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Current Regulations for Herbal Products

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ABSTRACT

A review of the regulatory status of herbal drugs/products was done for few countries forming part of Asia, Africa, America, Europe, and Australia, to understand various categories under which the trade of herbal products is permitted and their premarketing requirements. A critical assessment was done, to know the hindrances in the process of harmonization of herbal products. It has been found that there is a lack of harmonization in the regulatory requirements of herbal products internationally, besides the issues of availability of herbs and their conservation. These are hindering the international trade and growth of the herbal products segment**.**

Keywords: Harmonization, herbal drugs, herbal products.

INTRODUCTION

Traditional medicine is a broad term encompassing health practices, approaches, knowledge and beliefs which incorporate herbal, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being. There has been a lot of interest, today, in the traditional medicine for its potential contribution to health care. However, there are a lot of concerns about the traditional medicine in areas of efficacy, safety and quality.

Several organisations have discussed these issues in their approach papers. A recent WHO fact sheet comments " Unregulated or inappropriate use of traditional medicines and practices can have negative or dangerous effects." Our own National Policy 2001on Indian Systems of Medicine includes issues such as drug standards, regulations and enforcement' and focuses the research agenda on clinical trials, pharmacology, toxicology, and drug standardization.

Among the traditional approaches, herbal medicines present unique challenges in research and regulations. Recent reviews have focused on the problems of quality, issues of clinical research, and need for new regulations for herbal therapies. In recent years, several regulatory guidelines are available in the area of herbal medicines. This article is a brief review of the regulatory issues in traditional medicine herbal research.

Current regulatory issues for herbal medicines

There are several regulatory concerns in relation to research applications and commercialization of herbal medicines.

Standardization of herbal drugs

For safe and effective use of herbal drugs, consistency in composition and biologic activity are essential requirements. However, herbal drugs frequently fail to meet this standard, as there are problems such as 1) difficulties in identification of plants, 2) genetic variability, 3) variations in growing conditions, 4) diversity in harvesting procedures and processing of extracts, and 5) the lack of information about active pharmacologic principles.

The use of chromatographic techniques and marker compounds for the standardization of herbal products can ensure batch-to-batch consistency; however, this does not ensure consistent pharmacologic activity or stability. With herbal medicines what is on the label and what is in the bottle may differ considerably. In a study of ginseng preparations, the amount of ginsenosides varied from 11.9-327.7% of the amount on the label. Medical letter cautions, "Their (herbal medicines) potency may vary and their purity is suspect," Australian medicines regulatory body the Therapeutic Goods Administration, suspended production license of Pan Pharmaceuticals after an audit, which revealed problems with company's quality control standards. The Lack of standardization of herbal drugs would be a serious problem for a researcher as he would not be able to rely on commercially available herbal products for his research studies.

Quality of herbal preparations

If an herbal remedy is effective, quality assurance is needed to ensure that the product has the expected effects. Even in the absence of data on efficacy, quality assurance is important, as quality is a critical determinant of safety as well. Adulteration of plants is serious problem. Some of the common adulterants are: botanicals, toxic metals, microorganisms, microbial toxins, pesticides, and fumigation agents.

A US investigation reported that 32 percent of marketed Asian patent medicines contained undeclared pharmaceuticals or heavy metals. The drugs most frequently found were ephedrine, chlorpheniramine, methyltestosterone, and phenacetin; 10 to 15 percent contained lead, mercury, or arsenic. The incidence of heavy metal contamination is not known, but one study showed that 64% of samples collected in India contained significant amounts of lead (64% mercury, 41% arsenic and 9% cadmium). This can cause serious harm to patients taking such remedies and could confound the assessment of safety in a clinical trial. Quality has to be assured at all stages – herbal raw materials, processing of herbals and finished herbal medicines.

Evidence of Clinical Efficacy

Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture, some herbal medicines and for some of the manual therapies. Only a small fraction of the thousands of medicinal plants used worldwide has been tested rigorously in randomized, controlled trials. Even if the animal studies or anecdotal clinical experiences are promising and use of an herb is widespread, such observations cannot predict the results of well designed randomized, controlled trials.

A recent review concluded that evidence-based studies on the efficacy and safety of traditional Indian medicines are limited. The data available is mostly experimental or in animals. Most trials do not report hard efficacy endpoints and duration of observation periods is generally short. The clinical relevance of the observed effects is not always clear. For instance, most Indian trials of hepato protective agents are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the herbal product.

