during dry weather. as soon as they ooze out of the plant but acacia after 2-3 wks of giving incision when it become hard
* Lvs, fls, fts not to be collected when covered with dew or rain.
* Any part which is discoloured or attacked by insects should be rejected
* While collecting take care to limits of foreign organic matter.
* Underground parts must be freed from soil.

into ripe or half ripe
of fully grown
e.g. cardamom
Bael, Tamarind
fennel, carum, coriander

ONTOGENETIC VARIATIONS

Mentha piperita	young plants high pulegone mature leaves high menthol.
Digitalis lanata	First year total glycosides highest Second year lanatoside C highest.
Agave sp.	Steroidal sapogenins from young; mature, old and flowering plants have successively fewer hydroxyl grps.
Papaver somniferum	Morphine content highest in capsules three weeks after flowering.
Datura stramonium	Hyoscine/Hyoscyamine ratio falls from 80% in young seedling to 30% in mature fruiting plant.

Harvesting is an important operation in cultivation technology as it reflects upon the economic aspects of crude drugs. An important point which needs attention here is the type of the drug to be harvested & pharmacopoeial standards which it needs to achieve.

DRYING OF MEDICINAL PLANTS

- ★ **Drying as soon as possible after collection.**
- ★ **Open air drying avoiding sun drying.**
- ★ **Drying by artificial heat/solar drying**
- ★ **Lvs, herbs, flowers between 20-40°C**
- ★ **Barks and roots between 30-60°C**
- ★ **Over drying should be avoided**
- ★ **Open air fast drying by cutting in thin slices (fruits, Underground parts) or chopping (aerial parts).**
- ★ **Slow drying where enzymatic action desired (Vanilla pods, Cocoa seeds, Gentian roots)**

Genetic Resources are a building block of any breeding & improvement programme, but a variety of medicinal plants is far behind than those of some other plant species. The species used for cultivation are only a small part of the whole diversity present in the world, hence germplasm collection, evaluation characterization & documentation are of special importance & great significance for utilization & conservation of med. plants.

IMPROVEMENT OF MEDICINAL PLANT

- **GENETIC IMPROVMENTS BY IMPROVED CULTIVARS**
  - **Introduction from other countries**
  - **Selecting desired genotype from existing variants Conventional Breeding**
- **BIOTECHNOLOGICAL APPROCHES**
  - **Anther/Haploid/Cell suspension culture for increasing genetic variability**
  - **Rapid Multiplication of Clones of selected genotypes through invitro Micro propagation**
  - **Through Protoplast Fusion/Somatic Hybridization by transfer of Genes from Distant Parents**
  - **Introduction of Transgenic Plants**
- **CULTURAL IMPROVEMENTS**
  - **Good Agrotechnological Practices (GAP)**
  - **Good Cropping systems (Multicropping)**
    - **Selection of Suitable Sites**
      - **Pests & Pest Control**

General approaches to obtain improved cultivars of medicinal plants may be adopted these are summarised in this slide.

Though success by this approach is not very encouraging & these are employed for the following advantages

Tissue culture technique can generate a higher degree of homogeneity of plant material Catharanthus sp.

Population increases in arithmetic progression whereas the agricultural produce in geometrical progression what man has reaped must be protected & future yield must be increased. Time between harvested & consumption is considerable — destruction by pests

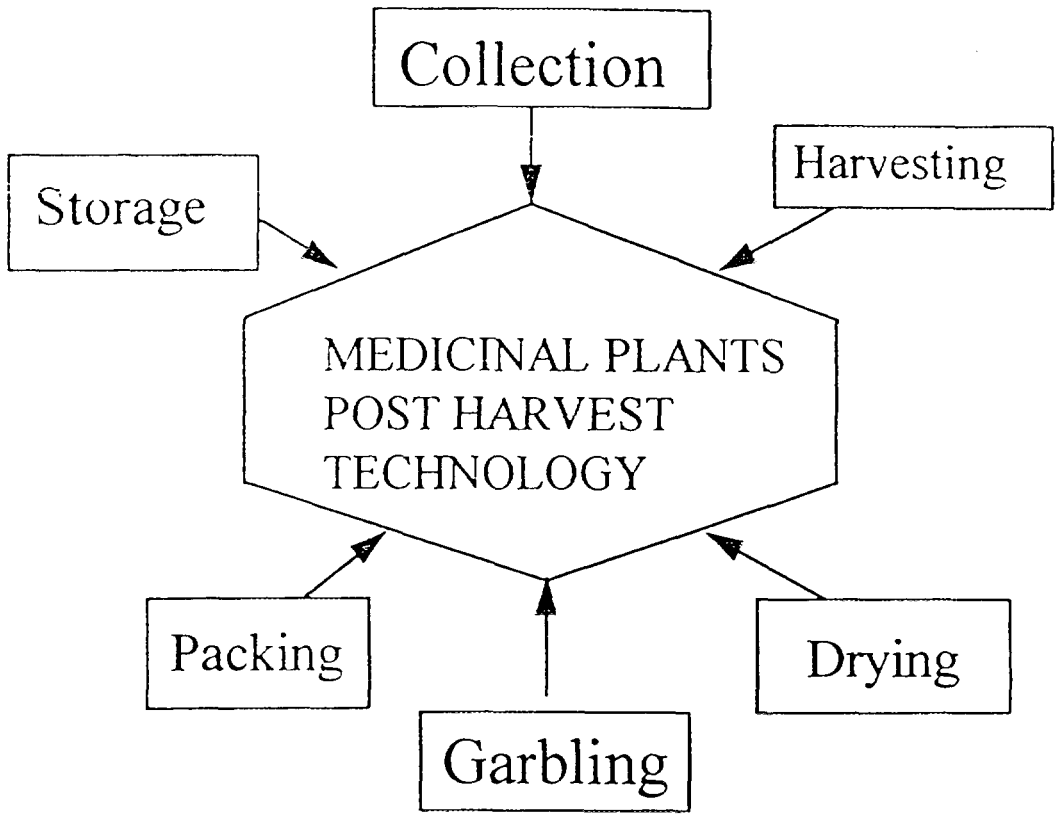


Figure: Segments of post harvest care of medicinal plants.

Much of the plant material enters the market in whole or unprocessed form, the harvesting ~~& post harvesting~~ practices are fairly basic giving products which are not that clean & are liable to be contaminated. Therefore, post harvest technology involving proper garbling, drying, packaging & storage. Therefore cleanliness & free from microbes is critical, pesticide residue must be absent. After collection of crude drugs these are required to be processed prior to marketing the reasons for prepn of drugs for the market are to stabilize them & in transport & storage & to ensure the absence of organic matter & adulterants/substitutes. Market & pharmaceutical elegance

(Storage)
Preservation of the plant drugs needs sound knowledge of their physical & chemical properties
A good quality of drugs can be maintained, if these are stored properly. All the drugs should be
Stored in neat clean rodent-insect free place under water proof & fire proof [illegible] conditions

STORAGE OF MEDICINAL PLANTS

* **Neat and clean place free from rodents and insects.**

* **Temperature and humidity control.**

* **Moisture during storage biggest enemy.**

* **Dried material stored in sacks, bales wooden cases, Card board boxes.**

* **No spray of insecticide/pesticide during storage.**

number of drugs
absorb moisture to the
extent of 25% of their
weight. The moisture
not only increases
the bulk of the drugs
it also causes impairment
in the quality of crude drugs
the excessive moisture
facilitates enzymatic
reactions resulting
in decomposition of
the active components
e.g. digitalis, wild Cherry bark.
certain & ergot racemes
mould infestation due
to moisture

Radiations due to direct sunlight cause destruction of active principles.
Squill, aloe stored in powdered state becomes highly hygroscopic & forms rubbery mass
Swertia chirata in powdered state loses bitter principles
Types of insects, nematode, worms, moulds & mites infest the crude
drugs during storage - Common pest Lepidoptera attacks drugs.

Earth Summit of 1992 at Rio-de-Janeiro, it is high time for the Diversity Rich but Technological Poor Countries to evolve suitable and assured strategies for conservation, evaluation and

STRATEGIES FOR BIODIVERSITY CONSERVATION

- Proper Identification & Inventorying
- Geographical Information System (GIS)/Economic Mapping
- Impact of overexploitation on Supporting Habitats
- Ensuring "IN SITU " Conservation
- Assuring supply through Domestication /Agrotechnology
- Establishment of Gene Bank
- Micro and Macropropagation of Elite Plants
- Development of Low-Tech, Location specific, ECO friendly, value added Medicinal plant Products
- Ensuring free access to Medicinal Plant Resources for R&D Activities Stringent laws to prevent overexploitation
- Legal Protection to Indigenous knowledge and provision of Benefit sharing

It is shocking to learn that out of 250,000 (may be 750,000) higher plants on the planet earth around 50-60% will be destroyed in ten years

no sooner the medicinal importance of a wild plant comes to surface, it is being over exploited and many medicinal plants have been listed in this category. The loss of biodiversity occurring irreversibly in the world over is the most pressing issue of utmost concern to humanity.

METHODS OF BIODIVERSITY CONSERVATON

- **Gene Bank**
- **Seed Bank**
- **Tissue Culture Repository**
- **Field Collection**
- **"IN SITU" Conservation**
- **"IN VITRO" Conservation**

The major objective of genetic conservation is to store plant germ plasm for future uses. It is normally stored in the gene banks, in field collections (or field gene banks), or in their natural habitat (IN SITU CONSERVATION)

Genebank is a place where plant germ plasm is maintained & made available to breeders & other scientists. Normally dried seeds are kept in air tight containers & kept in a cold storage room.
This is the easiest & most convenient & economical method to conserve germplasm but it is restricted to plants which produce ~~seeds~~ orthodox seeds i.e. The seeds which will not lose their viability with in a short time upon drying.

