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## Quality and regulatory affairs of herbal drugs: A world-wide Review

G. Sushma, Subal debnath<sup>1</sup>, Santhosh Kumar C, <sup>1</sup>Atul N Chandu.

Sri krupa Institute of Pharmaceutical Sciences, Vil. Velkatta, Kondapak (mdl), Dist. Medak, Siddipet, Andhra Pradesh – 502 277.

<sup>1</sup>Pydha College of Pharmacy, Kakinada, Andhra Pradesh.

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### ABSTRACT

Herbal medicine is still the mainstay of about 75 - 80% of the world population, mainly in the developing countries, for primary health care. This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available. According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times. This review highlights the current advances in knowledge about the safety, efficacy, quality control, marketing and regulatory aspects of botanical medicines. Phytotherapeutic agents are standardized herbal preparations consisting of complex mixtures of one or more plants which contain as active ingredients plant parts or plant material in the crude or processed state. Regulatory affairs and clinical trails should be made on herbal drugs to improve their availability.

### Corresponding author

#### G. Sushma

Email: sushma.gangapuram@gmail.com

Sri krupa Institute of Pharmaceutical Sciences, Vil: Velkatta, Mdl: Kondapak,

Dist: Medak, Siddipet Andhra Pradesh – 502277. Phone: 9866513914.

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## 1. INTRODUCTION:

Herbal medicine is still the mainstay of about 75 - 80% of the world population, mainly in the developing countries, for primary health care<sup>1</sup>. This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available. According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times<sup>2</sup>. The use of plants for healing purposes predates human history and forms the origin of much modern medicine.

Many conventional drugs originated from plant source. Examples include aspirin (willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy). Medical history from the beginning of time is filled with descriptions of persons who used herbs to heal the sick of the society. However, parallel to the onset of the industrial revolution we witnessed the rise of allopathic medicine. Herbal medicine was also an effective healing method, but was viewed less enthusiastically. Herbal products were discarded from conventional medical use in the mid 20<sup>th</sup> century, not necessarily because ineffective but they were because they were not as economically profitable as the newer synthetic drugs<sup>3</sup>. In the early 19<sup>th</sup> century, scientific methods become more advanced and preferred, and the practice of botanical healing was dismissed as quackery.

## 2. Herbal Medicine

The WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous system of medicine. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparations for therapy. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years. The classical Indian texts include Rigveda, Atharvaveda, Charak Samhita and Sushruta Samhita<sup>4</sup>.

## Regulation of Herbal Medicine

Herbal remedies form a potpourri that ranges from plants that people collect themselves and then take for health reasons to approved medical products. Many herbal products fall between the far ends of this regulatory range: unlicensed preparations are thought to account for over 80 per cent of herbal sales. European Union legislation requires herbal products to be authorized for marketing if they are industrially produced and if their presentation or their function, or both, bring them inside its definition of a borderline is difficult.

Many medicine-like products on the British herbal market remain unregistered for two reasons: acceptable data on efficacy, safety and quality may not be available, and the licensing fee is high. Special licensing procedures for herbal medicines are already in force in Germany, where regulatory evaluations of medicinal herbs have been laid down in more than 300 monographs, and in France more than 200 herbs have been listed as acceptable ingredients of phytomedicines.

## Safety Issue of Herbal Medicines

Traditional herbal products are heterogeneous in nature. They impose a number of challenges to quality control, quality assurance and the regulatory process. Most herbal products on the market today have not been subjected to drug approval process to demonstrate their safety and corticosteroids and poisonous organic substances in harmful amount. Hepatic failure and even death following ingestion of herbal medicine have been reported. A prospective study shows that 25% of the corneal ulcer in Tanzania and 26% of the childhood blindness in Nigeria and Malawi were associated with the use of traditional eye medicine.

## Need for Clinical Trials

To gain public trust and to bring herbal product into mainstream of today healthcare system, the researchers, the manufacturers and the regulatory agencies must apply rigorous scientific methodologies and clinical trials to ensure the quality and lot-to lot consistency of the traditional herbal products. A well-designed clinical trial is the method choice to prove the safety and effectiveness of a therapeutically product. Manufacturers of the herbal products must adhere to the requirements of

good manufacturing practices (GMPs) and preclinical testing before these products can be tested on human. The basic principle and design of the clinical trials for herbal products are the same as those for single component chemical product<sup>5</sup>.

