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**EFFICACY AND SAFETY EVALUATION OF HERBAL MEDICINES  
AND DEVELOPMENT OF NEW PLANT-BASED DRUGS**

Discussion paper

Prepared by

**B. N. Dhawan**  
UNIDO Consultant

\* Jointly organized by the United Nations Industrial Development Organization (UNIDO)  
and the World Health Organization (WHO), Regional Office for Africa.

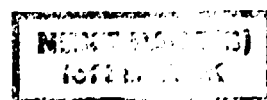
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## INTRODUCTION

The World Health Organisation has estimated that upto 80% of the world's population depends on traditional medicine for its primary health care (Bodecker, 1995). In addition, many important drugs in modern medicine are based on, or derived from, compounds isolated from plants. These are major, but not the only reasons for developing countries to invest in plant based pharmaceuticals and also for the global resurgence of interest in plant based drugs. The development of modern drugs is not only expensive (upwards of 200 million US\$ per drug) but also takes a long time (12-20 years) and testing of a large number of new molecules (Di Masi et al., 1991). Most synthetic drugs utilise fossil resources like petrochemicals, which are non-renewable and not available everywhere. The manufacturing processes are usually not environmental friendly. Many synthetic drugs produce serious side effects and are not very effective in management of several chronic diseases. By contrast plant based drugs have had a long history of clinical use and better patient tolerance and acceptance. The source is renewable, locally available and processing is simpler and environmentally friendly. There have been several major breakthrough during recent years including Gugulipid from Commiphora wightii for hyperlipidemia (Dhawan, 1989), taxol from Taxus baccata for ovarian cancer (Lenaz and De Furia, 1993) and artemisinin from Artemisia annua for malaria (Qinghaosu Group, 1979). Moreover, over 80% of the plants have not yet been scientifically investigated for their biological activity.

### DEVELOPMENT OF NEW DRUGS

As pointed out above, development of a new drug today is a lengthy process and has to follow the guidelines of the regulatory agency of the concerned country, even though there is a general consensus on procedures to be followed. The procedures have become more streamlined during the last few decades following the thalidomide tragedy. During the development of a new drug stress has to be on assessing its potential benefit (efficacy) and risk (safety) to the individual as well as the society. Various phases in the development of a new drug have been shown schematically in Figure 1 but only the biological evaluation and animal toxicity studies will be briefly discussed here. It may be pointed out that in case of drugs with long established traditional use detailed toxicity may not be necessary initially (WHO, 1991) unless a new dosage form is used or some toxic effects are reported clinically.

### SELECTION OF PLANTS

It is not desirable to lay down very strict criteria for selection of plants but at the same time initial selection of plants is important. The major criteria should include evidence of effective (and extensive) use in the country and the region as well as of safety, assured plant availability from wild or cultivated sources, export potential etc. The endemic plants and threatened species require special considerations. Plants yielding novel compounds also should be evaluated on a priority basis.

A major problem in plants having folk use or often even those used in traditional systems of medicine is that data are

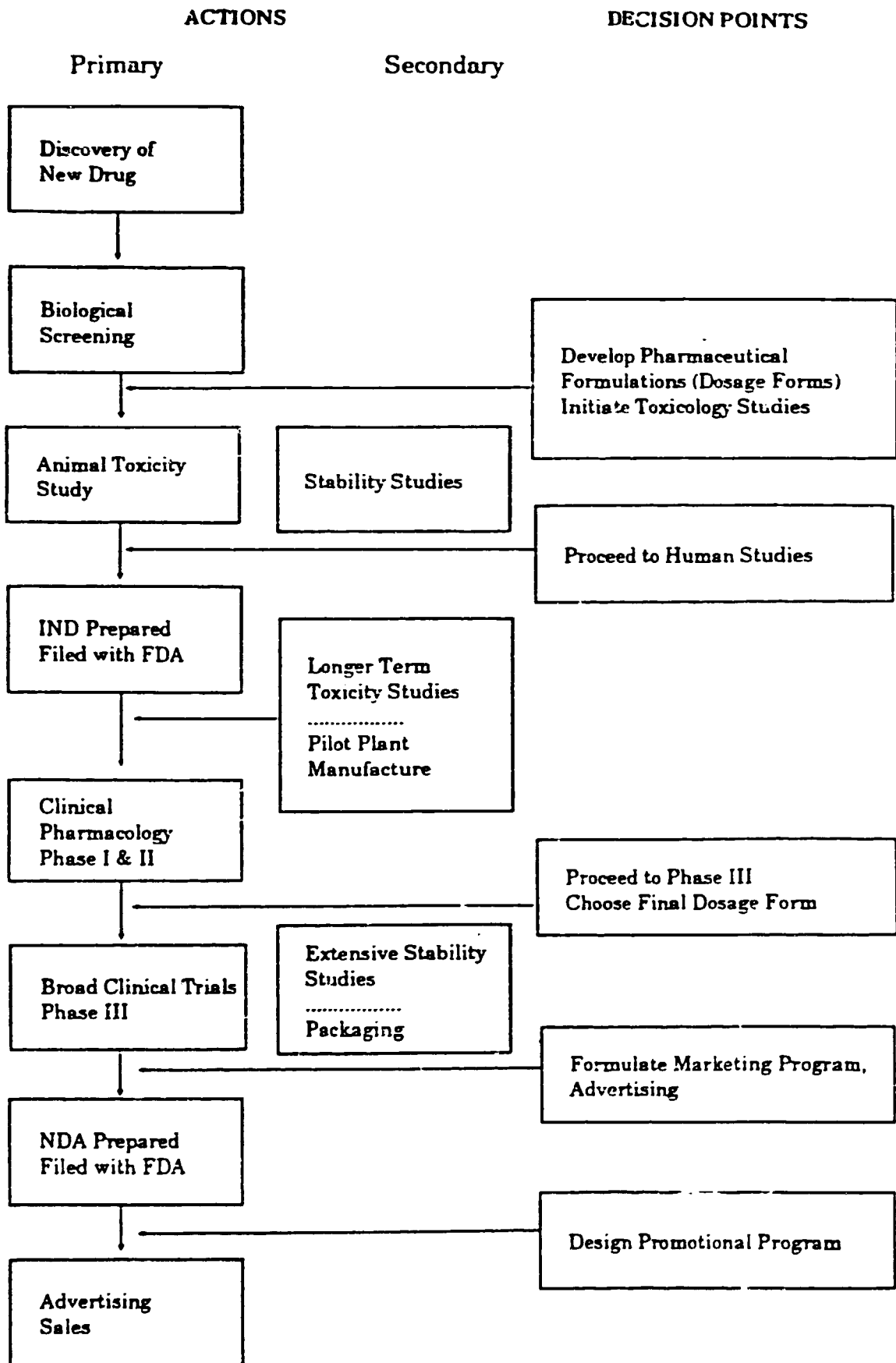


Figure 1. Development of a new drug.

not easily available or decipherable. It is necessary that preparation of national/regional formularies be encouraged so that available information is not lost. WHO is developing guidelines for this purpose and some model monographs are under preparation on plants having a wide global use (X. Zhang, Geneva, personal communication).