Best way to let them grow in their natural habitat

for most species of medicinal plants, The best method for their conservation is to grow them in gardens or collection pots since they may not produce seeds or produce recalcitrant seeds i.e seeds which lose their viability with in short time upon drying. Field collections of medicinal plants have been established in some countries, but generally speaking, they are mainly for exhibition purposes & do not hold accessions of great genetic

This is novel technique which will become more important in future. It is a wide range of techniques including in vitro culture of organ, tissue, cells & protoplasts. Very useful technique for those med. plants which do not produce seeds or whose seeds do not germin

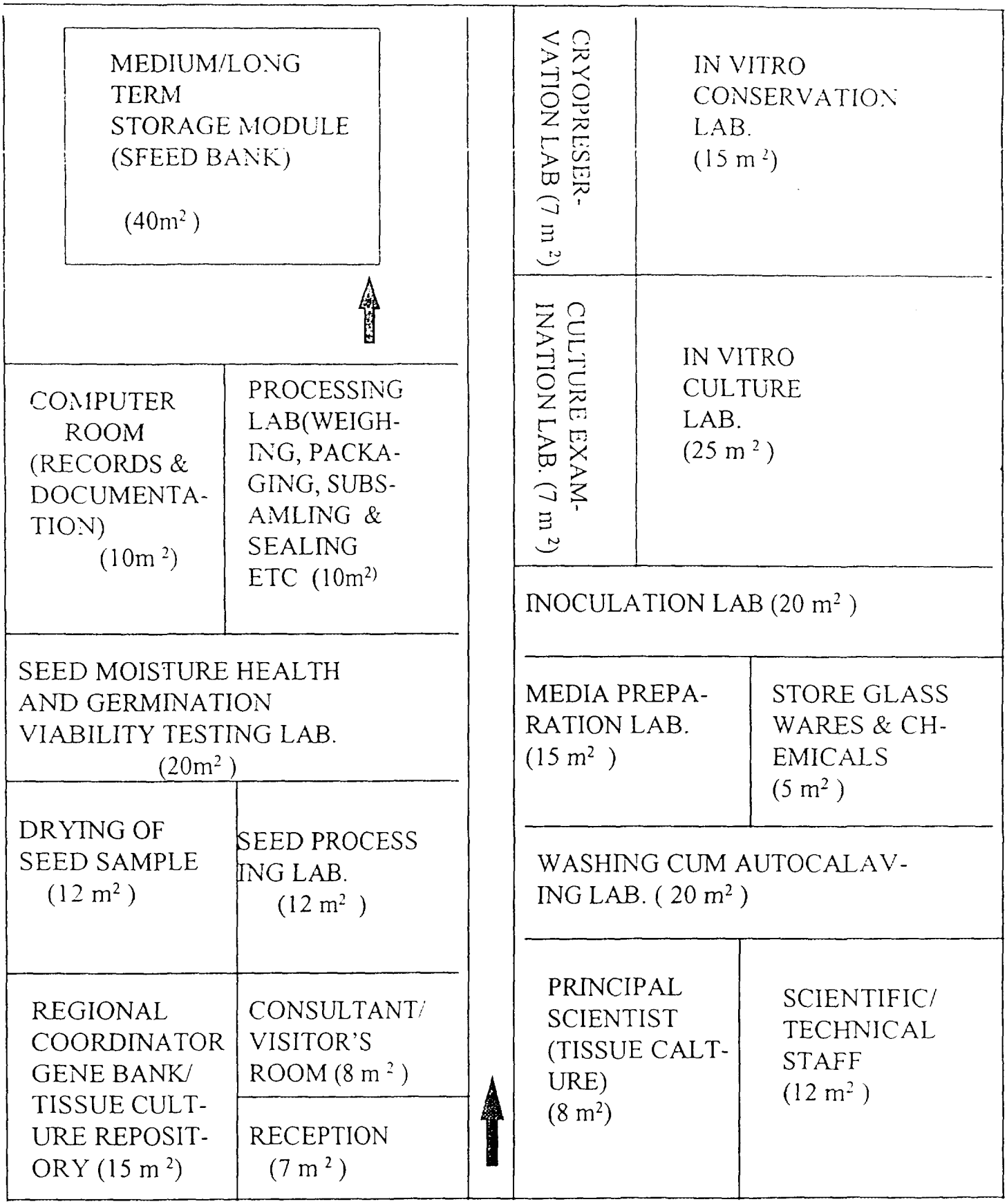
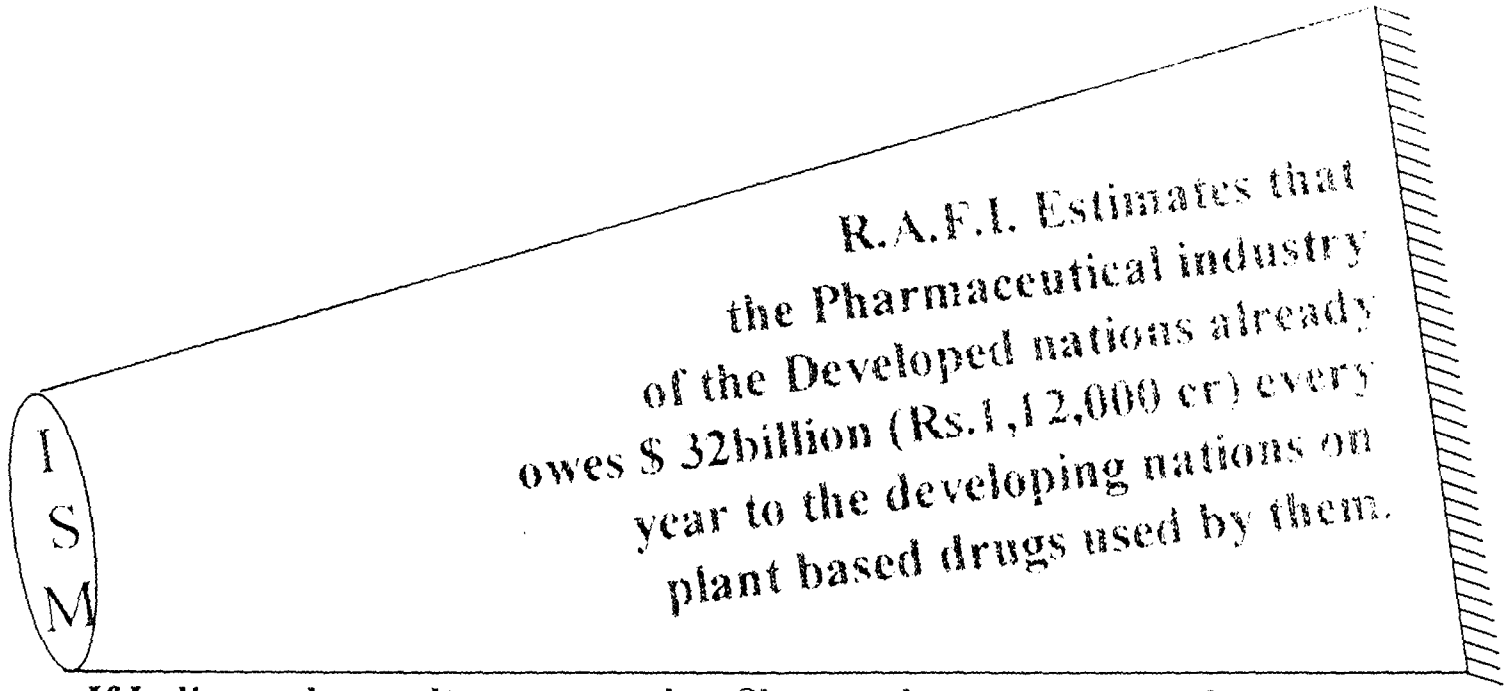


Figure 3 : Conceptual Design of a Gene bank for Medicinal Plants

INDIGENOUS KNOWLEDGE PLAYED AN IMPORTANT ROLE IN DISCOVERY OF DRUGS AND WILL CONTINUE TO DO SO, THEREFORE, IT CALLS FOR LEGISLATION TO SECURE INTELLECTUAL PROPERTY RIGHT FOR INDIGENOUS PEOPLE

At present, intellectual property as it relates to biodiversity prospecting is a hotly debated issue throughout the developing world. Since most of the chemically unknown flora & associated medicinal lore exists in developing & underdeveloped countries, especially those which still possess extensive tropical forests



If India needs royalty on cucumber She may have to pay royalty on potatoes

The Rural Advancement Foundation International (R.A.F.I.) a canada based non profit organisation estimates that the pharma industry owes - .....

NEEM PESTICIDE PIRACY OF THIRD WORLD

* NEEM TREE NOT PATENTABLE

* AZADIRACHTIN (DAVID MORGAN 1970) NOT PATENABLE

* ON NEEM PRODUCTS OVER 80 PATENTS (48 OF INDIAN ORIGIN) HAVE BEEN GRANTED IN INDIA

* GRACE CO'S VENTURE LAST YEAR TO SECURE US PATENT FOR EXCLUSIVE RIGHTS TO MAKE PESTICIDES FROM NEEM

* OVER 200 ORGANISATIONS FROM 35 NATIONS INCLUDING INDIA HAVE CHALLENGED GRACE CO's PATENT RIGHT WHICH IS USURPATION OF "THE AGE-OLD BIOLOGICAL PROCESS USED BY MILLIONS OF INDIAN FARMERS"

PATENT SECURED BY U.S.CO ON NEEM PESTICIDE AMOUNTS TO PIRACY OF THIS WORLD

A global coalation of over 200 countries from 35 nations.

What is the true nativity of Azadiracta indica? Is it an authentic part of the gene heritage of India? Is it beyond national identification*? Questions of this kind could have excited the imagination of only eccentric souls till recently. But now in the wake of TRIP (Trade related Intell. Prop), the genetic ancestory of Neem tree has become the subject of fierce cross border contentions. The U.S. based multinational W. R. Grace Co. ventured to secure US patent for the exclusive right to make pesticide from Neem.

MOVE FROM TRADITIONAL VALUES TO COMMERCIALISM

- IN A COUNTRY OF VEDIC HERITAGE, THE NOTION OF "PRIVATE" INTELLECTUAL PROPERTY IS NEEDED EMBARASSING
- INFILTRATION OF COMMERCIALISM IN A TRADITIONAL SOCIETY IS NOT ALWAYS A MATTER OF NATIONAL COMFORT
- REALITY OF EVOLUTION OF MODERN SOCIETY ON THE BASIS OF COMMERCE, TECHNOLOGY, CONTRACTS AND QUID PRO QUO CANNOT BE WISHED AWAY
- IS IT MORAL FOR A VAID TO SELL MEDICINE OR TO CHARGE FOR TREATMENT OF PATENT OR FOR A TEACHER TO IMPART KNOWLEDGE TO A STUDENT FOR A FEE?
- IF QUESTION OF THIS KIND ARE NOT TOO DIFFICULT TO RESOLVE, WHY SHOULD NOT A PATENT REGIME BE RECOGNISED AS TRANSPARENT SYSTEM OF REWARD FOR AN INVENTOR OR AN INNOVATOR AND ROYALTIES BE PAID FOR USE OF SUCH PATENTS

TRANSGENIC PLANTS

PATENTS OF GENETICALLY ENGINEERED PLANTS MAY CAUSE ENOUGH WORRY TO EXPERTS AS IT IS NOT DIFFICULT FOR A COMPANY WHICH HAS OBTAINED SUCH A PATENT TO EXERCISE A MONOPOLY THROUGH OUT THE WORLD ASSUMING THAT PATENT LAWS WILL SOON BECOME SIMILAR IN ALL COUNTRIES

