

REVIEW ON QUALITY SAFETY AND LEGISLATION FOR HERBAL PRODUCTS

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ABSTRACT

In the last few decades, there has been exponential growth in the field of herbal medicine. The growing use of botanicals (drug and other products derived from plants) by the public is forcing moves to evaluate the health claims of these agents and to develop standards of quality and manufacture. It is clear that the herbal industry needs to follow strict guidelines and that regulations are needed. This article presents the element of methods of different aspects on quality control and standardization of herbal drugs and formulation. It is followed by international guidelines of WHO for manufacture quality control and evaluation of botanicals. Herbal drugs regulations in India is discussed in detail, followed by an overview of regulatory status of herbal medicine in USA, China, Australia, Brazil, Canada and Germany.

KEYWORDS: Herbal Medicine, Regulatory Requirements, WHO.

INTRODUCTION

According to European Union definitions, herbal medicinal products (medicines) are “medicinal products containing as active ingredients exclusively plant material and/or vegetable drug preparations.”

Herbal drug technology includes all the steps that are involved in converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge will remain important.¹

All countries where medicinal plants and traditional medicines are used are aware of the need for regulating the use of these medicinal substances. There is a need for countries to regulate the use of medicinal plants because there is a growing interest in herbal medicines in the population of these countries.²

Classification of herbal medicines

(Based on their origin, evolution and the forms of current usage)

Category 1: Indigenous herbal medicines

- 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.
- 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. Ayurveda, Unani and Siddha.

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.

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)

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

Category 1: Indigenous herbal medicines

- 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 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.³

REGULATORY REQUIREMENTS

- It is essential to know what regulatory and legislative controls on the manufacture and sale of such herbal medicines exist or required to be implemented in various places around the world.
- Linked to this area are the issues of quality control, both of the raw material and the finished product, and of standardization of herbal medicines.²

WHO ON BOTANICALS

- World health organization (WHO) has tried to establish internationally recognizable regulatory guidelines to define basic criteria for the evaluation of quality, safety and efficacy of botanical medicines.
- Guidelines for assessing the quality of botanical materials mainly emphasize the need to ensure the quality of medicinal plant products by using the modern techniques and applying suitable standards.
- In 1997, WHO developed draft guidelines for methodology on research and evaluation of traditional medicine(TM).
- It mainly focuses on current major debates on safety and efficacy of traditional medicine.
- It also tries to provide answer for some of the challenging questions concerning evidence base of the evaluation of botanical medicine, and also recommend new approaches for carrying out clinical research.
- Specific objectives of these guidelines are to harmonize the use of certain accepted and important terms in TM.
- Purity and quality of botanicals is a critical determinant of safety.
- The first stage in assuring quality, safety and efficacy of botanical medicines is identification and selection of the correct plant species.
- Regulatory authorities for control of raw material have suggested various methods. Most of the guidelines suggest macroscopic and microscopic evaluation and chemical profiling of the botanicals.

a) Characterization using sensory parameters like

Color, odor, taste and surface characteristics are studied in macroscopic evaluation. Size and shape of the plant part used is also taken into consideration.

b) However, since these characteristics are judged

Subjectively and substitutes and adulterants may closely resemble the genuine material, it is often necessary to substantiate the findings by microscopy and/or physicochemical analysis.

c) An examination by microscopy alone cannot

Always provide complete identification, though when used in association with other analytical methods it can frequently supply supporting evidence.

- Chemo profiling using HPLC, HPTLC and GC has wide applicability in quality control of herbal medicine.
- Spectroscopic analysis has also been suggested by certain pharmacopoeias for analysis of botanicals.

LIMITATIONS

- (i) Analysis of secondary metabolites is restricted to those plants that produce a suitable range of metabolites which can be easily analyzed and which can distinguish between varieties.
 - (ii) The metabolites being used as markers should ideally be neutral to environmental effects and management practices.
 - (iii) Establishing the presence of a marker compound in a herb is not sufficient to determine desired quality, since the marker compound may not be necessarily be responsible for the biological activity that is attributed to the whole herb.
- There is a need for new approaches that can complement or serve as an alternative for the existing methods.
 - Some of the newly emerging techniques for ensuring quality are Herboprint capillary electrophoresis and DNA analysis.

Toxic Contaminants

Over the past decade, several adverse effects of botanical medicines due to chemical composition of botanicals or extraneous matters present in/on the plant material have been reported.