### Present Status of Herbal Medicine

As per the available records, the herbal medicine market in 1991 in the countries of the European Union was about \$ 6 billion (may be over \$20 billion now), with Germany account for \$3 billion, France \$ 1.6 billion and Italy \$ 0.6 billion. In 1996, the US herbal medicine market was about \$ 4 billion, which have doubled by now. The Indian herbal drug market is about \$ one billion and the export of herbal crude extract is about \$80 million.

In a recent survey estimated that 39% of all 520 new approved drugs in 1983-1994 were natural products or derived from natural products and 60-80% of antibacterial and anticancer drugs were derived from natural products. Most botanists regard this estimate by the International Union for the Conservation of Nature (IUCN) as conservative, because it considers only species known to science, numerous undiscovered species pass from the world unrecorded and unmourned<sup>6</sup>. However, the following four herbal medicines have been found to be most promising in the treatment of viral hepatitis

- (i) Silymarin obtained from the seeds of *Silbum marianum*,
- (ii) Extracts of *Picrorrhiza kurroa*, popularly known 'Kutaki'
- (iii) Extract of many plant of the genus, *Phyllanthus*, have been used as hepatoprotective, of them, the most widely used ones have been *Phyllanthus niruri* and *Phyllanthus amarus*.
- (iv) Glycyrrhizin preparation have been used in the past for peptic ulcer as well as liver diseases with mixed results.

### Problems to be solved before Herbal Medicine Become Mainstream

To reach a stage where herbal products of assured quality and effectiveness become integrated into mainline medicinal treatment, several obstacles must be overcome. The prejudice of current practicing health-care professional who did not learn about phytomedicines during their academic

programs and, consequently, believe all of them to be ineffective forms a barrier. Orthodox medical practitioners are to be convinced of the efficacy of plant extract<sup>7</sup>.

### 3 Herbal medicinal products:

The following tests and acceptance criteria are considered generally applicable to all herbal medicinal products:

**a) Description:** A qualitative description of the dosage form should be provided (e.g., size, shape, color). The acceptance criteria should include the final acceptable appearance at the end of the shelf-life. If color changes occur during storage, a quantitative procedure may be appropriate.

**b) Identification:** Identification tests should establish the specific identity of the herbal substance(s) and/or herbal preparation(s), in the herbal medicinal product and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time. In the case of herbal medicinal products containing powdered or comminuted herbal substances, microscopical and macroscopical characterisation could be used for identification in combination with other methods, if justified.

**c) Assay:** In the case of products containing herbal substances and/or herbal preparations with constituents of known therapeutic activity, validated assays of the content of these constituents are required along with details of the analytical procedure(s). Where appropriate, a specific, stability-indicating procedure should be included to determine the content of the herbal substance(s) and/or herbal preparation(s) in the herbal medicinal product.

**d) Impurities:** Refer to the ICH/VICH Guidelines on impurities in new drug products/Guidelines on impurities in new veterinary products (CPMP/ICH/2738/99 and CVMP/VICH/838/99 as revised) and the European Pharmacopoeia General text on Residual Solvents for detailed information<sup>8</sup>.

❖ Impurities arising from the herbal substance(s) and/or herbal preparations e.g. contaminants such as

pesticide/fumigant residues, heavy metals, if controlled during the testing of the herbal substance/preparation, it is not necessary to test for these in the herbal medicinal product.

❖ Similarly, residual solvent arising from the manufacture of the herbal preparation (e.g. an extract) need not be controlled in the herbal medicinal product provided it is appropriately controlled in the extract specification. However, solvents used for example in tablet coating will need to be controlled in the dosage form.

❖ In cases where degradation products of the herbal substance/preparation are evident (e.g.) aglycones from hydroxyl anthracene glycosides), they should be monitored in the herbal medicinal product. Acceptance limits should be stated for such degradation products.

**e) Microbial limits:** There is a need to specify the total count of aerobic microorganisms, the total count of objectionable bacteria. These limits should comply with the European yeasts and moulds, and the absence of specific dosage forms addressed include solid oral herbal medicinal products, and liquid oral herbal medicinal products. Application of the concepts in this guideline to other dosage forms is encouraged.