PATENTING RECIPES FROM NATURE'S KITCHEN

1. Have I purified compound from nature ?
2. Do I have an unpredictable use for a known natural component ?
3. Have I made an analogue to natural product ?
4. Have I isolated biologically pure culture or cell line ?
5. Have I finger printed something new or unexpected ?
6. Have I made a new combination ?
7. Have I created a new method of preparation ?
8. Have I created a new method of use for a known or even previously patented invention ?
9. Have I created a new recombinant product that differs from the known naturally derived product ?
10. Have I created a new plant or animal ?

world literature on patents related to medicinal & aromatic plants claimed between 1980-92 based upon the [illegible] & related publications reviewed

PATENTING TREND MED. PLANT PRODUCTS

* OUT OF 750 PATENTS (1980-1992) ACCOUNT FOR MEDICINAL AND 184 FOR AROMATIC PLANTS

* THRUST ACTIVITY AREAS INCLUDE ANTICANCER, ANTIIFLAMMATORY, CARDIAC ACTIVITY, CNS, ANTIMICROBIAL, HYPOGLYCAEMIC AND ANALGESIC

* COSMETICS-HAIR DYE, PREVENTION OF HAIR LOSS, HAIR SHAMPOO, SKIN CREAMS, EYE LOTIONS

* JAPAN HAS MAJOR SHARE OF PATENTS

* APPLE, MELON, WATERMELON, POTATO STARCH, CABBAGE, CARROT, SWEET POTATO HAVE BEEN PATENTED FOR VARIOUS PHARMACOLOGICAL ACTIVITIES

PROTECTING INDIGENOUS DRUGS UNDER IPR MAJOR RECOMMENDATION

* INVENTORY OF MEDICINAL PLANTS INDIGENOUS TO INDIA AND USED IN ISM
* PRESERVATION OF GERMPLASM OF ALL PLANTS USED IN ISM
* ADOPT MODERN METHODS FOR PREPARATION, QUALITY CONTROL WITH PROVEN CLINICAL EFFICACY AND SAFETY ENABLING SUCH PRODUCT TO BECOME PATENTABLE ENTITIES

* DEVELOP AGROTECHNOLOGIES OF MED.PLANTS SO AS TO IMPROVE VARIETIES OF PLANTS WHERE IPR CAN BE PROTECTED

* CORRECT & ELABORATED TRANSLATIONS OF OUR ANCIENT SCRIPTURES TO PROVIDE NEW LEADS TO INDIAN SCIENTISTS FOR ISM DRUGS

* OUR LEGAL PROFESSION SHOULD UNDERSTAND SCIENCE BEHIND NEW DEVELOPMENTS OF IPR

* EXTENSIVE & INTENSIVE RESEARCH ACTIVITIES ON ISM DRUGS

* EMPLOYING CURRENT KNOWLEDGE OF SCIENCE WITH A VIEW TO GENERATE IPR WEALTH OUT OF CULTURAL HERITAGE OF ISM

* THOROUGH ACCESS TO PATENTS AND CRITICAL SCRUTINY THEREOF

* PROMOTING QUALITY RESEARCH IN ISM

depending upon the requirements and degree of sophistication of the preparation methodology (Fig 4). These range from direct use of plant material to the production of extracts, standardized extracts, partially purified extracts, groups of phytochemicals to pure phytopharmaceuticals. The range represents an increasing degree of application of modern research & technology.

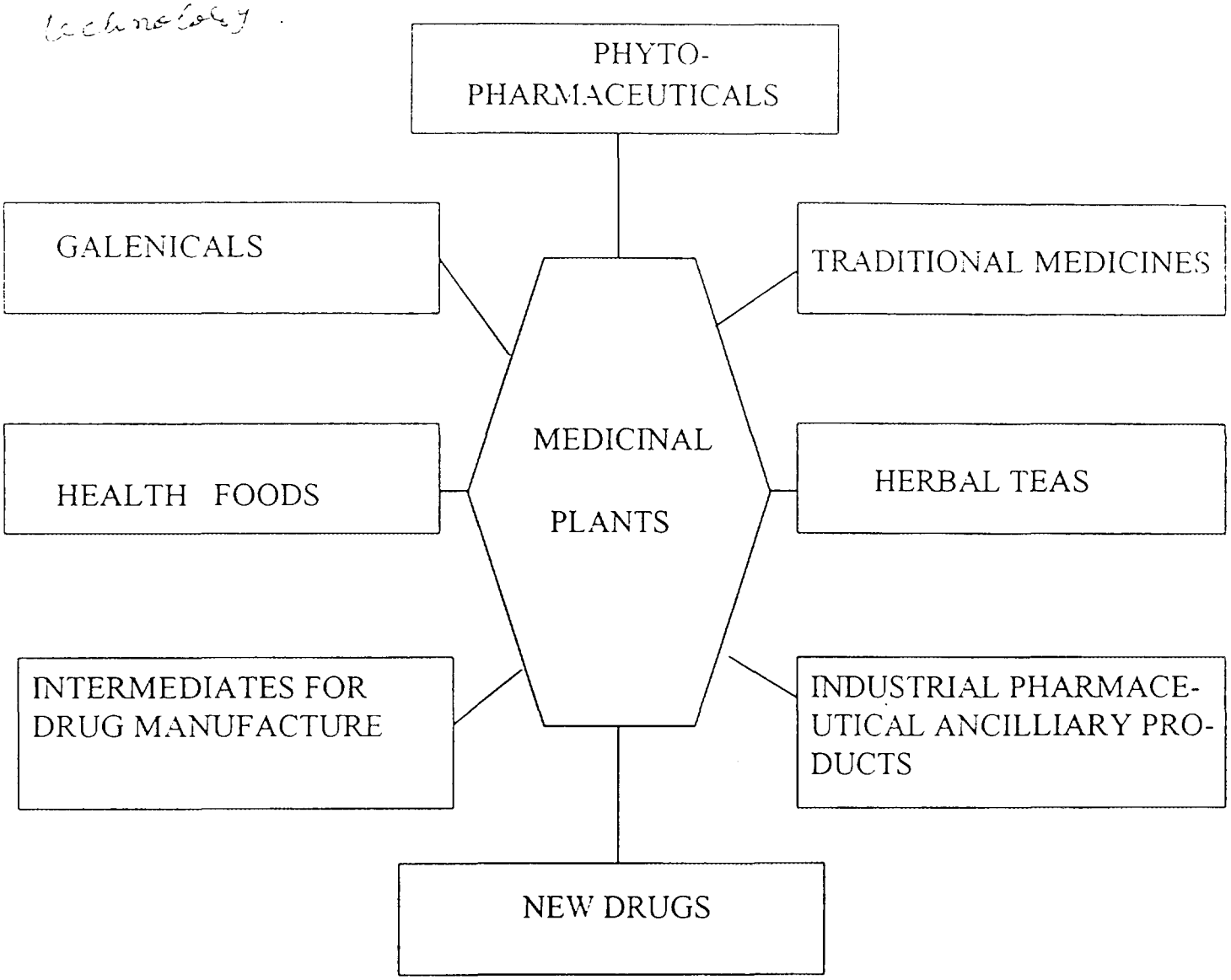


Figure 4 : INDUSTRIAL USES OF MEDICINAL PLANTS

Thus plants as drugs are mainly used in one of the following form

Crude drugs — Fresh, dried, powder as such or formulated

Extract : Fresh juice, Extract or decoction, tincture syrup both as traditional or modern drugs.

Pure phytoconstituents : a) as drugs mainly in modern medicine
b) as chemical intermediate for semi-synthetic

COMPOUNDING OF HERBAL DRUGS

DECOCTION

Slight Simmering
Normal Simmering
Long Simmering

MACERATION

INFUSION

INFUSION

INFUSION IS PREPARED BY STEEPING THE
HERBAL MATERIAL IN COLD OR BOILING
WATER. COLD INFUSION IS PREPARED WHEN
THE ACTIVE PRINCIPLES ARE HIGHLY VOLATILE
OR COULD BE DECOMPOSED BY HEAT, BY STEEPING
THE HERB IN WATER FOR SEVERAL HOURS. A
HOT INFUSION COULD BE MADE BY POURING
BOILING WATER OVER THE HERB AND STEEPING
IN A COVERED CONTAINER FOR 10-30 MIN.

MACERATION

THE HERB SHOULD BE CUT INTO SMALL PIECES OR POWDERED, IMMERSED IN THE SOLVENT IN A CLOSED CONTAINER AND ALLOWED TO STAND FOR A PERIOD OF TIME, USUALLY 1-7 DAYS, WITH FREQUENT AGITATION. THE MIXTURE IS THEN STRAINED AND THE MARC IS PRESSED. THE TOTAL LIQUID IS CLARIFIED BY FILTRATION OR BY DECANTATION AFTER STANDING.

DECOCTION

THE METHOD OF SIMMERING [illegible]
TO YIELD SOLUBLE INGREDIENTS
CALLED DECOCTION. IT IS USUALLY
PREPARED BEFORE USE. FRESH HERB
SHOULD EITHER BE CRUSHED, SLICED
CUT INTO SMALL PIECES. DRIED HERB
SHOULD EITHER BE GROUND OR MADE
BRUISED. DECOCTION COULD BE OBTAINED
BY DECANTATION OR STRAINING WHILE
HOT. UNLESS OTHERWISE SPECIFIED, THE
AMOUNT OF WATER SHOULD BE ENOUGH
TO COVER THE HERBAL MATERIAL
SIMMERING PERIOD CAN BE DIVIDED INTO
THREE TYPES DEPENDING ON THE NATURE
OF THE NATURE OF THE CRUDE DRUG.

SLIGHT SIMMERING

SUITABLE FOR FLATULENT PREPERATIONS WHICH USUALLY CONTAIN VOLATILE SUBSTANCES. PUT THE CRUDE DRUG IN BOILING WATER, ALLOW TO BOIL ANS SIMMER FOR 1-2 MIN IN A COVERED CONTAINER.

NORMAL SIMMERING

SUITABLE FOR GENERAL CRUDE DRUGS. PUT THE DRUG IN WATER, THEN HEAT TO BOIL AND SIMMER FOR 10 MIN.

LONG SIMMERING

SUITABLE FOR SPECIAL CRUDE DRUGS SUCH AS BARK, WOOD ETC. IN GENERAL, ADD WATER TO THE CRUDE DRUG AND BOIL UNTIL 1/3 OF TOTAL VOLUME IS LEFT.

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 & dosage forms. These advances can be & should be applied in production of new formulations or dosage forms traditional medicines & their dosage forms.