The selection of plants is also guided by the objectives of the programme. Generally, these include validation of claims in ethnomedicine (or in traditional systems of medicine); development of standardised extracts or new drugs and introducing them in National Health Care programmes or it may be discovery of new lead molecules. Each country may have a different thrust area depending upon the national disease pattern. Plants to be selected for use in primary health care should be locally available and easily identifiable in addition to having a wide margin of safety.

#### EFFICACY EVALUATION

Efficacy evaluation or biological screening is the first major step once a plant is identified for new drug development. The pharmaceutical companies in developed countries are interested only in isolating and characterising new compounds to be developed as drugs. In developing countries, however, such a programme should have several objectives. These, in order of priority should be (a) to provide a rationale for clinical use of the preparation, (b) demonstrate lack of activity so that its use may be eliminated, (c) to develop standardised extracts or pure compounds as new drugs for modern system of medicine, and (d) to provide novel lead molecules for new drug



development. Natural products continue to be a major source of new lead molecules (Hylands and Nisbet, 1991).

These are usually several ways in which a particular activity may be evaluated by a pharmacologist. The cost and availability of material and animals constitute major constraints, hence choice of appropriate tests system is vital, specially for the initial primary screening. The selected tests should permit detection of desired activity rapidly, comprehensively and inexpensively (Irwin, 1962). The procedures are often said to be quick and dirty. The major objectives of any screening programme are to unequivocally establish the presence of biological activity, to classify it and to make at least a rough estimate of potency. The information is largely descriptive and qualitative and is followed by in-depth studies on promising plants.

#### Types of Screening

The screening programmes may broadly be divided in two subtypes depending upon the ultimate objectives:

i) Individual activity screening: The procedure utilises very few tests and is directed towards a specific pharmacologic activity e.g. antimalarial, spermicidal etc. Such studies are easier to organise and are, therefore, more often undertaken. Perhaps the most extensive studies have been under the "Anticancer Drugs from the Natural Products" project of National Cancer Institute, U.S.A. (Suffness and Doursos, 1979). We have screened Indian plants for antiviral activity (Rastogi and Dhawan, 1990) and spermicidal activity (Setty et al., 1977). Elisabetsky et al. (1992) evaluated Amazonian nerve tonics as anti-depressant agents. African plants have been screened for molluscicidal and fungicidal

activity (Cepleanu et al., 1994). Additional studies have been reviewed by Dhawan (1991). The Chinese experience has been reviewed by Peigen (1991) and the African scene by Sofowora (1993).

ii) Broad-based screening: Such a programme is particularly useful where available information on a plant is scanty or none. The main objective is to find out if a plant product is pharmacologically inert or has any exploitable potential. The strategy is to employ simple and quick tests to cover a broad area of biological activity. Such programmes were initiated in several countries in the early 1960s including USSR (Aliev, 1962), West Indies (Feng et al., 1962), U.S.A. (Farnsworth et al., 1966) and India (Dhar et al., 1968). The African studies deal more with phytochemical screening (Mabran, 1991; Ikhiri et al., 1992).

#### Construction of a Screening Programme

As pointed out earlier, the tests selected should be able to identify the main pharmacological activity, be preferably at least semi-quantitative and also provide information about other effects of the plant material being studied. In the recent years, stress is being laid on in vitro test systems but in most cases confirmatory tests on mammalian species are required.

The in vitro studies may need culture of micro-organism (for chemotherapeutic activity), purified enzymes or receptor membranes or isolated tissues from mammalian species including tissue samples from slaughter houses. For in vivo studies it is preferable to use conscious animals (rodents are most convenient) but anaesthetised animals with appropriate surgical intervention (cat, dog or rodents) may also be needed.

Some consideration has to be given to the route of administration and calculation of appropriate dose. The preferred route for conscious animals is oral, since it is also going to be the desirable route for clinical studies. The route of administration in most cases produces only a quantitative change in the response. If the plant material is being used clinically the dose can be extrapolated to other species by the use of appropriate parameters such as the surface area ( Dhawan and Srimal, 1984) etc. A conversion based on body weight has been shown in Table 1. In other cases the LD50 is determined and the starting dose can be  $\frac{1}{2}$  LD50 for crude materials and  $\frac{1}{5}$  LD50 for pure compounds.

It is important to identify the parameters to be measured and to know the correlation between the effect being studied in the animal and its postulated clinical effects. The following guidelines are useful in selecting the tests:

i) Does it measure what it is supposed to measure? For example, it will be unwise to use cataleptic activity, an undesirable effect of neuroleptics, as an indicator of the tranquillising activity. It is equally important to know about the reliability of the test system selected i.e. how consistently it measures what it does measure?

ii) The test system should be capable of being used for materials of varying grades of purity: crude extracts, semipurified materials and pure active constituents. For in vivo tests the preferred route of administration is oral but care is necessary in the choice of the vehicle.

iii) It is necessary to have in-built safety mechanisms like periodic testing of known standard compounds or placebos (preferably under unknown code numbers).

TABLE 1. EXTRAPOLATION OF DOSES BETWEEN VARIOUS SPECIES BASED ON BODY WEIGHT

To	Mouse	Rat	Monkey	Dog	Man
From	20 g	150 g	3 kg	8 kg	60 kg
Mouse	1	1/2	1/4	1/6	1/2
Rat	2	1	1/2	1/4	1/7
Monkey	6	2	1	3/5	1/3
Dog	6	4	5/3	1	1/2
Man	12	7	7	2	1

Example: Mouse dose 120 mg/kg. Human dose  $120 \times 1/12 = 10$  mg/kg

These considerations are important in establishing the realibility of the programme but a possible criticism can be that it will only detect already known types of biological activity rather than novel activity. This should be satisfactory for validating a traditional use but from the global industry's point of view it is more rewarding to detect activity which is new, unexpected or unique.