#### 4. QUALITY AND REGULATION OF HERBAL DRUGS

This review highlights the current advances in knowledge about the safety, efficacy, quality control, marketing and regulatory aspects of botanical medicines.

Phytotherapeutic agents are standardized herbal preparations consisting of complex mixtures of one or more plants which contain as active ingredients plant parts or plant material in the crude or processed state. A marked growth in the worldwide phyto-therapeutic market has occurred over the last 15 years. For the European and USA markets alone, this will reach about \$7 billion and \$5 billion per annum, respectively, in 1999, and has thus attracted the interest of most large pharmaceutical companies. Insufficient data exist for most plants to guarantee their quality, efficacy and safety.

The idea that herbal drugs are safe and free from side effects is false. Plants contain hundreds of constituents and some of them are very, such as the most catatonic anti-cancer plant derived drugs, digitalis and the pyrrolizidine alkaloids, etc. However, the adverse effects of phyto-therapeutic agents are less frequent compared with synthetic drugs, but well-controlled clinical trials have now confirmed that such effects really exist. Several regulatory models for herbal medicines are currently available include in prescription drugs, over-the-counter sub-stances, traditional medicines and dietary supplements<sup>9</sup>.

**(A) Evaluation of the efficacy and safety of herbal medicines.** The existence of controlled clinical trials depending on the particular country and existing legislation herbal products used for diagnosis, cure, mitigation, treatment, or prevention of diseases are normally regulated as drugs. However, in some countries, including the United States, botanical products are marketed as “dietary supplement”.

Other countries treat the herbal preparations as drugs, and to be registered these products need to be tested to prove their safety and clinical efficacy. However, so far, few programs have been established to study the safety and efficacy of herbal medicines as originally proposed by the WHO Guidelines for the assessment of herbal medicines. Since 1978, more than 4000 herbal medicines have been submitted to pharmaco-vigilance. Germany and most herbal drugs have been withdrawn from the market because of important toxic effects and risks for human use<sup>9</sup>. Among these, we may mention the plants which contain pyrrolizidinic alkaloids, aristolochic acid, berberine, or curcubitacins.

#### **(B) Regulatory aspects and approval of herbal drugs:**

The legal process of regulation and legislation of herbal medicines changes from country to country. The reason for this involves mainly cultural aspects and also the fact that herbal medicines are rarely studied scientifically. Thus, few herbal preparations have been tested for safety and efficacy. The WHO has published guidelines in order to define basic criteria for evaluating the quality, safety, and

efficacy of herbal medicine aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area<sup>10</sup>.

Furthermore, the WHO has prepared pharmacopoeia monographs on herbal medicines and the basis of guidelines for the assessment of herbal drugs several regulatory models for herbal medicines currently exist, including prescription drugs, over-the-counter drugs, traditional medicines and dietary supplements. Thus, the need to establish global and/or regional regulatory mechanisms for regulating herbal drugs seems obvious. A summary of the regulatory processes related to herbal drugs in some selected countries is presented below.

### **Argentina**

The Herboristerias are authorized for sale as plant drugs but not as mixtures. Mixtures of plant drugs are controlled. In 1993, a Ministry of Health regulation determined the obligatory registration of medicinal herbs. The Argentinian National Pharmacopoea established control over the existence of crude extracts, extracts or fractions of complex chemical composition, and pure active principles. About 889 monographs exist in Argentina. About 56 describe crude drugs alone and 33 describe extracts or fractions. However, there is lack of control of raw materials, lack of control over the wild plant, lack of scientific criteria for the collection of plants, and lack of control over methods of drying, conservation or grinding.

### **Australia**

The Australian Parliament established the working party on Natural and Nutritional Supplements to review the quality, safety, efficacy and labelling of herbal and related products (Therapeutic Good Act, 1990). The act provides: "that traditional claims for herbal remedies be allowed, providing general advertising requirements are complied with and providing such claims are justified by literature references".