PROCESSING TECHNOLOGY

- Simplify and Modernize Methods of Production
- Develop Process Parameters at
- Lab, Bench, Pilot Scale
- Optamize Processing Conditions for
- Yield, Energy Use, Loss Prevention, Cost Effectiveness
- Develop Protocols for
- Process Control, Quality Control
- Set up Centralized unit for Production
- Develop new Formulations & Dosage forms
- Determine Pharmacokinetic/Bioavailablity/Bioequivalence parameters wherever possible

PROCESSING TECHNOLOGY STAGES

Stage		
Can be done at remote villages	I	1. Harvesting Authentic Material
		2. Good Post Harvest Treatment
	II	3. Stage I Followed by Comminution
		4. Packaging of Powders as Uniform Dosage
		5. Formulation of Pills from Powders
		6. Production of Medicinal Wines (Need Sugar source)
	III	7. 1,2, & 3 Followed by aqueous extraction
		8. Preparation of Standardized extracts
		9. Formulation into Dosage forms, Capsules, Sachets
In most developing countries	IV	10. Stage III followed by other dosage forms such as Tablets, Syrups & Ointments
		11. 1,2, & 3 Followed by preparation of extracts with other solvents
	V	12. Fractionation of Extracts
		13. Bioactivaition screening
		14. Formulation into Dosage forms
Developing countries capable of investing large sums of money & establish joint ventures with	VI	15. Isolation of Phyto Pharmaceuticals from 8,11 & 12
		16. Conversion into Semisynthetic Drug
		17. Formulation of 15 & 16 into Dosage forms
	VII	New Drug Development → many countries do not have facilities & money for installation of stage VII

The processing activities leading to different medicinal plant based products are indicated in earlier Fig 5. The first stage in the processing sequence is to ensure the quality of raw materials. Criteria for determination of authenticity, purity & quality of raw material have to be developed & made available in the form of monographs which could be used by suppliers to ensure quality required.

Stages

The extent to which a process technology could be introduced at rural level will depend upon many factors

of these stages: First stage can be done in rural villages — rural people have to be trained in post harvest techniques of packaging

The establishment of other stages of processing will depend upon the level of development of the village/country

Stages IV & V in most developing countries

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

BULK PRODUCTION - UNIT OPERATIONS

- Comminution (Crushing & Pulverizing)
- Aqueous/Alcoholic Percolation/Extraction
- Concentration : Recovery of Solvent
- Drying of Product
- Steam Distillation of Volatile compounds
- Separation of water-immiscible Volatile components
- Filtration and Purification by Crystallisation
- Fractional Distillation

It is useful to set up a multipurpose 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 medicinal aromatic plants & these engineering drawings could be made available to interested Countries. UNIDO plant is of simple design & construction & can be easily fabricated, installed, operated & maintained. It is expected that such pilot plant would lead to setting up industrial units utilizing locally cultivated

PARAMETERS AFFECTING EXTRACTION

- Swelling of plant material
- Diffusion, pH, Particle size, Temperature
- Choice of solvent
- Use of chemical properties
- Mode of Extraction

    * Maceration
    * Decoction
    * Percolation
    * Soxhelt Extn.

- Physical form of Extract desired

Some time it is more difficult to prepare standerdized extract than to prepare pure product.

In most countries, the manufacturing premises of the pharmaceutical industry units are inspected and approved by the Drug Regulatory Authorities before production commences & inspection is also done during the course of operation. This ensures observance of GMP. Wherever production of traditional medicines is undertaken on a large scale in factories, these units should also be subjected to the system of inspection & registration. Similarly publication of product information and promotion should be controlled by Drug Regulatory Authorities

GOOD MANUFACTURING PRACTICES (GMP)

neat clean healthy surrounding designed constructed adapted & located & operations to suit

adequate

* Premises
* Working space & Storage Area
* House keeping
* Loss Prevention
* Raw material
* Equipment Design
* Production Procedures & Documentation
* Packaging Material
* Quality Control
* Personnel
* Waste Disposal

understood Approved Rejected

batch record

requisite qualification training & adequate no.

appropriate arrangement for disposal.

These points have direct relevance to GMP

Quality & safety of pharmaceutical prod is ensured by follow proper procedures for inspect & checks before, during and af manufacture; these cannot ensured by mere one-time inspection at the end of processing. This facet is becoming more & simply emphasis & thus some voluntary & some statutory codes have been developed to ensure observance of GMP

The single + most important factor which stands in the way of wider acceptance of herbal drugs is the non-availability or inadequacy of standards for checking their quality by physico-chemical or bioassay methods. This also prevents modification of the method or modernization as there is no way to establish equivalence

STANDARDIZATION OF HERBAL DRUGS

Standardization of the presumed active compound of a herbal drug in general does not reflect reality. Only in a few cases does drug activity depend on a single compound. Generally, it is the result of the concerted action of several active compounds as well as of inert accompanying substances. Though these inert accompanying compounds do not directly affect pathological mechanism, it is reasonable to use the complex mixture of a phytoconstituents provided by a medicinal plant because the inert substances might influence resorption bioavailability and excretion of active compounds, Further, by inert plant components the stability of the active compounds might be increased and the rate of side effects be minimized. If there are different active compounds present in a drug they might have an additive or a potentiating effect.

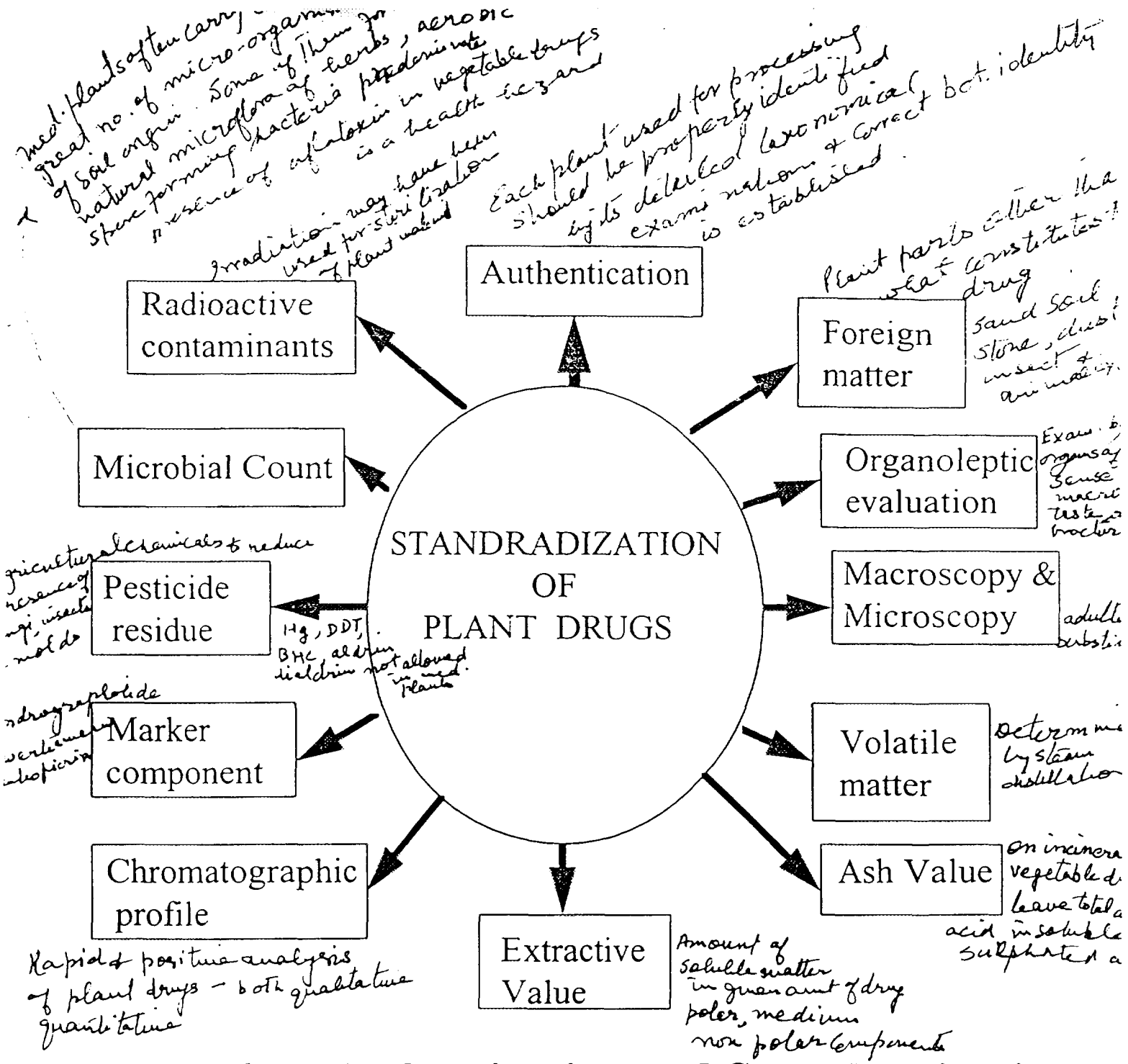
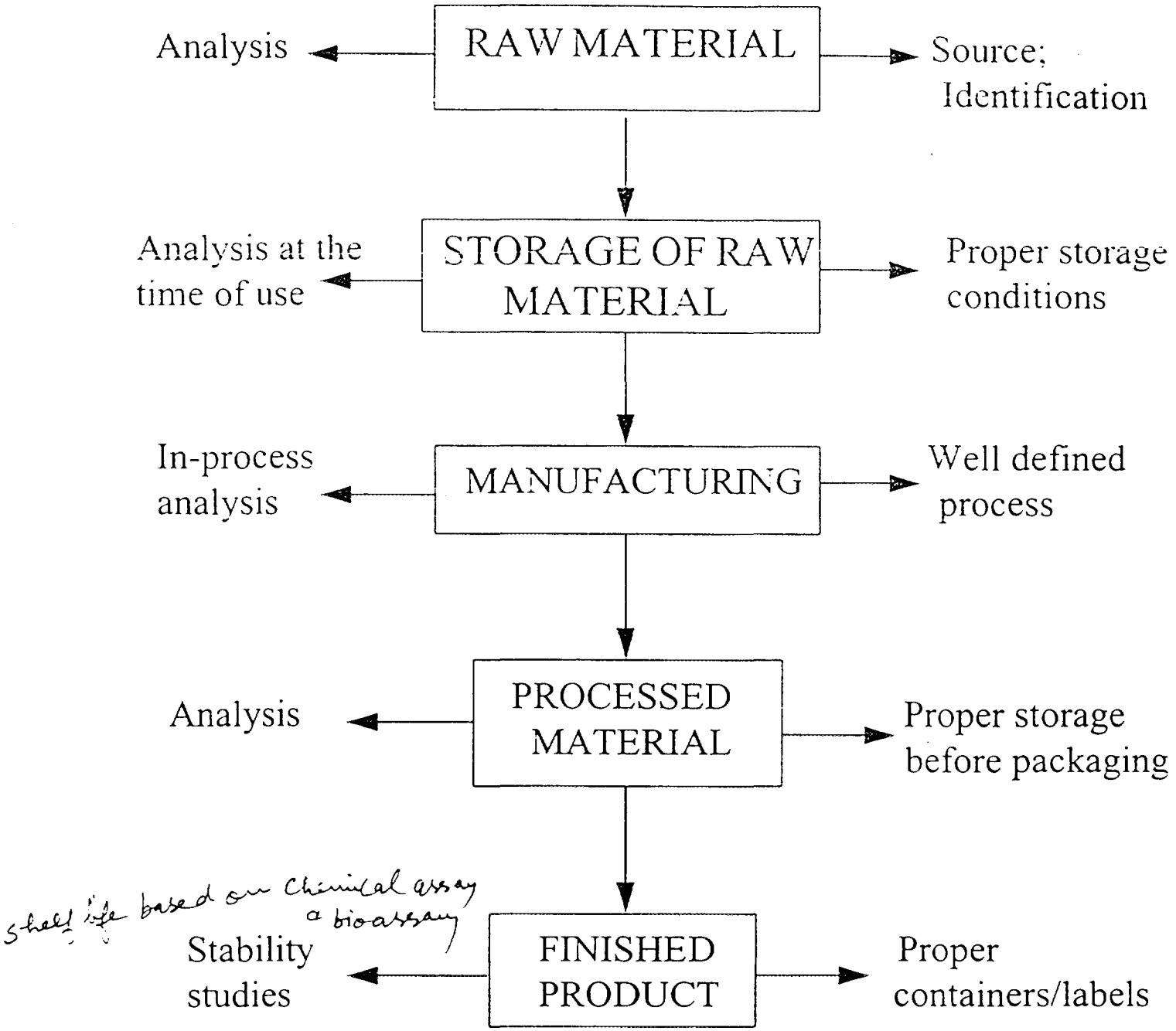