I will like to again stress the need of inbuilt safety mechanisms. Wherever possible a negative (vehicle only/sham operated) and a positive (treated with a known effective drug) controls should be concurrently run. Caution is also necessary in extrapolating results from in vitro studies. There may be non-specific effects with crude extracts. Further, a metabolic activation occurs in several natural products leading to the production of active metabolites. Such activities will be missed if in vitro systems only are used.

It is not possible to provide details of tests available for various types of activity but these are available in several publications (Turner, 1965; Turner and Hebborn, 1971; Dhawan and Srimal, 1984).

#### FOLLOW UP STUDIES

Follow up studies are undertaken once a standardised extract or a pure compound shows promising activity. These studies can be summarised under 3 heads.

#### Specific Pharmacological Actions

These will involve an indepth study of the effects having therapeutic potential. Several models and animal species have often got to be used. Quantitative data including ED50 values

and potency compared to standard drug are determined. The time course of action, dosage schedules and mechanism of action are also studied. Whenever necessary, drug-interactions are also investigated.

#### General Pharmacology

It is necessary to investigate the effects on other organ systems like the central nervous system, cardiovascular system etc. The information is necessary to be able to predict possible side effects and precautions during its clinical use and ways of counteracting the side effects. Such studies may also provide leads about other possible uses of the new product.

#### Pharmacokinetic studies

These studies are designed to estimate the rate and degree of absorption, distribution, excretion and metabolism of the new drug. It may be stated that while pharmacodynamic studies investigate what the drug does to the animal system, the pharmacokinetic studies find out what the body does to the drug. These studies determine the effective plasma concentration and its duration and provide vital data for deciding the dose schedule. They also provide information, for example, about the ability of the compound to cross the blood brain (or placental) barrier, protein binding, enterohepatic circulation etc. Working out the metabolism of a new molecule is difficult and time consuming even more so when extracts containing several compounds are to be investigated. Species variation also are quite common.

## TOXICITY STUDIES

The toxicity studies also have several segments and the duration and other details are usually determined by the National Regulatory Agencies. They are related to the frequency and duration of clinical use. The WHO general guidelines (WHO, 1993) have been given in Table 2.

### Acute Toxicity

Acute toxicity studies need to be carried out in at least 2 species, by the route intended for clinical use. In addition, at least one more route needs to be used in one species to ensure systemic absorption. The studies are usually performed in mice and rats. Mortality is observed for 3 days after parenteral administration and for 7 days after oral administration. LD50 and 95% confidence limits are calculated after mortality has been observed with graded doses. Approximate LD50 can be quickly determined initially by the procedure of Horn (1956).

### Long Term Toxicity

The duration of such studies is decided by the duration of clinical use and has been summarised in Table 2. The studies must be carried out in at least 2 species, a rodent and a non-rodent (usually beagle dog or rhesus monkey) using animals of both sexes. A control group of animals receives the vehicle alone and three other groups receive graded doses of the test drug 7 days a week by the intended route of clinical use. The lowest dose is generally 2.5 times the therapeutic dose and should usually be nontoxic. The intermediate dose should cause some symptoms but not death while with the highest dose some observable toxicity should be obtained. At CDRI, these doses are 5 and 10

TABLE 2. DURATION OF TOXICITY STUDY

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Period of Clinical Use	Duration of Toxicity Study
Single administration	2-4 weeks
Less than one week	2-4 weeks
1-4 weeks, repeated	4-12 weeks
1-6 months	3-6 months
Over 6 months	9-12 months

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times the effective dose but the dose in the highest group is escalated if necessary. Besides behavioural and periodic biochemical monitoring all the animals are autopsied at the end of the study for detailed biochemical and histological studies. The number of rodents and nonrodents in each group should be 6-10 and 2-3 of either sex for studies under 6 weeks and 15-30 and 4-6 respectively for studies of longer duration.

#### Terratogenicity

The data are needed if the drug is to be used in women of child bearing age. The two species commonly employed are the rat and the rabbit. The drug is administered to pregnant dams during the period of organogenesis and here also 3 dose levels are employed by the intended clinical route of administration. About 20 rodent and 12 non-rodent are used in each group and the control group receives the vehicle only. At autopsy, the number of living and dead fetuses is recorded. The sex, weight and any malformations in the fetuses are recorded. Half the fetuses are processed for skeletal anomalies and the other half for visceral anomalies.

#### Mutagenicity

Variety of short term tests have been proposed. The commonly used tests include the Ames test for gene mutation in Salmonella typhimurium (Ames, 1971), in vitro chromosomal aberration tests, the micronucleus test in mice and the dominant lethal test in mice or rats (Rohrborn, 1968). The information supplements data from teratogenic studies and also indicates if carcinogenic studies are necessary.

### Carcinogenicity

These studies are generally required in drugs likely to be used for prolonged periods e.g. oral contraceptives, drugs exhibiting mutagenic potential or if the drug or its metabolites are related to a known carcinogen. The study is performed in 2 species and at 3 sublethal dose levels. The study may have to cover greater part of animals's life span and usually lasts about 12-24 months. Rats, mice and hamsters are generally employed. The strain used should not have a high incidence of spontaneous tumors. Detailed histopathological studies are undertaken on each animal at death or autopsy at termination of the study.

### Reproductive Studies

These are to be undertaken in drugs to be used chronically in women of child bearing age. Two species, one non-rodent, have to be used. For fertility studies, drug is administered to both males and females for a sufficient number of days before mating. In the females, the medication is continued throughout pregnancy. Each group should include around 20 pregnant rodents and 6-8 non-rodents. A detailed examination of the litters as well of spontaneous abortions is performed. In perinatal studies, the drug is administered during the last 1/3rd of pregnancy and during the lactation period at a dose which causes low fetal loss. The young ones are sacrificed after weaning and detailed macroscopic and microscopic studies are performed.

## THE CDRI PROGRAMME ON NATURAL PRODUCTS

The Central Drug Research Institute initiated systemic exploration of natural products (terrestrial plants), marine flora and fauna) in early 1960s and has developed a multiprolonged strategy that has been quite successful. CDRI utilises 5 different approaches depending upon the test material but the major efforts are directed to the first 2 approaches.