### **Canada**

In 1986, the Canadian Health Protection Branch (HPB) constituted a special committee (3 pharmacists, 2 herbalists, 1 nutritionist and 1 physician) and classified herbal drugs as "Folk

Medicine". The regulation is based on traditional uses, as long as the claim is validated by scientific studies. In 1990, the HPB listed 64 herbs that were considered to be unsafe. In 1992, the HPB submitted a regulatory proposal to the Canadian Parliament and listed another 64 herbs that were considered to be adulterants. The Canadian regulatory system is consistent with WHO guidelines for the assessment of herbal medicines.

### **France**

Approximately 200 herbs are approved as OTC in France with varying claims. Licensing approval for phytomedicines is subject to regulations generally required for all drugs. There is only one type of license, but for some plant drugs and preparations, this license is granted on the basis of an adapted documentation and an abridged application. In 1990, 115 herbs plus 31 laxatives were involved in this approval procedure. Currently, about 205 herbal drugs are listed.

### **United States of America**

Since 1994, herbal medicines have been regulated under the "Dietary supplement health and Education Act of 1994". On the basis of this law, herbal medicines are not evaluated by the Food and Drug Administration and, most important, these products are not intended to diagnose, treat, cure, or prevent diseases. The US government has established the "Office of Alternative Medicine" at the National Institutes of Health (NIH) with the following aims:

- 1) To explore the potential role of dietary supplements in the improvement of health;
- 2) To promote the scientific study of supplements for maintaining health and preventing chronic diseases;
- 3) To compile a database of scientific research related to supplements
- 4) To coordinate NIH funding for dietary supplements related to the treatment of chronic disease

### **The guidelines set by WHO can be as follows:**

a. Reference to the identity of the drug. Botanical evaluation – sensory characters, foreign organic matter, microscopical, histological, histochemical evaluation, quantitative measurements, etc.

b. Reference to the physiochemical character of the drug. Chromatographic profiles, ash values, extractive values, refractive index, polarimetric readings, moisture content, volatile oil content, etc.

c. Reference to the pharmacological parameters. Biological activity profiles, bitterness values, haemolytic index, astringency, swelling factor, foaming index, etc.

d. Toxicity details – heavy metals like cadmium, lead, arsenic, mercury, etc. Pesticide residues.

$$\text{Maximum residue limits} = \frac{\text{Acceptable daily index} \times \text{body weight} \times \text{extraction factor}}{\text{Mean daily intake of drug} \times \text{safety factor} \times 100} \times \text{Therapeutic doses}$$

**e. Microbial contamination** – Total viable aerobic count, pathogenic bacteria like enterobacteria, *E. coli*, salmonella, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, etc. and presence of aflatoxins etc.

**f. Radioactive contamination.**

### 5.Utilization of guidelines

These guidelines for the assessment of herbal medicines are intended to facilitate the work of regulatory authorities, scientific bodies and industry in the development, assessment and registration of such products. The assessment should reflect the scientific knowledge gathered in that field. Such assessment could be the basis for 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 requires close liaison between national institutions that are able to keep under regular review all aspects of production and use of herbal medicines, 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<sup>11</sup>.

### The objectives of these guidelines are to:

1.support Member States, in the context of the WHO International Drug Monitoring Programme, to strengthen national pharmacovigilance capacity in order to carry out effective safety monitoring of herbal medicines

2. Provide technical guidance on the principles of good pharmacovigilance and the inclusion of herbal medicines in existing national drug safety monitoring systems; and where these systems are not in place, to facilitate the establishment of an inclusive national drug safety monitoring system

3. Provide standard definitions of terms relating to pharmacovigilance, and safety monitoring of herbal medicines

4. Promote and strengthen internationally coordinated information exchange on pharmacovigilance, and safety monitoring of herbal medicines among Member States

5. Promote the safe and proper use of herbal medicines.

### 6. Guidelines related to Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP):

The coordinating agency should adhere to the principles set out in the WHO Guidelines on Good Agricultural and Collection Practices for Medicinal Plants (for GACP) and manufacturers and assemblers should follow WHO Good Manufacturing Practices (for GMP).

Manufacturers of herbal medicines should obtain a licence and register their products. The quality control system for production should be in place. The implementation of a credible concept of quality assurance, e.g. identifying and eliminating potential sources of contamination, should be a primary goal of the manufacturers rather than the implementation of all individual technical aspects<sup>12</sup>.