The essential ingredient in most formulations is not precisely defined. High quality studies are necessary to evaluate and compare the value of traditional Indian drugs to modern medicine. A fundamental problem in all clinical research of herbal medicines is whether different products, extracts, or even different lots of the same extract are comparable and equivalent. For example, Echinacea products can contain other plant extracts; use different plant species (E. purpurea, pallida or angustifolia), different parts (herb, root, both), and might have been produced in quite different manners (hydro- or lipophilic extraction). Even different species may be known by the same name in local language. Brahmi refers to Centellaasiatica and Bacopamonniera.

The herbal industry is not required to conduct clinical trials, and the industry professionals argue that it would be not be possible to recover the high research costs, as herbal products can not be patented as easily as new chemical entities. Nevertheless, randomized, controlled trials are the best way to demonstrate the efficacy of any medicine, herbal or conventional.

Safety Concerns - Adverse Reactions and Drug Interactions

Herbal medicines are generally considered comparably safer than synthetic drugs. While this

may be probably correct, case reports show that severe side effects and relevant interactions with other drugs can occur. For instance, the herb Ephedra marketed as a dietary aid in USA, led to at least a dozen deaths, heart attacks and strokes. Other well-known safety issues have been hepatotoxicity of kava and renal effects of aristolochic acid. Besides, drug interactions of herbal drugs are of a serious concern. For example, hypericum extracts can decrease the concentration of a variety of other drugs by enzyme induction. Serious adverse effects have been reported when the addition of St. John's wort caused serum levels of cyclosporine and antiretroviral agents to fall to sub therapeutic levels. Garlic is reported to increase clotting time in patients taking warfarin.

Lack of regulatory standards regarding the efficacy and safety of herbal products did not arouse much concern in the past, as these products were often perceived as so safe that even if they were ineffective, little harm resulted. However, the situation is changing now and there is an increasing body of literature on the side effects and interactions of herbal medicines. Besides the direct risks of adverse effects and drug interactions there is an indirect risk that an herbal remedy without demonstrated efficacy may compromise, delay, or replace an effective form of conventional treatment. WHO has urged the governments to establish regulatory mechanisms to control the safety and quality of products.The above issues have led to an increasing regulatory focus on herbal products in US and Europe[1].

Classification of herbal medicines

Herbal medicines can be classified into four categories, based on their origin, evolution and the forms of current usage. While these are not always mutually exclusive, these categories have sufficient distinguishing features for a constructive examination of the ways in which safety, efficacy and quality can be determined and improved.

Category 1: Indigenous herbal medicines

This category of herbal medicines is historically used in a local community or region and is very well known through long usage by the local population in terms of its composition, treatment and dosage. Detailed information on this category of TM, which also includes folk medicines, may or may not be available. It can be used freely by the local community or in the local region.However, if the medicines in this category enter the market or go beyond the local community or region in the country, they have to meet the requirements of safety and efficacy laid down in the national regulations for herbal medicines.

Category 2: Herbal medicines in systems

Medicines in this category have been used for a long time and are documented with their special theories and concepts, and accepted by the countries. For example, Ayurveda, Unani and Siddha would fall into this category of TM.

Category 3: Modified herbal medicines

These are herbal medicines as described above in categories 1 and 2, except that they have been modified in some way–either shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications. They have to meet the national regulatory requirements of safety and efficacy of herbal medicines.

Category 4: Imported products with a herbal medicine base

This category covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin. The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation of herbal medicines in the recipient country.

Minimum requirements for assessment of safety of herbal medicines

Safety category

A drug is defined as being safe if it causes no known or potential harm to users. There are three categories of safety that need to be considered, as these would dictate the nature of the safety requirements that would have to be ensured.

- Category 1: safety established by use over long time
- Category 2: safe under specific conditions of use (such herbal medicines should preferably be covered by well-established documentation)
- Category 3: herbal medicines of uncertain safety (the safety data required for this class of drugs will be identical to that of any new substance)

Data will be required on the following

- Acute toxicity
- Long-term toxicity

Data may also be necessary on the following:

- Organ-targeted toxicity
- Immunotoxicity
- Embryo/fetal and prenatal toxicity
- Mutagenicity/genotoxicity
- Carcinogenicity

General considerations for assessment of safety of herbal medicines

Any assessment of herbal medicines must be based on unambiguous identification and characterization of the constituents. A literature search must be performed. This should include the general literature such as handbooks specific to the individual form of therapy, modern handbooks on phytotherapy, phytochemistry and pharmacognosy, articles published in scientific journals, official monographs such as WHO monographs, national monographs and other authoritative data related to herbal medicines and, if available, database searches in online or offline databases, e.g. WHO adverse drug reaction database, National Library of Medicine's Medline, etc. The searches should not only focus on the specific herbal medicinal preparation, but should include different parts of the plant, related plant species and information originating from chemotaxonomy. Toxicological information on single ingredients should be assessed for its relevance to the herbal medicines.