### Drugs Used in Traditional System of Medicine

The drugs are carefully selected by an extensive scan of texts of traditional systems of medicine and discussions with the traditional physicians. It is important to distinguish between the drugs used in traditional systems of medicine and those having a folk-lore use. The plants are collected and identified by qualified botanists and the first extracts are prepared the way they are used in the traditional systems of medicine. Appropriate test systems are selected and once activity is detected, and needs more detailed follow up, efforts are made to develop a standardised extract whenever feasible. A major breakthrough has been the marketing of guggulipid, a hypolipidemic agent from gum of Commiphora wightii, which has been a long history of use. Seven other products are in advanced stages of development and their current status has been summarised in Table 3.

It is pertinent to point out that standardised extracts are being developed in the case Sapindus mukorosi, Picrorhiza kurroa, Streblus asper and Tephrosia purpurea, as was done with Commiphora. Such extracts generally contain several closely related compounds, are usually more effective than single compounds, the yield is much higher thus conserving

TABLE 3. CURRENT STATUS OF CDRI LEADS FROM TRADITIONAL SYSTEM  
OF MEDICINE

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<b>A. <u>BEING MARKETED</u></b>		
1. PSORALEA CORYLIFOLIA (PSORALEN)		LEUCODERMA
2. COMMIPHORA WIGHTII (GUGULIPID)		HYPOLIDEMIC
<b>B. <u>UNDER CLINICAL TRIALS</u></b>		
1. CURCUMA LONGA (CURCUMIN)	PHASE III	NSAID
2. SAPINDUS MUKOROSI (CONSAP)	PHASE III	SPERMICIDAL
3. ARTEMESIA ANNUA ( $\alpha$ $\beta$ ARTETHER)	PHASE III	ANTIMALARIAL
4. PICRORHIZA KURROA (PICROLIV)	PHASE II	HEPATOPROTECTIVE
5. BACOPA MONNIERA (BACOSIDES)	PHASE II	NOOTROPIC
<b>C. <u>UNDER PRECLINICAL EVALUATION</u></b>		
1. STREBULUS ASPER		MACROFILARICIDE
2. TEPHROSIA PURPUREA		ANTI-LEISHMANIAL

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plant material and the technology less complicated. In most cases, HPLC has been used for standardisation of the extract using selected active compounds as markers. Several of them have unique properties. Curcumin is a safe anti-inflammatory agent. It also inhibits platelet aggregation but not prostacyclin synthesis suggesting its value in treatment or prevention of vascular thrombosis. Picroliv, containing at least 60% of 1:15 mixture of iridoids picroside I and kutkoside, exhibits hepatoprotective, anticholestatic, antiviral and immunomodulatory properties. Consap, containing total saponins of Sapindus mukorossi, has an advantage over Nonyl-9 since its action is not pH dependent.

#### Broad Based Biological Screening

Most of the terrestrial plants and the marine flora and fauna have not been investigated earlier for biological activity, hence they are subjected to broad based screening using over 100 in vitro and in vivo test systems. A list of these tests has been given in Table 4. All samples are collected by qualified botanists and authenticated before being included in the programme. A 50% ethanolic extract is first made for primary screening. Cut off limits have been set for each test after studying standard drugs. For in vivo tests acute LD50 is first determined. Subsequent tests are performed at  $\frac{1}{2}$  LD50 for crude extracts and at  $\frac{1}{5}$  LD50 for purer preparations. In the case of extracts with promising activity bioassay linked chemical fraction is undertaken to isolate and characterise the active constituents for detailed developmental studies. Nearly 4000 terrestrial (belonging to over 1500 genera

TABLE 4. TYPES OF BIOLOGICAL ACTIVITY INVESTIGATED AT CDRI AND THE TEST SYSTEMS UTILISED

Activity	Test done
1	2
A. Antiviral	<ol style="list-style-type: none"> <li>1. Encephalomyocarditis virus(mouse)</li> <li>2. Japanese encephalitis virus(mouse)</li> <li>3. Ranikhet disease virus, chorioallantoic membrane(CAM), chick embryo fibroblast monolayers(CEF), <i>in vitro</i></li> <li>4. Vaccinia virus - CAM and CEF</li> <li>5. Herpes simplex virus</li> <li>6. Semliki forest virus(mouse)</li> <li>7. Interferon inducers(mouse)</li> </ol>
B. Antibacterial <i>in vitro</i> unless mentioned otherwise	<ol style="list-style-type: none"> <li>1. <i>Escherichia coli</i></li> <li>2. <i>Klebsiella pneumoniae</i></li> <li>3. <i>Mycobacterium leprae</i> (<i>in vivo</i>, mouse)</li> <li>4. <i>Mycobacterium tuberculosis</i> (<i>in vivo</i> also, guinea pig)</li> <li>5. <i>Pseudomonas aeruginosa</i></li> <li>6. <i>Staphylococcus aureus</i></li> <li>7. <i>Streptococcus faecalis</i></li> </ol>
C. Antifungal	<ol style="list-style-type: none"> <li>1. <i>Aspergillus fumigatus</i></li> <li>2. <i>Candida albicans</i></li> <li>3. <i>Cryptococcus neoformans</i></li> <li>4. <i>Sporotrichum schenckii</i> (<i>in vitro</i> only)</li> <li>5. <i>Trichophyton mentagrophytes</i></li> </ol>
D. Antiprotozoal	
(a) Antinmoebic	<ol style="list-style-type: none"> <li>1. Axenic culture(<i>in vitro</i>)</li> <li>2. Intestinal infection (rat)</li> <li>3. Hepatic infection (rat)</li> <li>4. Meningoencephalitis (mouse)</li> </ol>
(b) Antimalarial	<ol style="list-style-type: none"> <li>1. Blood schizonticide (mouse, rat, mastomys, monkey)</li> <li>2. Casual prophylatic (mouse, mastomys, monkey)</li> <li>3. Antirelapse (monkey)</li> <li>4. Gametocytocidal (monkey)</li> </ol>
(c) Antileishmanial	<ol style="list-style-type: none"> <li>1. <i>In vitro</i> (promastigote)</li> <li>2. <i>In vivo</i> (mouse, hamster)</li> </ol>
E. Anthelmintic	
(a) Filaria	<ol style="list-style-type: none"> <li>1. <i>Litmosoides carinii</i> (cotton rat, mastomys)</li> <li>2. <i>Brugia malayi</i> (cat, mastomys)</li> <li>3. <i>Acanthocheilonema viteae</i> (mastomys)</li> </ol>
(b) Hookworm	<i>Ancylostoma ceylanicum</i> (rat, hamster)
(c) Tapeworm	<i>Hymenolepis nana</i> (mouse, rat)
F. Anticancer	<i>In vitro</i> , cell line
G. Endocrinal	
(a) Antifertility	
In female	<ol style="list-style-type: none"> <li>1. <i>In vivo</i> <ol style="list-style-type: none"> <li>i) Anti-implantation (rat, hamster)</li> <li>ii) Abortifacient (rat)</li> </ol> </li> </ol>