### INDIA

#### Chapter: It comprises of two parts

Part 1.Good manufacturing practices factory premises

Part 2. Requirement of plant and equipment.

Regulating authority: Govt. of India (Ministry of Health and Family Welfare Department)

### QUALITY MANAGEMENT

INDIAN GMP do not stress the role of senior management for quality management at require separate QA and QC disciplines , but specify the QA of concept or system further it states that

1. Personnel for quality assurance and quality control operation shall be suitably qualified and experienced.

- Return duties of technical and quality control operation shall be laid and follow strictly.
- Each technical person should suitably trained perform the assigned responsibilities they shall be subjected to regular in service training
- Concept of self-inspection the supplemented with a quality audit procedure is to be followed

### PERSONNEL:

Requires manufacturing operation to carried out under the super vision of the technical staff with prescribed qualification and practical experienced but no exact detailed of qualification / subjects are period in given- The guideline requirement adequate training and in service training of personnel but does not require any approval or assessment of it neither its specify anything about qualification of the personnel giving the training.

### DOCUMENTATION

Indian GMP in 12batch manufacturing and packing records plus the relevant test records must be retain.

### PRODUCTION:

1) Indian GMP guide does not goes and depth in explaining the action required to prevent labeling mixup.

### Quality Control:

1. Indian GMP requires reference /retained sample from each batch to the product manufacture shall be maintain that in quantity which is at least quantity of the drug required conduct all the test accept sterility and pyrogen / bacteria and endotoxin but are not mentioned about retention period.

2. All GMP classify QC under the quality assurance discipline while Indian GMP does not specifically states about that relation.

### 7. CONCLUSIONS AND FUTURE DIRECTIONS:

A search of the literature shows that over the last 15 years a great growth and worldwide interest in herbal medicines has taken place, both in developed and developing countries. The growth of the botanical market has attracted much interest on the part of the pharmaceutical companies, which has in turn stimulated the appearance of pre-clinical pharmacological studies and of well controlled and randomized clinical trials to prove their safety and efficacy.

So far insufficient data exist to provide an accurate assessment of the quality, efficacy and safety of most herbal medicines. In my view, it is too early to predict the future of herbal drugs. However, the herbal drug market will certainly continue growing at elevated rates in the first years of the next millennium, but special attention needs to be paid to the following aspects:

❖ Emphasis on well-controlled and randomized clinical trials to prove the safety and efficacy of herbal medicines. The widespread interest in phytotherapeutic agents over the last decade has attracted the attention of the most important pharmaceutical companies, and most certainly the quality control, efficacy and safety of herbal drugs will be greatly improved in the near future.

However, these trials need to be conducted in such a way as to take into account the international guidelines that define such studies. As has occurred recently in some countries, standardized phytotherapeutic agents of proved quality, efficacy and safety will certainly be increasingly prescribed by physicians and dispensed by pharmacists, and perhaps they will be subsidized by health insurance systems in most countries.

❖ An improvement in the processes of regulation and a global harmonization will be desirable and certainly necessary, and the general tendency is to utilize the German Commission E experience which combines scientific data and traditional

knowledge(monographs). Several regulatory models for herbal medicines currently exist, including prescription drugs, over the-counter substances, traditional medicines and dietary supplements. Thus, the need to establish global and/or regional regulatory mechanisms for regulating herbal drugs seems obvious.

Emphasis has been placed on domestication, production and biotechnological studies and genetic improvement of medicinal plants. The trend towards the domestication and planting of medicinal plants instead of the use of wild harvested plants will offer great advantages, since it is possible to provide uniform and high quality raw material. As mentioned before, the uniform quality of raw material is the first pivotal step in the process of developing good quality herbal drugs, avoiding misidentification, adulteration, contamination, etc.

An important advantage of the process of domestication is the real and quality of raw materials through genetic selection and breeding and the development of medicinal plants resistant to microorganism-induced diseases, free of undesirable secondary metabolites, or rich in bioactive constituents. Finally, but not less important, a more detailed legislation about the intellectual property of herbal drugs is urgently needed. The concern and difficulties related to the patenting of herbal medicines have precluded the financial incentives that could be provided to pharmaceutical industries.

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