Specific requirements for assessment of safety of four categories of herbal medicines

Before any category of herbal medicine listed above is introduced into the market, the relevant safety category needs to be reviewed and the required safety data obtained, based on that particular safety category.

Category 1: Indigenous herbal medicines

These can be used freely by the local community or region, and no safety data would be required. However, if the medicines in this category are introduced into the market or moved beyond the local community or region, their safety has to be reviewed by the established national drug control agency.If the medicines belong to safety category 1, safety data are not needed. If the medicines belong to safety category 2, they have to meet the usual requirements for safety of herbal medicines. Medicines belonging to safety category 3, i.e. 'herbal medicines of uncertain safety', will be identical to that of any new substance.

Category 2: Herbal medicines in systems

The medicines in this category have been used for a long time and have been officially documented. Review of the safety category is necessary. If the medicines are in safety categories 1 or 2, safety data would not be needed. If the medicines belong to safety category 3, they have to meet the requirements for safety of 'herbal medicines of uncertain safety'.

Category 3: Modified herbal medicines

The medicines in this category can be modified in any way including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation, or medical indications based on categories 1 and 2. The medicines have to meet the requirements of safety of herbal medicines or requirements for the safety of 'herbal medicines of uncertain safety', depending on the modification.

Category 4. Imported/exported products with a herbal medicine base

Exported products shall require safety data, which have to meet the requirements for safety of herbal medicines or requirements for safety of 'herbal medicines of uncertain safety', depending on the safety requirement of the importing/recipient countries

Minimum requirements for assessment of the efficacy of herbal medicines
Claims categories

- Acute disease: Diseases that have a rapid onset and a relatively short duration.
- Chronic disease: Diseases that have a slow onset and last for long periods of time. Diseases of acute onset could also progress to a chronic state.

In most cases, severe diseases refer to a life-threatening illness or those diseases in which delayed treatment will lead to deterioration of the disease state or loss of capability to cure them. For example, severe cardiovascular, gastrointestinal, endocrine, haematological diseases, and immune disorders and diseases fall into this group.

- Health condition: Problems related to health conditions are those which, with time, could recover spontaneously, even without any medical intervention, e.g. loss of appetite, hay fever, menopause, etc. The efficacy for this category could be supported by data in existing well-established documents such as national pharmacopoeia and monographs as well as other authoritative documents such as WHO

monographs. Pre-clinical and clinical data of efficacy may not be necessary**.**

- The assessment of efficacy for herbal medicines in categories 1 and 2 are not required if they are used locally;
- For medicines in category 3, pre-clinical data and clinical data may or may not be required depending on the modification(s).
- For medicines in category 4, efficacy data are required

iv)Quality assurance of herbal medicinal products

Quality assurance of herbal medicinal products is the shared responsibility of manufacturers and regulatory bodies. National drug regulatory authorities have to establish guidelines on all elements of quality assurance, evaluate dossiers and data submitted by the producers, and check post-marketing compliance of products with the specifications set out by the producers as well as compliance with Good Manufacturing Practices (GMP).

The manufacturers have to adhere to Good Agricultural and Collection Practices (GACP), GMP and Good Laboratory Practice (GLP) standards, establish appropriate specifications for their products, intermediates and starting materials and compile a well-structured, comprehensive documentation on pharmaceutical development and testing. The producers should make continued efforts to improve standards and adapt them to the present state of knowledge. A cooperative approach between different manufacturers, e.g. by establishing drug master-files for specifications and quality control, should be encouraged.

Coordinating quality control

A coordinating agency on GACP should be established to facilitate the availability of good quality herbal medicines to the market by giving training and advice to small producers and farmers. To encourage implementation of GACP, incentives should be given to producers of botanical raw materials. These include giving technical and logistic support in the selection of appropriate sites for agricultural production, providing seeds and seedlings, selecting fertilizers and pesticides, providing or giving advice on machinery for harvesting and primary processing. The government should honour efforts by issuing certificates to producers and farmers who adhere to the GACP, based on the country situation. Implementation of such requirements is only possible if the production and marketing of herbal medicines is subject to an adequate registration scheme by a drug regulatory authority.

b) Quality assurance

Elements of quality assurance are:

- adherence to GACP, GMP and GLP guidelines;
- setting specifications; and
- quality control measures

c) Quality control for herbal medicinal products

All herbal-based medicinal products should meet the requirements for safety, efficacy and quality, as per the Categories of Herbal Medicines (see the section on Minimum requirements for assessment of safety of herbal medicines).All imported herbal medicinal products need to meet the requirements for safety, efficacy and quality control regulations in the importing countries. To control the quality of imported herbal medicinal products, the following requirements should be taken into consideration.