Figure 6 : Authentication and Strandardization of herbal raw material.

Vegetable drugs are inevitably "inconsistent" because of their composition and, hence standardization, may be influenced by several factors such as age of the plant & origin, harvesting period, method of drying + so on, one should use a cultivated plant material to remove many causes of inconsistency.



shelf life based on chemical assay & bioassay

Figure 7 : GENERAL PROTOCOL FOR STANDARDIZED PRODUCTION OF PLANT DRUGS

Quality assurance of traditional remedies rely upon manufacturing practices with adequate batch analysis & standardized method of preparation. Various processes used in the manufacture of herbal drugs lack standardized methods large scale commercialisation of 82 herbal drugs necessitates scientifically evolved standardized method of plant drug General protocols of production are given

ISO 9000 QUALITY MANAGEMENT SYSTEM

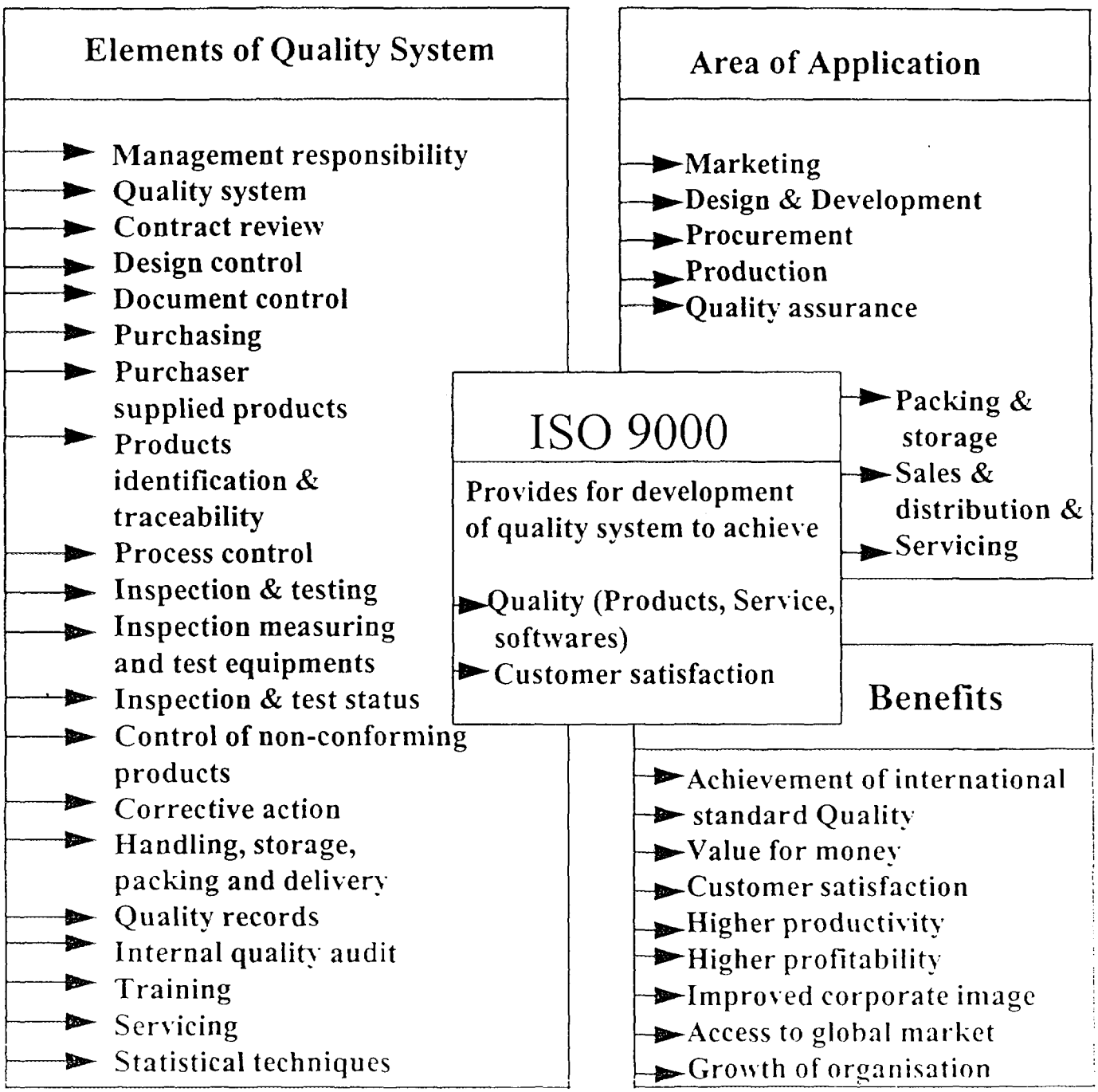
The sole Objective of International Organisation for Standardisation(ISO), Geneva, is to Promote Development of Standardisation and Related Activities in the World to Facilitate International Exchange of Goods & Services to Develop Cooperation in the Sphere of International Scientific, Technology and Economic Activities.

ISO 9000 SERIES OF STANDARDS

- ISO 8402 ⟶ Quality Vocabulary

- ISO 9000 ⟶ Guidelines for Selection and use of Standards
- ISO 9001 ⟶ Quality assurance model for Design/ Development, Production, Installation and Servicing
- ISO 9002 ⟶ Quality assurance model for Production and Installation
- ISO 9003 ⟶ Quality assurance model for final inspection and test
- ISO 9004 ⟶ Guidelines for establishing quality management system

Figure 8 : ISO 9000 - Elements, Application and Benefits



CLINICAL EFFICACY EVALUATION

- Processing Plant in Traditional Manner
- Dosage Formulation Ensuring Stability
- Short term Toxicological Studies
- Well Designed Protocols for Clinical Studies
- Double Blind Clinical Trials wherever Possible
- Using Appropriate Plcebo Control
- Fullproof Biostatistical Analysis
- Quality Control Stability Studies well conducted

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

Commonly used animal models may not be adequate in many situations & need experimental models have to be developed or straightway clinical studies may be initiated after short-term safety studies in animal models (WHO 1993)

There is a growing realization that it may be quicker & more cost effective to undertake initial clinical studies with medicinal plant products which had been used extensively with no reports of untoward reactions. Some authorities suggest a short-term toxicity evaluation before clinical studies but others advocate consideration of the necessary tests where suitable animal models are not available e.g. psychiatric disorders, straightway clinical trials

Regulatory bottlenecks the legal situation of herbal preps differs from country to country

In some countries ... whereas in others countries these are regarded as food & therefore are not allowed to make any therapeutic indication claim. Developing countries however often have a great number of traditionally used herbal medicines but they have hardly any legislative criteria to establish these traditionally used herbal medicines as part of drug legislation

REGULATORY ASPECT

Different Countries Have Adopted Different Approach With Regard to

LICENSING | **DISPENSING** | **MANUFACTURING**

TRADING **IN ORDER TO ENSURE**

SAFETY, QUALITY AND EFFICACY OF MEDICINAL PLANTS AND PRODUCTS THEREOF.

Legislative controls in respect of medicinal plants have not evolved to a structured control model. There are different ways in which countries define medicinal plants or herbs or products thereof & countries have adopted different approaches with regard to licensing, dispensing, manufacturing and trading to ensure the safety, quality & efficacy of medicinal plants & products thereof. As in many countries the situation in herbal medicines is not clearly regulated by law & the products thereof are unregistered & not controlled by regulatory bodies, a special licensing system is regarded

POINTS ADDRESSED BY W.H.O. GUIDELINES

- **Pharmaceuticals Assesment**
  - * Crude Plant Material
  - * Plant Preparation
  - * Finished product
  - * Stability

- **Safety Assesment**
  - * Toxicological studies
  - * Documentation of safety based on experience

- **Assesment of efficacy and intended use**
  - * Pharmacological activity
  - * Evidence required to support indications

- **Combination Products**
- **Product Information for the consumer**
- **Promotion**

PHARMACOPOEIAL STATUS OF HERBAL DRUGS

- 1P, BP, USP, INT.P
- British Herbal Pharmacopoeia
- Japanese standards for Herbal Medicines (JSHM)
- Ayurvedic Formulary of India
- Ayurvedic Pharmacopoeia of India
- W.H.O. Guidelines
- Botanical * Physicochemical
- Pharmacological * Toxicological

Several Pharmacopoeias including IP, BP, USP, Pharmacopoeia of Repu of China, USP etc. cover monographs + quality control tests for ... of the medicinal plants used in those countries but basica... These pharmacopoeia are designed to cater the chemical ba... medicines. The Int. P. follows current WHO guides

1st BHP by BHMA in 1971. Single monographs on herbs ... drugs. BHP in 1983 contains 338 monographs based on ... BHMA is now jointly ... with European Scientific Cooperative on Phytotherapy (ESCOP) for ... the status of Phytom... throughout Europe to ... in the harmonization of regulatory status at European level.