1	2
	<ul style="list-style-type: none"> <li>iii) Tubal occluding (monkey)</li> <li>iv) Blastotoxic (rat)</li> <li>v) Oxytocic (cat)</li> </ul>
	2. <i>In vitro</i>
	Abortifacient (rat uterus)
In male	<ul style="list-style-type: none"> <li>1. Antispermatic (rat)</li> <li>2. Spermicidal - <i>in vitro</i></li> <li>3. Semen coagulant - <i>in vitro</i></li> </ul>
(b) Hypoglycaemic	Rat, Rabbit
H. Central nervous system (mouse and rat)	<ul style="list-style-type: none"> <li>1. Gross effects on behaviour</li> <li>2. Body temperature</li> <li>3. Analgesia</li> <li>4. Supramaximal electroshock seizure pattern</li> <li>5. Barbiturate potentiation and antagonism</li> <li>6. Amphetamine hyperactivity and toxicity</li> <li>7. Strychnine/metrazol seizures</li> <li>8. Antireserpine</li> <li>9. Phenylquinone writhing</li> <li>10. Rotarod</li> <li>11. Learning and memory tests</li> </ul>
I. Cardiovascular and autonomic effects (cat, dog, rat)	<ul style="list-style-type: none"> <li>1. Blood pressure</li> <li>2. Respiration</li> <li>3. E.K.G.</li> <li>4. Antiarrhythmic <i>in vitro</i> (guinea pig auricle) <i>in vivo</i> (rat, aconitine arrhythmia)</li> </ul>
J. Hypolipidaemic	Serum cholesterol, triglycerides and lipoproteins in normal and high fat fed/triton treated animals
(a) Lipid lowering <i>in vivo</i> (rat, rabbit, monkey)	
(b) Cholesterol biosynthesis	Rat liver slice
(c) Inhibition of platelet aggregation	<i>in vitro</i> and <i>ex vivo</i>
K. Anti-inflammatory	<ul style="list-style-type: none"> <li>Carrageenin paw edema (mouse, rat)</li> <li>Granuloma pouch (rat)</li> <li>Adjuvant arthritis (rat)</li> <li>Ulcerogenic index (rat)</li> </ul>
L. Other pharmacological activities	
(a) Acute toxicity (LD 50)	mouse, rat (i.p., oral)
(b) Diuretic	Rat
(c) Spasmolytic	Isolated guinea pig ileum
(d) Neuromuscular conduction	Cat
(e) Immune responses	<ul style="list-style-type: none"> <li>PCA (mouse, rat)</li> <li>Haemagglutination (mouse)</li> <li>Cell mediated immunity (rat)</li> </ul>
(f) Hepatoprotective	Rat (liver damage by CCl <sub>4</sub> , thioacetamide, paracetamol and galactosamine)
(g) Antipeptic ulcer	Rat
(h) Adaptogenic	Rat

from about 200 families) and 600 marine products have been screened. About 20% plants materials show significant and often new activity. A summary of the results is given in Table 5. The marine products not only exhibit a higher proportion of activity but the pattern is also different. There is a much higher percentage of anti-implantation, anti-viral and CNS stimulant activity, for example.

The more promising leads from these plants are being pursued. A diterpene, coleonol (synonym forskolin) from Coleus forskohli, has potent cardiovascular effects (Dubey et al., 1981) and increases adenyl cyclase activity (Seamon, 1984). It also inhibits platelet aggregation and lowers intraocular tension. Several plants have yielded potent spasmolytic agents. These include 3 sesquiterpenes from Cedrus deodara (Kar et al., 1975), the coumarins clausimarins from several species of Clausena (Patnaik and Dhawan, 1982) and angelicin from Heracleum thomsoni (Patnaik et al., 1987). Neuromuscular blocking activity has been observed in the new erythrina alkaloid isococculidine (Kar et al., 1977) and quaternary alkaloid isocorydine methochloride from Cocculus laurifolius (Mukherjee et al., 1984). Anticancer activity was found in the glycoside ipolearoside from Ipomea leari, naphthoquinones arnebins from Arnebia nobilis and saponin celsioside from Celsia cromondalina (Rastogi and Dhawan, 1982).

#### Special Tests Indicated by Chemical Structure

Chemists isolate diverse types of new compounds from natural products. Most of these should be subjected to a broad based biological screening but some times the chemical structure is suggestive of a particular type of biological activity. In such cases only tests for the specific activity are required. For example, a new glycoside asclepin has been isolated from Asclepias curassavica. It was a cardenolide, hence tests were selected which would identify and quantify cardiotonic activity. The compound has a digoxin like profile but with higher safety margin (Patnaik and Dhawan, 1978).



TABLE 5. COMPARATIVE BIOLOGICAL ACTIVITY OF TERRESTRIAL PLANTS  
AND MARINE ORGANISMS

Activity	Plants %	Marine %
Antiimplantation	0.4	3.1
Antimicrobial	0.5	0.0
Antiviral	1.4	5.1
Cardiovascular	2.7	3.1
CNS depressant	2.6	2.0
CNS stimulant	0.0	6.4
Diuretic	1.5	6.7
Hypoglycaemic	0.5	2.2
Oxytocic	0.7	0.2
Spasmogenic	0.0	2.0
Spasmolytic	2.0	0.7
Toxic	0.0	2.7
Others	8.8	0.0
-----		
Total	21.1	34.2

### Semi-synthetic Compounds by Lead Optimisation

In several cases, the compound isolated from a natural product may possess only mild activity or exhibit some undesired property. An effort is made in selected cases to prepare a derivative to optimise the activity. Thus, hyatin, a bisbenzylisoquinoline alkaloid from roots of Cissampelos pareira L., was quaternised and hyatin methiodide produced potent neuromuscular blockade (Pradhan et al., 1958). In phase III clinical trials, it did not exhibit much advantage over d-tubocurarine and was, therefore, not marketed (Pradhan et al., 1964). More recently,  $\alpha$ - $\beta$  arteether derivative of artemisinin has been prepared which is effective against Plasmodium cynomolgi B and P. knowlesi in monkeys (Dutta et al., 1989) and in clinical studies it shows excellent results in treatment of P. falciparum malaria (unpublished observations).