Microbial contamination

- Risk assessment of the microbial load of medicinal plants has become an important subject in the establishment of Modern Hazard Analysis and Critical Control Point (HACCP) schemes.
- Various guidelines such as WHO, British Herbal Pharmacopoeia (BHP), Indian Herbal Pharmacopoeia, European Pharmacopoeia has issued special guidance for assessing microbial contaminations of both raw as well as processed botanicals.
- All these guidelines provide specific limits for the contaminants.
- The Indian Herbal Pharmacopoeia (2002) recommends the WHO limits for microbial contamination.

Pesticide Residue

- Every country producing medicinal plant materials (naturally grown or cultivated) should have at least one control laboratory capable of performing the determination of pesticide in accordance with the procedure specified in Quality Control Methods for Medicinal Plant Materials.
- The guidelines suggests intake of pesticides residue from medicinal plant materials should be less than 1 per cent of total intake from all sources, including food and drinking water.
- Chromatography (mostly column and gas) has been recommended as the principal method for the determination of pesticide residues.
- WHO suggests that plant materials of unknown history should be tested for groups of compounds rather than individual pesticides and in case where the pesticide to which the plant material is exposed is known or can be identified by suitable means, an established method for determination of that particular pesticide should be employed.

Heavy Metals

- Many herbal products contain undisclosed heavy metals.
- WHO has proposed the maximum amounts of lead (10mg/kg) and cadmium (0.3mg/kg) based on Allowed Dietary Intake values.
- The methods for determining the content of arsenic, lead and cadmium have been given in WHO Quality Control Methods for Medicinal Plant Materials.
- Atomic absorption spectrometry is a more precise technique, enabling individual elements to be assayed.

Radioactive Contamination

Even at maximum observed levels of radioactive contamination with the more dangerous radio nuclides, significant risk is associated only with consumption quantities of over 20 kg of plant material per year so that risk to health is most unlikely to be encountered given the amount of medicinal plant material that would need to be ingested. Additionally, the level of contamination might be reduced during the manufacturing process. Therefore, no limits for radioactive contamination are proposed.⁴

HERBAL DRUG REGULATIONS IN INDIA

- Recognizing the global demand, Government of India has realized Good Manufacturing Practices (GMPs) for the pharmacies manufacturing Ayurvedic, Siddha and Unani medicines to improve the quality and standard of drugs.
- The new rules came into force from June 2000 as an amendment to the Drugs and Cosmetics Act, 1940.
- Department of Indian Systems of Medicine and Homeopathy (ISM&H) is trying to frame safety and efficacy regulations for licensing new patent and proprietary botanical medicines.

- Indian Pharmacopoeia covers few Ayurvedic medicines. Monographs have been given for some ayurvedic drugs like clove, guggul, opium, menthe, senna.
- The ayurvedic pharmacopoeia of India gives monographs for 258 different Ayurvedic drugs. The standards mentioned are quite inadequate to build quality of the botanical materials.
- Indian Drug Manufacturers Association (IDMA) has published Indian Herbal Pharmacopoeia (2002) with 52 monographs of widely used medicinal plants found in India. The latest available scientific data has been incorporated in these monographs. (4)
- Ayurvedic, Siddha and Unani Drugs Technical Advisory Board-mentioned in section 33-C
- The Ayurvedic, Siddha and Unani Drugs Consultative Committee- mentioned in section 33-D
- Misbranded drugs-mentioned section 33E
- Adulterated drugs-mentioned in section 33EE
- Spurious drugs-mentioned in section 33EEA
- Regulation of Manufacture of Ayurvedic, Siddha and Unani (ASU) Drugs-Section-33-EEB states the regulations on manufacture and sale of ASU drugs.

(A) Requirements of factory premises and hygienic conditions-described in schedule 1 (Rule 157)

(B) Manufacture on more than one set of premises

(C) Prohibition of manufacture and sale of certain Ayurvedic, Siddha and Unani drugs-mentioned in section-33-EEC

(D) Power of Central Government to Prohibit Manufacture etc. of ASU Drugs in Public Interest-mentioned in section-33-EED⁵

- Government Analysts-mentioned in section 33F
- Inspectors-mentioned in section 33G
- Penalty for manufacture, sale, etc., of Ayurvedic, Siddha or Unani drug in contravention of this Chapter-As prescribed under section 33-I
- Penalty for subsequent offences-As mentioned in section 33J
- Confiscation-As mentioned under the section 33K
- Application of provisions to Government departments.-As mentioned in section 33L
- Cognizance of offences-As mentioned in section 33M
- Power of Central Government to make rules-As mentioned in section 33N
- Power to amend First Schedule-As mentioned in section 33-O⁶