Published in 1993 is now available 248 articles on herbal medicines

1000 single drugs
8000 compound drugs recognised
A.P.C. Chose 444 preps of Ayurveda & listed 458 single drugs used in them

80 monographs on single drugs vol. I published.

No pharmacopoeia of the world is comprehensive enough to cover all the medicinal herbs & no any pharmacopoeia is capable to give concrete methodology for routine quality control of medicinal herbs. Inspite of worldwide efforts in this direction limitations of basic approach to establish standards like synthetic drugs.

In 1974, International Trade Centre (ITC) conducted a study [illegible] plants & their derivatives" - since that study no updates have been undertaken. Recently ITC (1992) carried out a limited study on selected medicinal plants.

TRADE AND MARKETING

ESTIMATED SALE OF HERBAL MEDICINES	IN US $ MILLIONS	ANNUAL GROWTH RATE (%)
EUROPEAN COMMUNITY	6,000	5-8
REST OF EUROPE	500	8-12
NORTH AMERICA	1,500	15
JAPAN	2,100	15
CHINA 70,000 TONS OF HERBAL MATTER (5000 OFFICIALLY RECOGNISED PLANTS)	571	DRUGS MANUFACTURED FROM THIS HERBAL MATTER IS WORTH US $ 1.4 BILLION

In China 40% of the urban + 90% of the rural patients still rely upon botanical based prescriptions

Situation in India is similar

INDIA: 2,500 OFFICIALLY RECOGNISED PLANTS 7000 LICENSED MANUFACTURING UNITS 55000 LICENSED AYURVEDIC PHARMACIES

(Grunwald, 1994)

THIRD WORLD 60,000 PLANTS

TRADE AND MARKETING

		US $ BILLION
GERMAN HERBAL HEALTH CARE-PRODUCTS		1.7
IN US: 125 MILLION PRESCRIPTIONS INVOLVING PHYTOPHARMACEUTICALS		11.0
HERBAL TEAS, DIETARY SUPPLEMENTS AND HERBAL DRUGS	1993	1.3
	1994	2.8
JAPAN & EUROPE	**1996**	**4.0**

PHARMACOLOGIALLY ACTIVE PHYTOCONSTITUENTS WORLD WIDE IN USE ESTIMATED 250

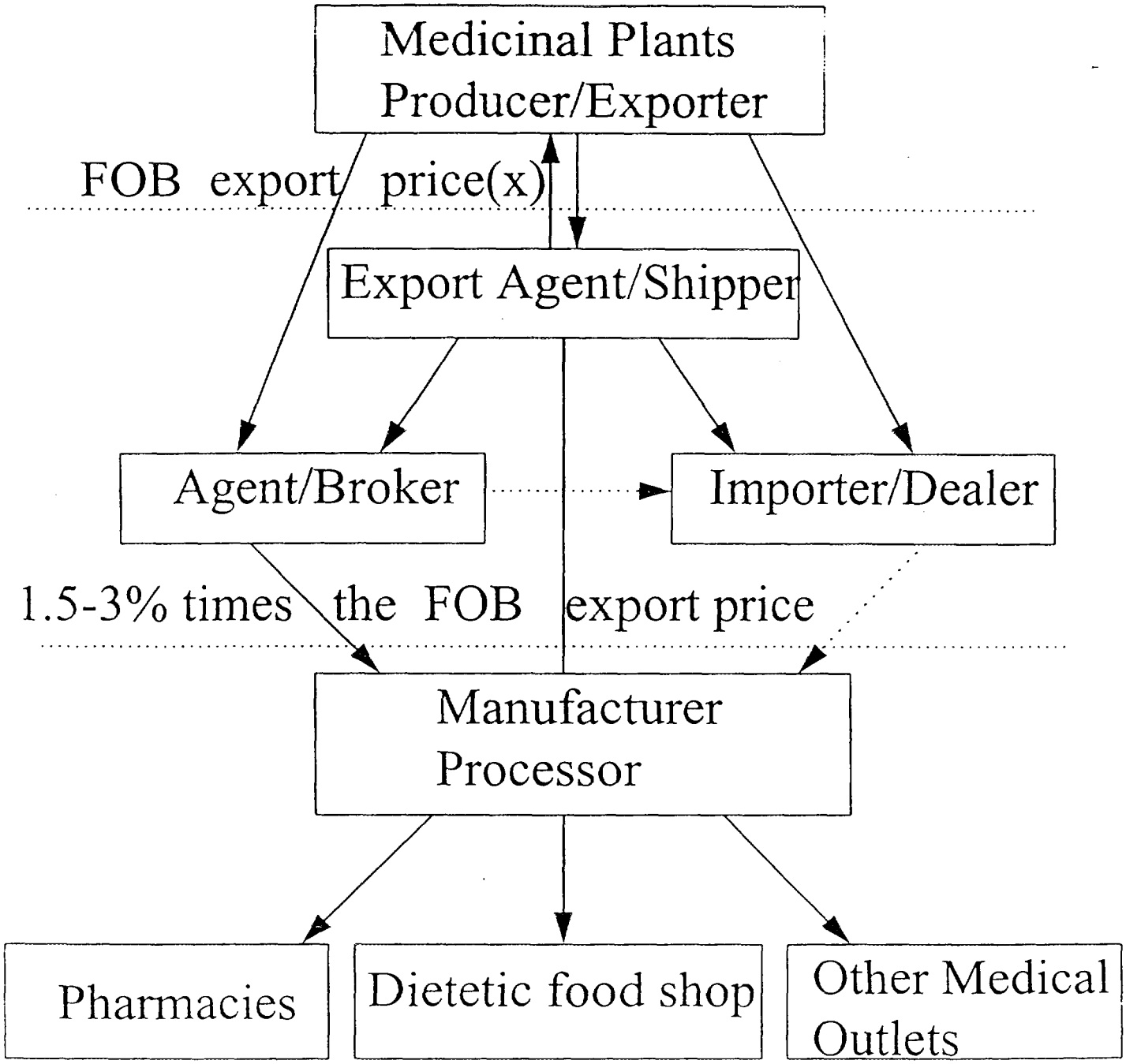


Figure 9 : Trade structure for medicinal Plants in Western Europe (El-Nabulsi, 1996)

In western Europe, Germany is the largest import market, where the trade is concentrated in the hands of about 20-drug trading companies. Approximately one third of the imported products are re-exported towards other European countries - The figure illustrates the flow of trade in Eastern Europe. The leading importers/brokers and processors in EU are established in France Germany, Italy & Switzerland (127). Direct trade between medium & large producer/exporter in developing countries & processors in ... tend naturally tending to rise

RESURGENCE OF INTEREST IN PLANT BASED DRUGS

DEMERITS OF MODERN DRUGS	MERITS OF PLANT DRUGS
• HIGH COST (250 m US $) & LONG TIME (~ 15 YEARS) FOR DEVELOPING NEW DRUG	COST EFFECTIVE, LONG HISTORY OF USE, PUBLIC ACCEPTANCE & BETTE PATIENT TOLERANCE
• TOXICITY-IATROGENIC DISEASES	SEVERAL RECENT BREAK THROUGHS GUGGULIP, ARTEMESININ, TAXOL
• MOST SYNTHETIC DRUGS USE FOSSIL RESOURCES LIKE PETROCHEMICALS-NON-RENEWABLE	RENEWABLE SOURCE
• ENVIRONMENT POLLUTION BY CHEMICAL INDUSTRY	CULTIVATION AND PROCESSING ENVIRONMENT FRIENDLY
• INADEQUACY IN MANAGEMENT OF CERTAIN CHRONIC DISEASES	PLANTS CONTINUE TO BE MAJOR SOURCE OF NEW LEAD GENERATOR

In marketing several points seem to warrant particular attention

MARKETING STRATEGY

- SHARP AND CONSTANT EYE UPON MARKET
- CENTRALLY ADMINISTERED RESOURCES FOR MARKET SURVEY
- LONG TERM SUPPLY ARRANGEMENTS WITH INDUSTRIAL BUYERS
- DEVELOPING COUNTRIES MUST ELIMINATE DETRIMENTAL PRACTICES
- GREATER RESPONSIVENESS TO MARKET NEEDS
- SHOULD ACTIVELY PROTECT CULTIVATORS
- PRODUCTION PROCESSES COMPETITIVE IN WORLD MARKET

Plants are a reservoir of chemical agents with therapeutic potential what has been missed is collation of data gathered in trial & error in what has been virtually a prolonged clinical trials.

RESEARCH AND DEVELOPMENT

- Development of Agrotechnology
- Development of Technology for Bulk Production of Medicinal Products
- Development of Quality Control Standards for Raw Material and for Finished Products
- Development of New Formulations and Dosage forms Suited to Prevailing Climatic Conditions & Adapted to Locality Available Raw Material
- Assimilation of Acquired Technology and its Continuous Improvement to make products competitive
- Bioequivalence/Bioavailability/Pharmacokinetic studies on the Dosage forms Developed
- Search for New Plant Sources for known Drugs and for New Drugs from Locally Available plants

TABLE-2 GLOBAL OCCURRENCE OF DISEASES

(Per million Nos.)

DISEASES	Index
1. HEART DISEASE	38
2. HYPERTENSION	55
3. ASTHMA	25
4. RESPIRATORY INFECTIONS	95
5. TUBERCULOSIS	15
6. AMOEBIASIS	285
7. DIARRHOEA	526
8. TYPHOID	48
9. HELMINTHIASIS	340
10. PEPTIC ULCERS	37
11. IRON DEFICIENCY	223
12. DIABETES	25
13. ALLERGIES	122
14. MALARIA	19
15. VENEREAL DISEASES	61
16. PSYCHIATRIC DISORDERS	62

it is necessary to prioritize the thrust areas to obtain the output by research efforts & allow resources. Several factors help in determining priorities. These include distribution of flora, natural/geographical diseases & availability of modern health care etc. Global priorities in developing new drugs so as to get maximal financial returns.