### Initial Clinical Studies

There is growing realisation that it may be quicker and more cost effective to undertake initial clinical studies with natural products which have been used extensively with no reports of untoward reaction. Some authorities suggest a short toxicity evaluation before clinical studies (Roy Chaudhury, 1992) but others do not consider even this to be necessary (WHO, 1991). Initial clinical studies are also useful in diseases where suitable animal models are not available e.g. menstrual disorders, fistula-in-ano, eclampsia; in the case of formulations having many constituents and for major health problems where modern drugs are not available and an urgent solution is required. The drugs used for clinical studies must be prepared using GMP, clinical trial properly designed and a double blind randomised procedure followed whenever feasible.

Once activity is demonstrated, isolation and characterisation of active constituents can be taken up. In recent years we have demonstrated the efficacy of an Ayurvedic formulation in controlling excessive uterine bleeding following application of intra-uterine contraceptive device in a certain proportion of women (Dhawan, 1987). The active constituent from one of the plants has thereafter been isolated. The Indian Council of Medical Research has similarly obtained evidence that results of treatment of anal fistula by a medicated thread, Kshar sootra, are better than those obtained with surgery (ICMR, 1991).

The detailed results of CDRI research in medicinal plants have been published and reviewed (Dhawan, 1981, 1986, 1989, 1995; Dhawan and Rastogi, 1991; Kamboj and Dhawan, 1989; Rastogi and Dhawan, 1982).

#### CHOOSING THE PRIORITIES

It is necessary to prioritise the thrust areas to optimise the outputs of research efforts and other resources. Several factors help in determining the priorities. These include the distribution of flora, national or regional disease pattern, availability of modern health care etc. In addition, many countries also keep in mind the global priorities in developing new drugs so as to get a good financial return.

It has been pointed out above that from the point of view of flora, priority needs to be given to endangered as well as to endemic plants.

The disease pattern and hence the priorities have national characteristics but there are several diseases which are common

to African and in fact to most developing countries. These include protozoal and helminthic infections like malaria, filaria, onchocerciasis etc. Many of these diseases do not exist in developed countries and large pharmaceutical house, therefore, do not give high priority to develop new drugs for such conditions. There is a gross mismatch between the health needs of the developing countries and the interests of the pharmaceutical industry. These should, therefore, receive priority in national/regional plans. The above examples are only illustrative and each country could evolve its own list of priority for communicable diseases.

Primary health care usually requires comparatively milder medication and the acceptability of herbal medicines for such conditions is also much more. The main considerations should be adequate availability or possible cultivation throughout the country, lack of toxicity and ease of formulation. A concerted plan of action is needed and children should be familiarised with such plants even in the school curriculum. Suitable formularies should be prepared in local languages and setting up of small scale industries for production of such drugs should be encouraged.

The global thrust areas for drugs from natural sources include disease conditions whose incidence is increasing and where the modern drugs are either unavailable or unsatisfactory. The following major areas for such efforts are well identified.

#### A. Infections

AIDS

Opportunistic infections

**B. Chronic Diseases****Arthritic Disorders****Liver Diseases**

- infective
- alcohol related

**Hyperlipidemia****C. Immunomodulators****D. Promoting Wound Healing**

- Decubitus ulcers
- Diabetic ulcers
- Varicose veins
- Immunocompromised patients

**E. Nootropic**

- Age related memory disorders
- Mentally deficient children
- Alheimers disease

It is important to keep the financial considerations also in view while deciding about the priorities. In areas where modern drugs are available, it will be useful to carry out a case by case study of the cost-benefit ratio of treatment by modern drugs vs. traditional drugs before embarking on detailed investigations.

**CONCLUDING REMARKS**

This report has mainly dealt with organisation of programmes for efficacy and safety evaluation of herbal medicines and this requires biologists with specialisation in several areas like pharmacology, microbiology, toxicology etc. It must, however, be pointed out that such an unit cannot work

in isolation and will need close collaboration with botanists, chemists, etc. preferably in the same campus. Other disciplines like pharmaceuticals and clinicals get involved as active materials are developed further.

Some prioritisation is necessary in term of type of pharmaceutical product to be developed. As discussed above, the modern pharmaceutical industry likes to isolate and characterise pure compounds and to develop them as drugs. This is not only a wasteful procedure in terms of the plant material but also adds to the cost and usually employs more complex technology. In the existing situation in most developing countries priority must be given to standardised extracts. These are much nearer to traditional dosage forms, hence have better public acceptance besides being relatively cheap and easier to prepare.

The drugs of traditional systems have been used for very long time and, therefore, it should be easier to place them on a scientific footing and develop standardised preparation. In most cases only minimal toxicology should be required and some authorities favour well planned clinical trials without testing for biological activity. As stressed above, this is particularly useful where polyherbal formulations are used. Accordingly, there can be 2 lines of approach for study of such drugs. These have been outlined in Fig. 2. A judicious mix of the 2 approaches will perhaps yield the best results. It is also important that preparations which are inactive or show toxicity should be weeded out from health care programmes.

Biodiversity prospecting in the changed economic scenario is like the nineteenth century Californian gold rush. Wealth and

technology is today concentrated in the North as biodiversity and poverty are in the South (Reid et al., 1993). The interests of bioprospecting corporations are not the same as those of people living in biodiversity 'hot spots' like Africa. The Intellectual Property Rights (IPR) are thus subject to conflicting concerns. Each country has to draw its own boundaries between the public domain and IPR based level of technology, commercial practices and social norms. It is, however, necessary to ensure that biodiversity is preserved and local people get an equitable return if local flora are exploited to provide new therapeutic aids.

A major difficulty in proper biological evaluation of natural products continues to be non-availability of sensitive test systems. Most of the currently used test systems have been developed for pure synthetic compounds and they are often not suitable for use with crude materials. Investigators are acutely aware of this and efforts are being made to adopt sophisticated techniques for evaluation of natural products. A few years ago, we investigated a product developed by the Unani system of medicine and claimed to improve myocardial function. The product was inactive in most of the commonly used cardiovascular screens. A study of regional circulation with radiolabelled microspheres, however, demonstrated a selective improvement in blood supply to the heart muscle (Gulati et al., 1985).