REGULATORY ASPECTS AND APPROVAL OF HERBAL DRUGS IN DIFFERENT COUNTRIES

The legal process of regulation and legislation of herbal medicines changes from country to country. The WHO has published guidelines in order to define basic criteria for evaluating the quality, safety, and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area. Furthermore, the WHO has prepared pharmacopoeic monographs on herbal medicines and the basis of guidelines for the assessment of herbal drugs. Thus, the need to establish global and/or regional regulatory mechanisms for regulating herbal drugs seems obvious.⁸

EUROPEAN UNION (EU)

- The European agency of evaluation of Medicinal Products (EMFA) provides general guidelines for setting uniform set of specifications for botanical preparations manufactured and sold in Europe.
- Botanicals that have been used for at least 30 years, with a minimum of 15 years in EU are eligible for registration as traditional medicinal products in EU.
- Preclinical and clinical studies are proposed if a completely new indication is requested for the botanical product has been already marketed for a different use.

- However, if the product has well-established medicinal use with recognizable efficacy and acceptable level of safety, these study are exempted.
- Further, due to complex composition of botanical preparation, pharmacokinetics studies are not suggested unless there are safety concerns.

AUSTRALIA

- Complementary medicine, including botanical medicines in Australia is regulated under therapeutic goods legislation.
- Based on risk, Australia has developed two approaches for regulation of these therapeutic
- Goods. Listed medicines are considered to be of lower risk than registered medicines.
- Most, but not all, complementary medicines are listed medicines, which are individually assessed by the Therapeutic Goods Administration for compliance with legislation. They are not evaluated before release. They may only be formulated from ingredients that have undergone pre-market evaluation for safety and quality and are considered at low risk. Listed complementary medicines may only carry indications and claims for the symptomatic relief of non serious conditions, health maintenance, health enhancement and risk reduction.
- Registered medicines are individually evaluated for safety, quality and efficacy before they are released onto the market.
- An important feature of risk management in Australia is that early market access for low risk complementary medicines is supported by appropriate post-market regulatory activity.⁴

CHINA

- If a new medicinal plant product or a crude drug is to be imported from abroad to be sold in the Chinese market, then the approval of the provincial department of public health is required. The Pharmacopoeia People's Republic of China has got a section on "Standard for Processing of Chinese Materia Medica".
- If Chinese herbal medicines are produced in factories either for export or for local use in other parts of the country, these have to be undergo quality control tests before being released.
- Another set of rigid criteria has been laid down for assessing patented traditional Chinese medicines. Only after assuring that the product conforms to the Chinese traditional system of medicines, that it is safe and that the ingredients are not incompatible with each other will the patent medicine be allowed to be released to the market.²

BRAZIL

- The legal requirements for registration of herbal medicines in Brazil demand complete documentation of efficacy, safety and well defined quality control.
- For old medicinal herbs already registered, the law established 5 and 10 years for the assessment of their safety and efficacy, respectively.

CANADA

- The Canadian regulatory system is consistent with WHO guidelines for the assessment of herbal medicines.

GERMANY

- Germany's Commission E (phytotherapy and herbal substances) was established in 1978. It is an independent division of the German Federal Health Agency that collects information on herbal medicines and evaluates them for safety and efficacy.
- Three possibilities for marketing herbal drugs exist: 1) temporary marketing authorization for old herbal drugs until they are evaluated for safety and efficacy; 2) monographs of standardized marketing authorization, and 3) individual marketing authorization.

- Evaluations are published in the form of monographs that approve or disapprove the herbal drugs for over-the-counter use.⁸

CONCLUSION

Quality of botanicals must be improved greatly if botanical medicines are to assume a respected place in the contemporary health care system. Various regulatory authorities and industry are trying to address this issue of quality worldwide. Regulatory authorities of different countries have contributed in developing guiding principles addressing issues related to these aspects of botanical medicine. This review discusses various regulatory issues related to quality of botanicals. Although, considerable progress has been made in characterizing botanical medicine, there is need for global harmonization of the botanical quality and health claims. International Conference on Harmonization (ICH) has tried to harmonize technical requirements for registration of pharmaceuticals for human use by setting specific guidelines. These guidelines may be applicable to uplift quality of botanicals globally.

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