GLOBAL DEMAND FOR DRUGS BY THE WORLD BY GROUPING ($ billion)

DISEASES / DRUGS	1990	2000
1. ANTIBIOTICS	18	42
2. CARDIOVASCULARS	15	45
3. ANTI-ARTHRITICS	10	30
4. PSYCHO-THERAPEUTICS	9	30
5. ANALGESICS	5	15
6. COUGH & COLD PREPS.	5	15
7. DIURETICS	3	9
8. STEROIDS	2	6
9. OESTROGENS	3	10
10. CANCER CHEMO-THERAPEUTICS	5	15
11. OTHERS	25	75
TOTAL	**150**	**450**

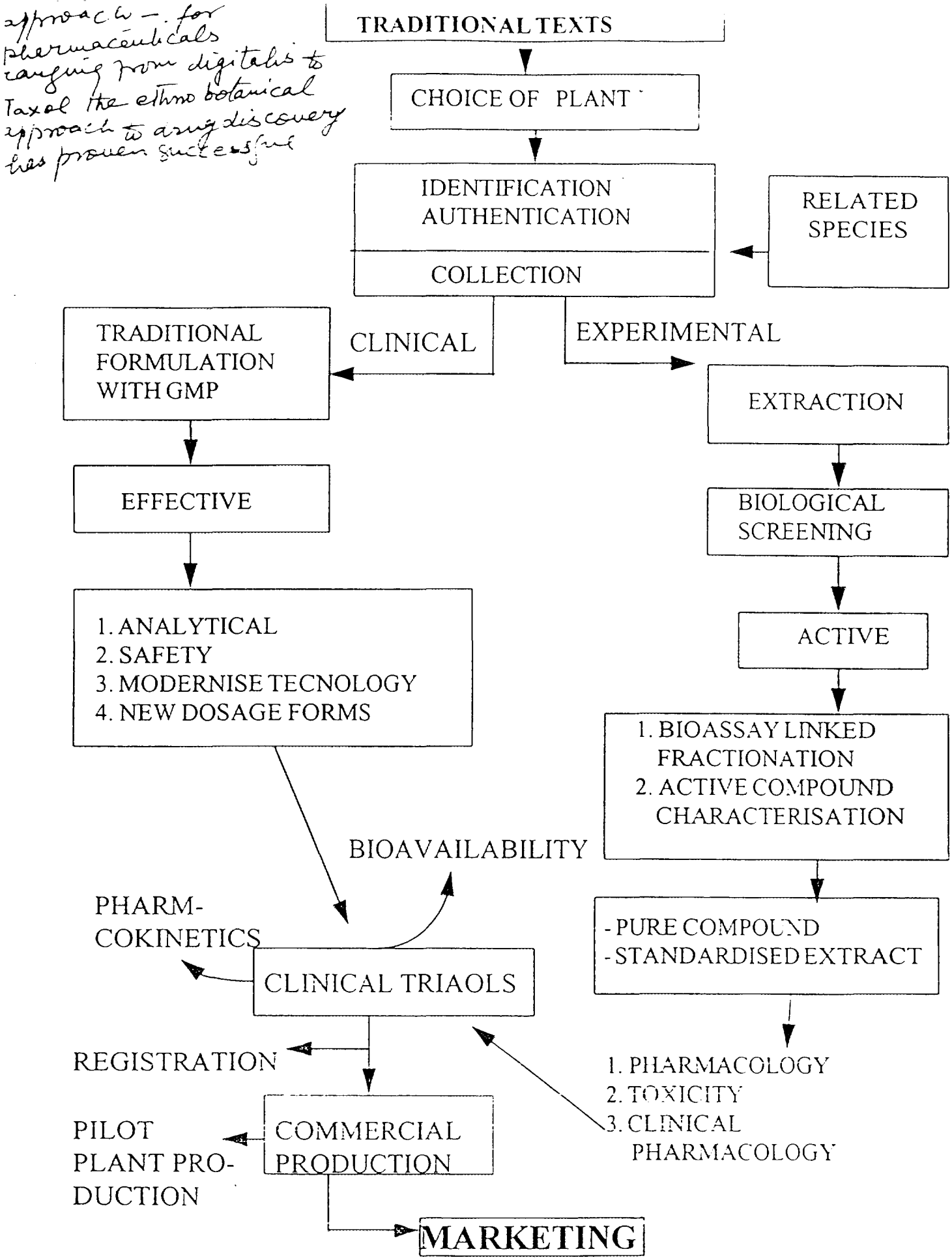


Figure 10 : Modern Approach for drug development from medicinal plant.

Multidisciplinary approach to drug development from medicinal plants used in traditional medicine has been tried in several technical assistance programmes by UNIDO beginning in Mid 1970. Major multidisciplinary programmes were implemented in Nepal, Thailand, Vietnam & DPR Korea.

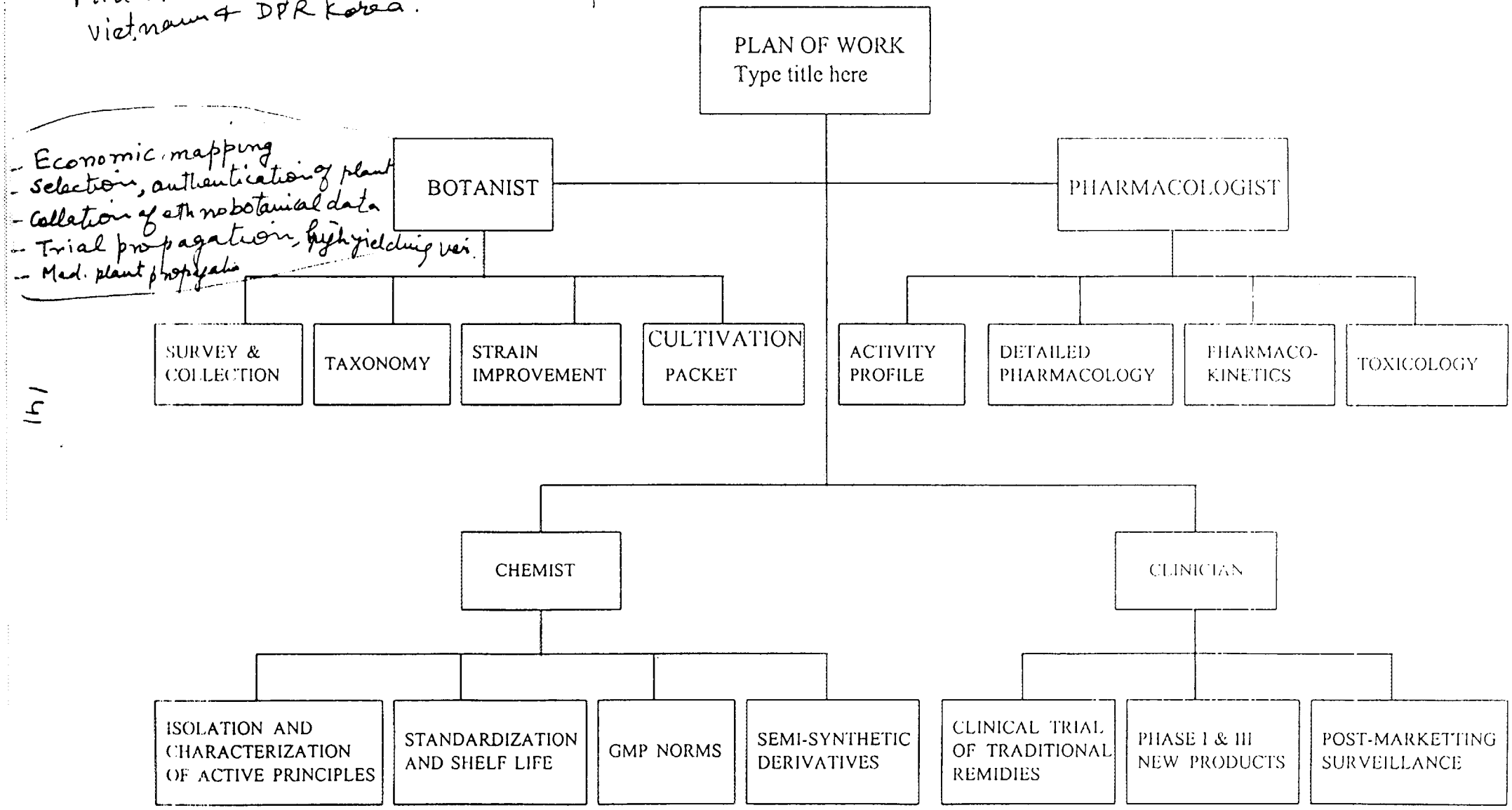


Figure 13: Multi-Disciplinary approach to drug development from medicinal plants

Since medicinal plants or their formulations have been in use in various countries under their respective systems of medicine like Ayurveda, Unani, Siddha systems in India & Chinese system in China, it would not be unethical to evaluate such plant products clinically first keeping in view the national priority, the target disease is selected & the formulation is evaluated clinically by modern physician using current protocols/criteria

If clinical efficacy is not demonstrated, the formulation should be withdrawn from the market & it is for the public awareness. But if the drug is found clinically efficacious its detailed toxicological studies should be undertaken. If found toxic, it may be discharged. If safe, it should be standardized using all modern analytical methods & regulatory aspects may be satisfied. Simultaneous by detailed Chemistry & Pharmacology should be studied.