Medicinal plants represent a rich renewable resource. If properly developed and exploited it can contribute significantly towards improvement in quality of life and in providing health care at affordable cost to inhabitants of developing countries while also helping their economic development.

THE TWO APPROACHES

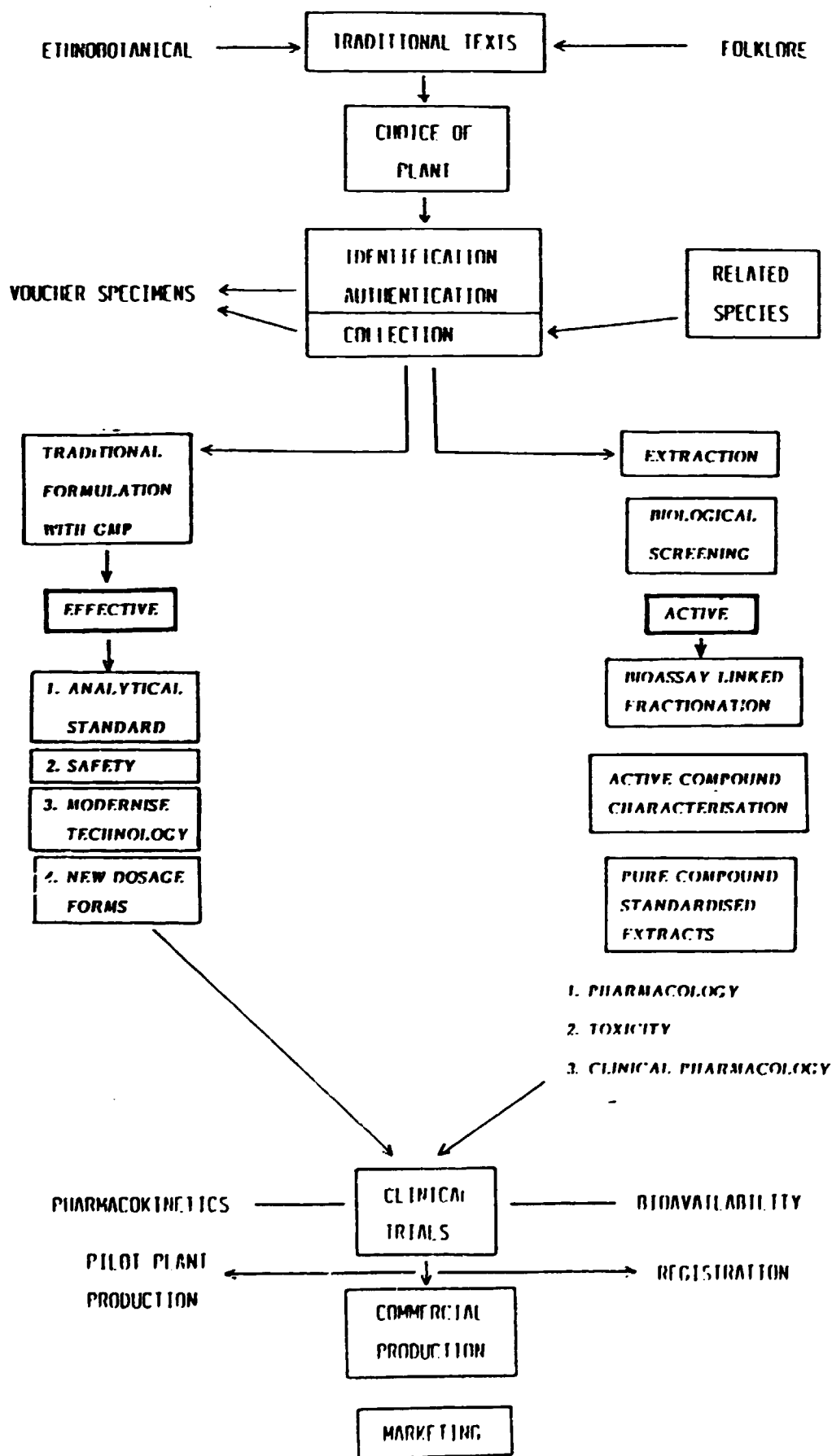


Fig. 2



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***GUIDELINES FOR THE  
ASSESSMENT OF HERBAL MEDICINES***

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**PROGRAMME ON TRADITIONAL MEDICINES  
WORLD HEALTH ORGANIZATION  
GENEVA, 1991**



## GUIDELINES FOR THE ASSESSMENT OF HERBAL MEDICINES

### Introduction

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

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

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

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

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

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

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

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

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

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

## **Assessment of quality, safety, and efficacy and intended use**

### ***Pharmaceutical assessment***

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

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

### ***Crude plant material***

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

### ***Plant preparations***

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

### ***Finished product***

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

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

**Stability**

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

**Safety assessment**

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

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

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

**Toxicological studies**

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

**Documentation of safety based on experience**

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

**Assessment of efficacy and intended use**

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

**Activity**

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

**Evidence required to support indications**

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

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

**Combination products**

As many herbal remedies consist of a combination of several active ingredients, and as experience on the use of traditional remedies is often based on combination products, the assessment should differentiate between



old and new combination products. Identical requirements for the assessment of old and new combinations would result in an inappropriate assessment of certain traditional medicines.

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

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

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

### ***Product information for the consumer***

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

The following elements of information usually suffice:

- name of the product
- quantitative list of active ingredient(s)
- dosage form
- indications
  - dosage (if appropriate, specified for children and the elderly)
  - mode of administration
  - duration of use
  - major adverse effects, if any
  - overdosage information
  - contraindications, warnings, precautions and major drug interactions
  - use during pregnancy and lactation
  - expiry date
  - lot number
  - holder of the marketing authorization

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

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

### ***Promotion***

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

### ***Utilization of guidelines***

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

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

**INTERNATIONAL GUIDING PRINCIPLES FOR BIOMEDICAL RESEARCH  
INVOLVING ANIMALS**

These guiding principles were published by the Council for International Organizations of Medical Sciences (CIOMS) in 1985. The basic principles are listed below:

- I. The advancement of biological knowledge and the development of improved means for the protection of the health and well being both of man and of animals require recourse to experimentation on intact live animals of a wide variety of species.
- II. Methods such as mathematical models, computer simulation and in vitro biological systems should be used wherever appropriate.
- III. Animal experiments should be undertaken only after due consideration of their relevance for human or animal health and the advancement of biological knowledge.
- IV. The animals for an experiment should be of an appropriate species and quality, and the minimum number required, to obtain scientifically valid results.
- V. Investigators and other personnel should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort, distress, or pain as ethical imperatives.
- VI. Investigators should assume that procedures that would cause pain in human beings cause pain in other vertebrate species although more needs to be known about the perception of pain in animals.
- VII. Procedures with animals that may cause more than momentary or minimal pain or distress should be performed with appropriate sedation, analgesia, or anaesthesia in accordance with accepted veterinary practice. Surgical or other painful procedures should not be performed on unanaesthetized animals paralysed by chemical agents.
- VIII. Where waivers are required in relation to the provisions of article VII, the decisions should not rest solely with the investigators directly concerned but should be made, with due regard to the provisions of articles IV, V, and VI, by a suitably constituted review body. Such waivers should not be made solely for the purposes of teaching or demonstration.

- IX. At the end of, or when appropriate during, an experiment, animals that would otherwise suffer severe or chronic pain, distress, discomfort, or disablement that cannot be relieved should be painlessly killed.
- X. The best possible living conditions should be maintained for animals kept for biomedical purposes. Normally the care of animals should be under the supervision of veterinarians having experience in laboratory animal science. In any case, veterinary care should be available as required.
- XI. It is the responsibility of the director of an institute or department using animals to ensure that investigators and personnel have appropriate qualifications or experience for conducting procedures on animals. Adequate opportunities shall be provided for in-service training, including the proper and humane concern for the animals under their care.

BASIC EQUIPMENT FOR BIOLOGICAL SCREENING OF NATURAL PRODUCTS

The laboratory should be air conditioned and the ambient temperature maintained between 22-25°C. In addition to the laboratory, animal rooms with temperature, humidity and light control are required, the number and size of rooms depending upon the requirement. Suitable animal cages and rack etc. are also needed.

The list of equipment has been divided according to the type of experiments and only main equipments have been listed.

A. Experiments on Gross Behaviour and CNS Effects (Rodents)

1. Observation cages
2. Activity Monitor
3. Electroconvulsometer
4. Anagesiometer
5. Electronic thermometer with rectal and skin probes
6. Sideman's Avoidance Box
7. Foot Plethysmometer
8. Rotarod (Tread Mill)

B. Cardiovascular In-vivo Experiments

1. 4 Channel Polygraph with Transducers and Preamplifiers
2. KEKG Machine
3. Electronic Stimulator
4. Respiratory pumps for large and small animals
5. Animal Tables
6. Shadowless Lamp
7. Surgical Instruments
8. Perfusion Pump

C. Isolated Tissue Experiments

1. Thermostatic Isolated Organ Baths - 2
2. Langendorff's Assembly for Isolated Heart
3. 2 Channel Polygraphs with Transducers and Preamplifiers
4. Electrodes
5. Electronic Stimulator
6. Aquarium Pump

D. Biochemical Assays

1. Double Beam Spectrophotometer
2. Refrigerated Centrifuge
3. Homogenisers
4. Flame Photometer
5. pH Meter
6. Ultracentrifuge
7. HPLC system
8.  $\beta$  and  $\gamma$ -Scintillation Counters

(6-8 are useful but not indispensable)

E. Microbiological Assays

1. Laminar Flow(Bench Top)
2. Incubators
3. Autoclaves
4. Binocular Microscopes
5. Photomicrography Setup
6. Centrifuges
7. Hot Air Ovens
8. Rotary Shaker
9. pH Meter

**\*E. Toxicology Laboratory**

1. Binocular Microscopes with Photomicrography Attachment
2. Fluorescence Microscope
3. Microtome
4. Tissue Processing and Staining Unit
5. Coulter Counter
6. Centrifuge
7. Autopsy Table
8. Shadowless Lamp
9. Surgical Instruments
10. Slide Cabinets
11. Spectrophotometer

**F. General Laboratory Facilities**

1. Animal and Chemical Balances
2. Water Distillation Unit
3. Refrigerators
4. Deep Freezers
5. Oxygen and Carbogen Gas Cylinders with Regulators
6. Stop Watches
7. Glasswares
8. Personal Computer
9. Metabolic Cages
10. Osmometer
11. Hair Clippers

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\*Can be added in Phase II.

CLINICAL STUDIES WITH NEW DRUGS

A permission from the National Regulatory Agency and from the appropriate Ethics Committee should be obtained before undertaking clinical studies. Before initiating any phase of clinical study, it is necessary to define the population to be studied, the criteria of response or evaluation, the dosage regimen and duration of study. The study must be planned with the help of a competent statistician and generally a fixed sample size design is used. Several procedures are used to eliminate the observer's bias. These include provision of a control group wherever feasible (patient could be self-control in cross-over design), use of placebo, randomisation, blinding and use of objectives criteria of response. The clinical studies can be divided in 3 phases and data from each phase have to be submitted to the Regulatory Agency for permission to initiate the next phase. An informed consent must be obtained from all the participants.

Clinical Pharmacology (phase I): These studies are performed in healthy adult male volunteers and are aimed to determine the maximum tolerate dose, data on pharmacodynamic effects including adverse reactions and initial pharmacokinetic data. Depending upon the clinical usage, single and multiple dose studies may be necessary. Clinical, physiological, biochemical and haematological parameters are monitored by trained investigators. At CDRI, double blind studies are done using a placebo control and usually 4 volunteers per dose. The design also ensures that only 1 volunteer is initially exposed to the higher dose. These studies may not be needed with plant drugs in local use for prolonged periods.

Exploratory Clinical Trials (Phase II): A limited number of patients are studied carefully to establish the therapeutic utility, dosage schedule and possible side effects. Additional pharmacokinetic data is also generated. The study is limited to 1-2 centres and 20-50 patients, depending upon the drug.

Multicentric Clinical Trials (Phase III): They are also termed confirmatory trials and they generate sufficient data about the efficacy and safety, generally in comparison with a standard drug. The trial should be spread over several centres and cover around 500 patients. Additional studies may be needed in drugs to be used in elderly patients or those with hepatic, renal or cardiac complications. In selected cases, data on drug interaction on bioequivalence may be required. At the end of these studies, the total data are submitted to the Regulatory Agency for permission to market the new drug.