Licensing authority

Licensing for importers, wholesalers, manufacturers and assemblers of herbal medicinal products should be issued by the national drug regulatory authority. Dealers of imported herbal medicinal products need to apply for one or more of the licences depending on the type of business involved, such as licence of importers, wholesalers, manufacturers and assemblers.

Import licence

The responsibility of applying for an import licence shall rest with local companies which are approved by the licensing authority to import herbal medicinal products and sell them in the importing countries.The following information related to the importing company is required for the application of an import licence:

- Particulars of the company;
- Particulars of the person making the application on behalf of the company;
- Certificate of company/business registration;
- Layout plan of the store.

Importers are required to provide information on each imported herbal medicinal product they deal with, and will be allowed to deal in approved products only. Detailed requirements for each imported herbal medicinal product are as follows:

- Full product formula (in the languages of the importing and exporting countries);

- A set containing labels, pamphlet, carton and specimen sales pack (in the languages of the importing and exporting countries, if necessary);
- Particulars of manufacturer(s) and assembler(s);
- Manufacturer's licence or certificate from the drug regulatory authority of the manufacturing country of origin. Pre-export Notification and Certificate of Free Sale of the herbal medicinal product should be obtained from the concerned authority.

Based on the above-mentioned minimum requirements, each national drug regulatory authority could develop its own requirements for quality control of imported herbal medicinal products.

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.

The following areas should be considered while studying the WHO guidelines:

- Control of raw materials (refer to the GACP and Quality Control Methods for Medicinal Plant Products);
- Control of starting materials and intermediate substances;
- In-process control (Standard Operating Procedure for Processing Methods should be mentioned);
- Finished product control (It should be performed with reference to the control of raw materials, starting materials and intermediate substances

Guidelines related to quality control

The purpose of quality control is to ensure quality of the products by adhering to appropriate specifications and standards. Information on appropriate standards can be found in official pharmacopoeias, monographs, handbooks, etc.In choosing analytical methods, the availability, robustness and validity of the methods must be considered, such as microscopic identification, thin layer chromatography (TLC), titration of active substance and, if possible, a full validation of more sophisticated methods, such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and gas chromatography-mass spectrometry (GC-MS). If such advanced methods are used, a full validation for each test would be necessary.

Product information for registration

This should include all necessary information on the proper use of the product. The detailed information of the herbal medicinal products should include the following requirements for registration:

- Quantitative list of ingredients; if this is difficult, it could be replaced by including the plant names and plant parts used (i.e. Latin name);
- Full product formula for imported herbal-based medicinal products (in the language of the importing and exporting countries);
- A set containing labels, pamphlet, carton and specimen sales pack;
- Particulars of manufacturer(s) and assembler(s);
- Manufacturer's licence or certificate from the drug regulatory authority. Pre-export notification and Certificate of Free Sale of the herbal-based medicinal product should be obtained from the concerned authority;
- Brand name of product;
- Dosage form;
- Indications;
- Dosage;
- Mode of administration;
- Duration of use;
- Adverse effects, if any;
- Contraindications, warnings, precautions and major drug interactions, if possible;
- Date of manufacture;
- Expiry date of product;
- Lot/Batch number;
- Storage condition.

CONCLUSION

Although there is a global interest in traditional herbal medicines, there are concerns about use of untested and unregulated medicines. The scientific community is concerned about the quality, standardization, clinical safety and efficacy of herbal remedies. The experience of allopathic industry suggests that regulations are necessary in order to support science and quality of research. Time has to come to accept the same for herbal remedies. Unless the research data on Indian herbal remedies meet the local and global regulatory standards, our traditional systems will find it difficult to compete with Chinese efforts. The golden dictum for herbal medicines is "Effective Regulations Improve Research".

The therapeutic value of various plants has been demonstrated by the successful development and use of plant derived conventional medicines. However, the advancement of T/HMPs has been slow due to limited scientific evidence of safety and efficacy, and less than desirable quality control. Major regulatory authorities have since stepped up the regulation of T/HMPs to address the concerns of safety, efficacy, and quality of T/HMPs. Standards proposed should be feasible for manufacturers, as well as adequate to safeguard public health. As the T/HMP industry becomes more established, existing regulations could be tightened and new standards (e.g., GACP) introduced. Although there are challenges that would be encountered along the way, they are not insurmountable. As exemplified by the US FDA approval of Veregen (the first botanical drug), the systematic gathering of adequate scientific evidence and application of quality control in the manufacture of T/HMPs is attainable. Overall, the general public will benefit considerably with greater application of science and regulatory oversight that can assure the safety, efficacy, and quality of T/HMPs.

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