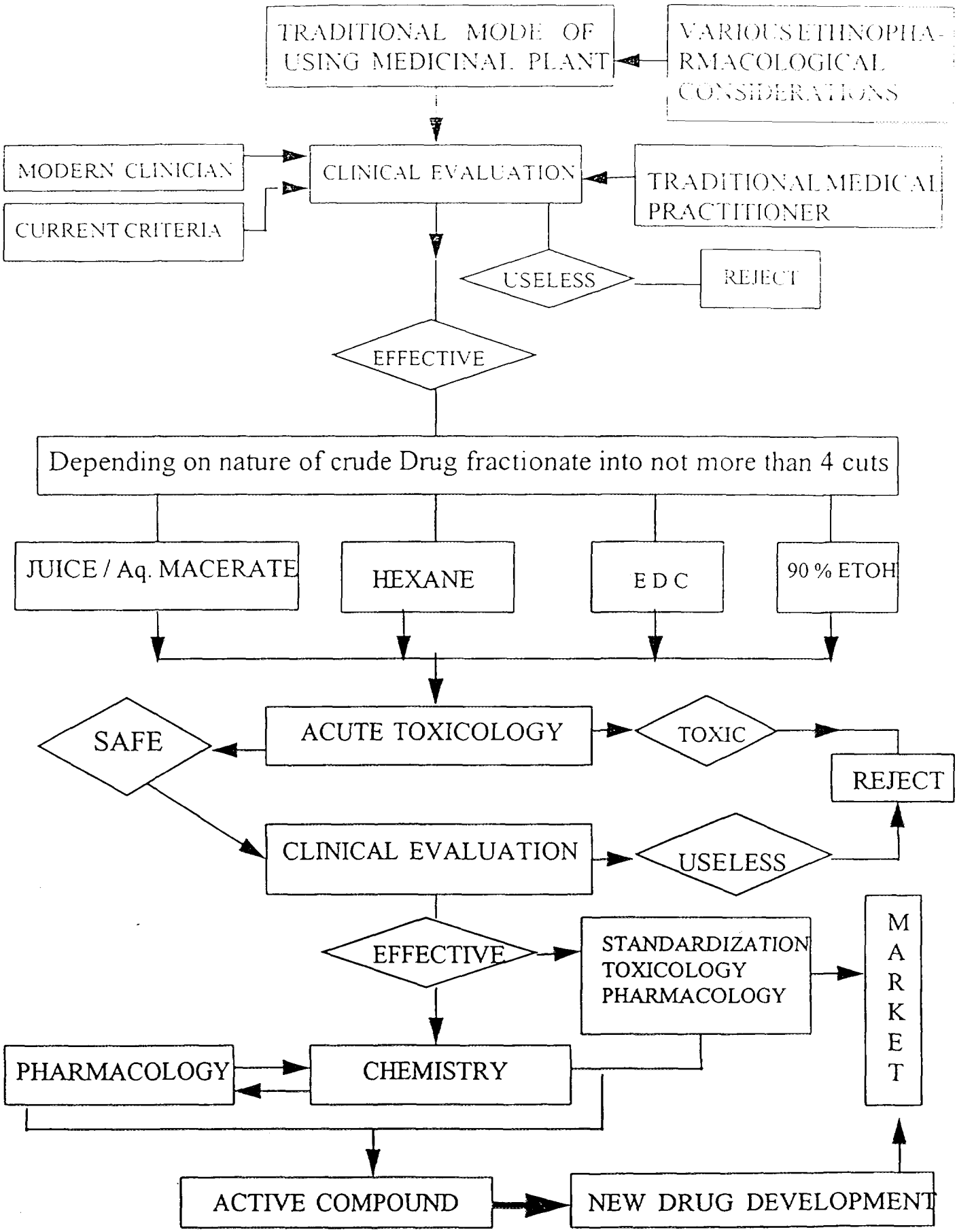


Figure 11 : Modern Approach For Drug Development From Medicinal Plant

For harnessing ~~Ayurveda~~ indigenous system of medicine for modern drug development, a different approach than that normally adopted for drug discovery from plant sources is called for.

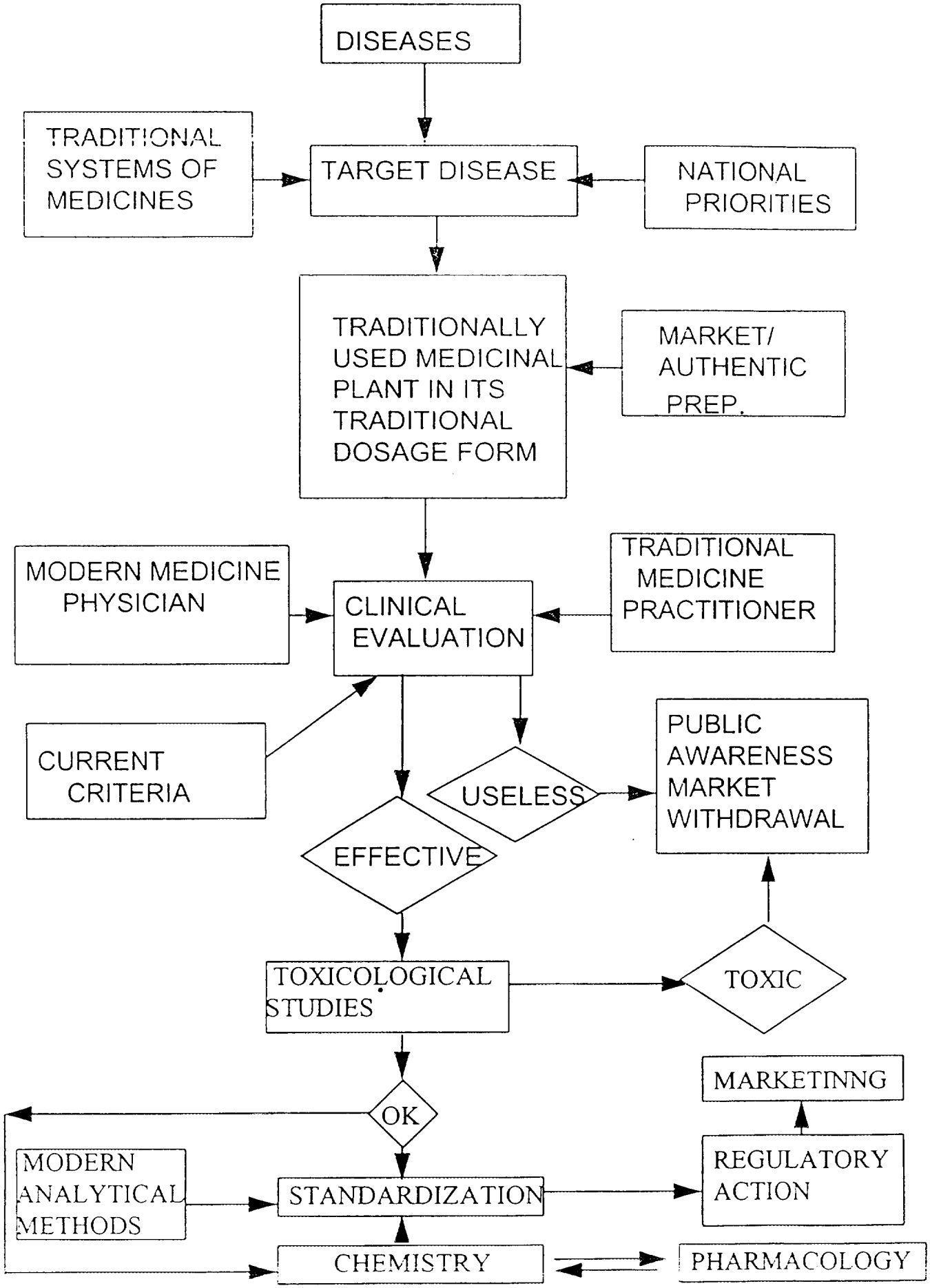
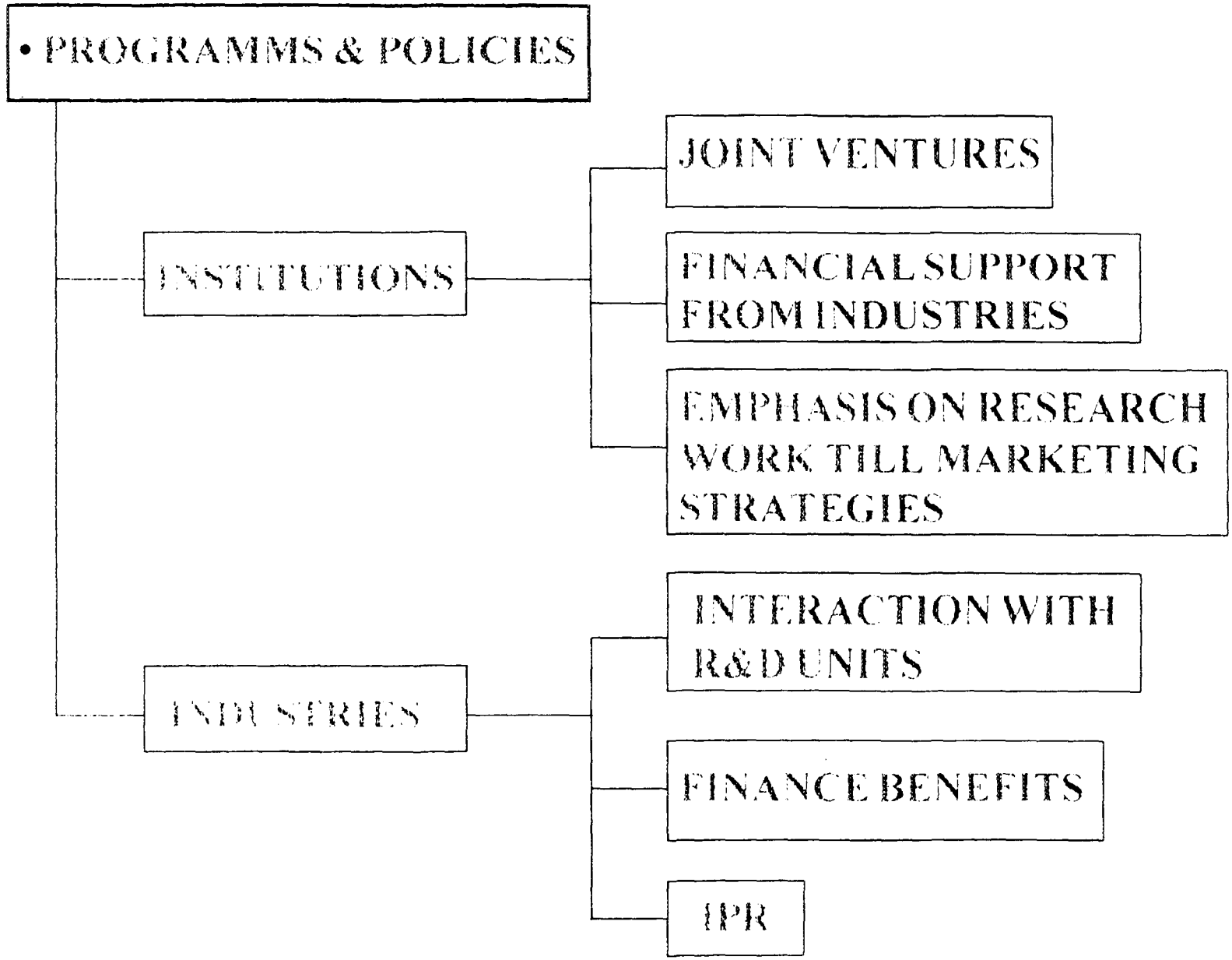


Figure 12 : Disease Oriented Approach for Drug Development from Plants


• PROGRAMMS & POLICIES
INSTITUTIONS
JOINT VENTURES
FINANCIAL SUPPORT FROM INDUSTRIES
EMPHASIS ON RESEARCH WORK TILL MARKETING STRATEGIES
INDUSTRIES
INTERACTION WITH R&D UNITS
FINANCE BENEFITS
IPR

medicinal plant research is beset with a number of problems & the major stumbling blocks are listed here

BOTTLENECKS OF HERBAL DRUG QUALITY CONTROL AT INDUSTRIAL SCALE

1. Irritating controversies regarding the botanical identity of the plant which cannot be applied when industries use powdered herb(s).
2. Inherent biological variation in the characteristic of the plant due to the site of collection, period of collection, processing and storage conditions.
3. Non-availability of a system where few labs could collaboratively test samples and agree on certain minimum quality requirements.
4. Absence of library of marker compounds or chemical compounds isolated from herbs (this is a great industrial opportunity or an opportunity for CSIR laboratories to create such a library of marker compounds and make them available as reference substances against payment)
5. Lack of proper communication and the will of medical fraternity to undertake biological or clinical examination of herbal drugs.
6. Non-availability of a system where standard or properly identified samples of herbs are made available to industry
7. Poor encouragement and almost absence of public test houses which can undertake analysis of herbs and herbal products.